Under the auspices of the European Society of Endocrinology

Advanced Practice in Endocrinology Nursing

Sofia Llahana
Cecilia Follin
Christine Yedinak
Ashley Grossman
Editors

With Paediatric Editors
Kate Davies and Margaret F. Keil

European Society of Endocrinology

Springer

Advanced Practice in Endocrinology Nursing

Sofia Llahana · Cecilia Follin
Christine Yedinak · Ashley Grossman
Editors

Advanced Practice in Endocrinology Nursing

With Paediatric Editors Kate Davies
and Margaret F. Keil

European Society of Endocrinology

Springer

Editors
Sofia Llahana
School of Health Sciences, City
University of London
London
UK

Cecilia Follin
Department of Oncology
Skåne University Hospital
Lund
Sweden

Christine Yedinak
Northwest Pituitary Center
Oregon Health and Sciences University
Portland, OR
USA

Ashley Grossman
Churchill Hospital
University of Oxford
Oxford
UK

ISBN 978-3-319-99815-2 ISBN 978-3-319-99817-6 (eBook)
https://doi.org/10.1007/978-3-319-99817-6

Library of Congress Control Number: 2018968596

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Sofia Llahana
Dedicated to my daughter Elise-Katerina, my husband Richard, and my parents and role models Eirini and Vasilis

Cecilia Follin
Dedicated to Anders, Jesper and Alexander

Christine Yedinak
Dedicated to my husband and cheerleader Marty

Ashley Grossman
Dedicated to my daughters: Emily, Sophie, Annabel, Camilla, Cordelia, and Elizabeth

Foreword

Endocrinology nursing is a fast-developing specialty with nurses performing advanced roles and expanding their practice to cover key roles in the future multidisciplinary centres of excellence like the PTCOE (Pituitary Tumor Centers of Excellence). This book has the merit of providing a comprehensive guide for nurses practising in all areas of endocrinology including bone metabolic diseases, obesity, and lipid disorders. Particularly interesting and modern are the chapters devoted to endocrine emergencies and endocrine abnormalities consequent to cancer treatment. Moreover, the book is suitable for nurses serving in both paediatric and adult endocrine units and at any level of expertise.

The book has been written by an international team of eminent nurses, physicians, surgeons, psychologists, and other healthcare professionals, which makes this book a valuable resource not only for nurses but also for other members of any multidisciplinary team. Patient advocacy groups have also contributed to most chapters with case studies and examples of collaborative working with healthcare professionals to improve patient care.

This is the first book ever published specifically for nurses working in endocrinology, but it is also an excellent resource for nurses working in other specialties such as internal medicine, gynaecology, urology, and rheumatology due to the wide range of topics covered in the book from fertility to osteoporosis and erectile dysfunction. Specialty trainees, general practitioners, students, psychologists, and expert patients wanting in-depth information will also find this book a useful resource.

The editors have led the way in advancing nursing practice, and this book is a reflection of their dedication to developing a solid doctrinal body for the discipline of endocrine nursing worldwide.

Milan, Italy — Andrea Giustina

Preface

We are extremely pleased and proud that our ambitious idea to write the first ever published book for endocrine nurses has finally come to fruition. We wanted this to be a useful resource for endocrine nurses across the globe working at different settings and levels of practice, from novice to expert and from bedside nursing to advanced practice nursing running independent nurse-led services. We recognised that this would be a challenging project to undertake, especially as the endocrinology nursing role varies significantly from country to country. We were, however, overwhelmed by the interest we received from colleagues who wanted to contribute to this book, echoing the great need for such a resource and especially from physicians and other healthcare professionals who recognise the endocrine nurse as a vital member of the multidisciplinary team.

The *European Society of Endocrinology* (ESE) formed our initial working hub and supported this textbook from its inception. We created a strong collaborative European and international network; 118 eminent authors from 15 countries contributed to this book. Most of our authors are nurses, but physicians, surgeons, psychologists, dieticians and geneticists have also contributed, emphasising the multidisciplinary focus of this book.

Built on the growing body of knowledge, expertise and the expanding nature of advanced practice in endocrinology nursing, this book provides a comprehensive resource to support nurses to develop their competence at different levels of their career. The authors in each chapter have done a tremendous job presenting a comprehensive review of anatomy, pathophysiology, diagnosis and treatment of different endocrine conditions supported by the latest evidence and clinical guidelines. Patient stories, case studies and good clinical practice examples are included to illustrate the impact of endocrine conditions on patients and their families, to stimulate the readers' critical thinking and reflection and to make information in this book applicable to their clinical practice. Many patient advocacy groups have contributed with case studies and educational resources, supporting the emphasis this book places on user involvement and shared decision-making in patient care.

Comprising of 13 parts and a total of 69 chapters, this book is a comprehensive resource for paediatric and adult nurses working in endocrinology but should also be useful for specialty trainees, general practitioners, students and expert patients. It also covers endocrine-related topics within other specialties such as fertility, osteoporosis, oncology, urology, gynaecology, obesity and metabolic disorders. Each part covers conditions within a specific

endocrine gland (pituitary, adrenal, thyroid, parathyroid and bone disorders and male and female reproduction) and other relevant endocrine conditions such as late effects of cancer treatment, neuroendocrine tumours, endocrine emergencies, obesity and metabolic disorders. There are two paediatric-specific parts (11 chapters); paediatric aspects have also been incorporated in many other chapters, where relevant. The final part focuses on advanced practice nursing (APN) presenting an overview of role development, definition and components of APN, including research, with many useful resources to support career progression within endocrinology nursing. The work by our part editors has been vital as they invited authors and coordinated and edited the chapters in each part; we could not have completed this book without their amazing contribution. We hope and trust this book will assist and advise all our colleagues to ensure the best possible patient care.

London, UK — Sofia Llahana
Lund, Sweden — Cecilia Follin
Portland, OR, USA — Christine Yedinak
Oxford, UK — Ashley Grossman

Acknowledgements

This book is a testament of a successful global collaboration of healthcare professionals, learned societies and patient advocacy groups, and it would not have been possible without the great effort that everyone put into this project.

We express our deep gratitude to our 118 authors who contributed to this book; this was an international multidisciplinary collaboration of nurses, physicians, surgeons, psychologists, geneticists, dieticians and nurse academics from 15 different countries. This book covers adult and paediatric topics; we are indebted to Kate Davies (UK) and Margaret Keil (USA) for editing the paediatric parts and for inviting and supporting authors who contributed with paediatric aspects to many other chapters where relevant in the book. Our gratitude also goes to our part editors who invited contributing authors and edited the chapters in each part: Judith van Eck (the Netherlands), Violet Fazal-Sanderson (UK), Gerard Conway (UK), Andrew Dwyer (Switzerland/USA), Ann Robinson (Australia), Philip Yeoh (UK), Anne Marland (UK) and Michael Tadman (UK). Their names are listed in the respective textbook parts.

The textbook was initiated and developed under the auspices of the European Society of Endocrinology (ESE) and has its full endorsement. We are very grateful to Professor AJ van der Lely, ESE President (2015–2019); Helen Gregson, ESE Chief Executive Officer; Professor Jérôme Bertherat, Chair of ESE Clinical Committee; members of the ESE Executive Committee; and, in particular, Professor Andrea Giustina, incoming ESE President (2019), who has supported this textbook since its inception in 2015.

Special thanks go to Professor Philippe Bouchard, past President of the ESE, and Professors Pia Burman and Richard Ross, past members of the ESE Executive Committee. Their support was instrumental in developing and establishing the ESE Nurses Committee, through which we met and worked together on this book and on other European and international projects.

We are also grateful to the following Nursing Organisations for their support and for approving this textbook as a valuable resource for endocrine nurses:

- The Federation of International Nurses in Endocrinology (FINE)
- The Endocrine Nurses Society (ENS)—USA
- The Endocrine Nurses' Society of Australia (ENSA)—Australasia
- The Pediatric Endocrinology Nursing Society (PENS)—USA, Canada

Representatives from many Patient Advocacy Groups across the globe contributed with case studies and educational resources; we are very grateful and have acknowledged their input in each respective chapter. We would also like to express our gratitude to patients and their families who shared their stories to help our readers understand the impact of endocrine conditions. We all learn so much from our patients and are grateful for the opportunity to be a part of their lives and to support them throughout different stages of living with their condition.

Very special thanks go to Nathalie L'Horset-Poulain, our Senior Publishing Editor, for her amazing guidance throughout this project. We have been very privileged to work with Nathalie and would not have been able to complete this book without her outstanding support. Special thanks also go to Marie-Elia Come-Garry (Associate Editor), Sushil Kumar Sharma (Project Coordinator), Vishal Anand (Project Manager) and all the other members of the Springer Nature Team for their support.

Finally, we would like to express our sincere gratitude to our families, but also the families of all of our authors, for their patience and support during the past 3 years. We sacrificed many weekends and evenings to produce this book and would not have been able to complete it without their unlimited and unconditional support and encouragement.

Sofia Llahana
Cecilia Follin
Christine Yedinak
Ashley Grossman

Contents

Part I Growth and Development

1 The Importance of Auxology for Growth Assessment 3
Terri H. Lipman and Megan K. Lessig

2 Short Stature, Growth Hormone Deficiency, and Primary IGF-1 Deficiency 13
Bin Moore, Amanda Whitehead, and Kate Davies

3 Disorders of Sex Development (DSD) 39
Kate Davies

4 Puberty: Normal, Delayed, and Precocious 63
Eileen Pyra and Wendy Schwarz

5 Treatment Issues in the Care of Pediatric Patients with Endocrine Conditions 85
Peggy Kalancha, Nicole Kirouac, and Eileen Pyra

6 Transition from Paediatric to Adult Services 101
Susie Aldiss

Part II Endocrine Disorders and Genetics in Childhood

7 Genetics and Family History 121
Kelly Mullholand Behm

8 Congenital Hyperinsulinism (CHI) 163
Claire Gilbert, Kate Morgan, Louise Doodson, and Khalid Hussain

9 Genetic Syndromes Presenting in Childhood Affecting Hypothalamic Function 179
Kathryn Clark

10 Genetic Syndromes Presenting in Childhood Affecting Gonadotropin Function 195
Sharron Close, Ana Claudia Latronico, and Marina Cunha-Silva

11 McCune–Albright Syndrome 207
Beth Brillante and Lori Guthrie

Part III Hypothalamus and Pituitary

12 Anatomy and Physiology of the Hypothalamic-Piuitary Axis 231
Kathryn Evans Kreider

13 Metabolic Effects of Hypothalamic Dysfunction 245
Cecilia Follin

14 Sella and Suprasellar Brain Tumours and Infiltrarive Disorders Affecting the HPA-Axis 255
Christine Yedinak

15 Dynamic Investigations and Diagnostic Testing 277
Christine Yedinak and Kate Davies

16 Diagnostic Imaging 305
Christine Yedinak

17 Non-functioning Pituitary Adenomas 321
Judith P. van Eck and Sebastian J. C. M. M. Neggers

18 Thyroid Stimulating Hormone Secreting Adenoma (TSHoma) 335
Christine Yedinak

19 Prolactin Producing Adenomas: Prolactinomas and Hyperprolactinemia 343
Christine Yedinak

20 Growth Hormone Producing Adenomas: Acromegaly 365
Karen J. P. Liebert, Daphne T. Adelman, Elisabeth Rutten, and Christine Yedinak

21 ACTH Producing Adenomas: Cushing's Disease 395
Raven McGlotten, Daphne T. Adelman, and Margaret F. Keil

22 Pituitary Surgery 415
Jürgen Honegger

23 Pituitary Surgery: Nursing Implications 433
Sarah Benzo and Christina Hayes

24 Radiotherapy 447
Ahmed Al Sajwani and Mark Sherlock

25 Hypopituitarism and Growth Hormone Deficiency in Adults . 469
Sofia Llahana, Anne Marland, Mila Pantovic, and Vera Popovic

Part IV The Thyroid Gland

26 Thyroid Anatomy and Physiology 497
Chloe Broughton and Bushra Ahmad

27 Thyroid Investigations 505
Victoria J. Stokes, Rabia Arfan, Theingi Aung, and Violet Fazal-Sanderson

28 Hyperthyroidism in Adults 519
Violet Fazal-Sanderson, Niki Karavitaki, and Radu Mihai

29 Thyroid Cancer 557
Ingrid Haupt-Schott, Geraldine Hamilton, and Petros Perros

30 Diagnosis and Management of Hypothyroidism in Adults 581
Raluca-Alexandra Trifanescu and Catalina Poiana

31 Thyroid Eye Disease 593
Rebecca Ford and Violet Fazal-Sanderson

32 Disorders of the Thyroid in Childhood and Adolescence 609
Suma Uday, Christine Davies, and Helena Gleeson

33 Thyroid Disease in Pre- and Post-Pregnancy 629
Dev A. Kevat and Lucy Mackillop

Part V The Adrenal Gland

34 Anatomy and Physiology of the Adrenal Gland 645
Phillip Yeoh

35 Diagnosis and Management of Congenital Adrenal Hyperplasia in Children and Adults 657
Alessandro Prete, Chona Feliciano, Irene Mitchelhill, and Wiebke Arlt

36 Adrenal Tumours: Adrenocortical Functioning Adenomas, Pheochromocytomas, Incidentalomas, and Adrenocortical Cancer 679
Andrew P. Demidowich, Miriam Asia, and Jérôme Bertherat

37 Diagnosis and Management of Adrenal Insufficiency in Children and Adults 705
Sofia Llahana, Irene Mitchelhill, Phillip Yeoh, and Marcus Quinkler

Part VI Female Endocrinology and Reproduction

38 Anatomy and Physiology of the Female Reproductive System . 739
Artemis Vogazianou

39 Assessment and Management of Women with Polycystic Ovary Syndrome (PCOS) 753
Rhonda Garad, Soulmaz Shorakae, and Helena Teede

40 Diagnosis and Management of Turner Syndrome in Children and Adults 771
Helen E. Turner and Irena R. Hozjan

41 Premature Ovarian Insufficiency, Menopause, and Hormone Replacement Therapy 803
Gerard S. Conway

42 The Endocrine System and Pregnancy 817
Margaret Eckert-Norton and Saundra Hendricks

Part VII Male Endocrinology and Reproduction

43 Anatomy and Physiology of the Hypothalamic-Pituitary-Gonadal (HPG) Axis 839
Andrew A. Dwyer and Richard Quinton

44 Classification of Hypothalamic-Pituitary-Gonadal (HPG) Axis Endocrine Disorders 853
Andrew A. Dwyer and Richard Quinton

45 Evaluation of Endocrine Disorders of the Hypothalamic-Pituitary-Gonadal (HPG) Axis 871
Andrew A. Dwyer and Frances J. Hayes

46 Testosterone Therapy in Adult Men with Hypogonadism 885
Sofia Llahana

47 Spermatogenesis and Assisted Fertility Treatment 903
Andrew A. Dwyer, Elizabeth Williamson, Margaret G. Au, and Channa Jayasena

48 Diagnosis and Management of Erectile Dysfunction in Men 925
Fiona Holden, Clare Akers, and Sofia Llahana

49 Genetic Counselling and Psychosexual Considerations in Male Health and Reproduction 943
Margaret G. Au and Sue Jackson

Part VIII Parathyroid, Calcium and Bone Disorders

50 Hyperparathyroidism and Hypoparathyroidism 957
Amy Mundy and Rachel Crowley

51 Calcium Disorders 975
Arthur D. Conigrave and Marsha M. van Oostwaard

52 Congenital and Acquired Bone Disorders in Children and Adults 989
Kirtan Ganda, Klaus Sommer, and Anne L. Ersig

53 Osteoporosis 1005
Sherwin Criseno

54 Vitamin D Deficiency and Treatment in Children and Adults . 1037
Yuk Fun Chan, Kerry-Lee Milner, Chris White, and Pauline Musson

Part IX Obesity and Disorders of Lipid Metabolism

55 Dietary and Behavioural Interventions in the Management of Obesity 1065
Clare Grace and Adrian Brown

56 Assessment of the Patient with Obesity and Bariatric Surgical Interventions 1085
Saira Hameed and Harvinder Chahal

57 Lipid Disorders and Familial Hypercholesterolaemia 1101
Alison Pottle

Part X Late Effects of Cancer Treatment in Relation to Endocrinology

58 Transition of Childhood Cancer Survivors 1123
Tanya L. Urquhart-Kelly and Jerry K. Wales

59 Endocrinopathy After Childhood Cancer Treatment 1133
Cecilia Follin

60 Neurocognitive Dysfunction and Psychosocial Issues 1149
Katharina Roser, Gisela Michel, and Katrin Scheinemann

Part XI Endocrine Emergencies

61 Management of Hyponatraemia in Adults and Children 1163
Phillip Yeoh and Anne Marland

62 Prevention and Management of Adrenal Crisis in Children and Adults 1183
Sofia Llahana, Kathrin Zopf, Irene Mitchelhill, and Ashley Grossman

63 Thyroid Emergency: Thyroid Storm and Myxoedema Coma . 1207
Paul V. Carroll

64 Diagnosis and Management of Pituitary Apoplexy in Adult Patients 1217
Stephanie E. Baldeweg

Part XII Neuroendocrine Tumours and Multiple Endocrine Neoplasia

65 Neuroendocrine Tumours 1229
Mike Tadman, Philippa Davies, Tara Whyand, and Lee Martin

66 Multiple Endocrine Neoplasia 1259
Mike Tadman and Lee Martin

Part XIII Advanced Practice Nursing in Endocrinology

67 Conceptualization, Definition, and Competencies of Advanced Practice Nursing with a Focus on Endocrinology 1281
Sofia Llahana, Andrew A. Dwyer, and Christine Yedinak

68 Role Development and Performance Facilitators in Advanced Practice Nursing 1303
Sofia Llahana

69 Research and Evidence-Based Practice: The Nurse's Role 1321
Lesley Baillie, Debbie Carrick-Sen, Anne Marland, and Margaret F. Keil

Correction to: ACTH Producing Adenomas: Cushing's Disease C1

About the Editors

Sofia Llahana, DNSc, MSc, BSc(Hons), RN, INP is a Senior Lecturer, Education and Research, and Programme Director for Advanced Clinical Practice at City, University of London. Dr Llahana was the first consultant nurse in endocrinology in the United Kingdom and worked at University College Hospital in London where she continues to maintain an honorary position. Her clinical and research interest is in pituitary and adrenal conditions, reproductive endocrinology, men's health, self-management, adherence to medication and behavioural medicine. Her current research portfolio includes ongoing and new investigator-led and collaborative national and European studies in adrenal insufficiency, testosterone replacement therapy, male reproduction, growth hormone deficiency, and type 2 diabetes. Dr Llahana is the Chair of the Nurses Committee and a member of the Executive Committee of the European Society of Endocrinology (ESE), a board member of the Federation of International Nurses in Endocrinology (FINE), and the only nurse member in the Scientific Committee for the International Congress in Men's Health. She also holds affiliations with several learned societies and patient advocacy groups in endocrinology.

Cecilia Follin graduated as a registered nurse from the Institution of Healthcare Science at the Medical Faculty of Lund University in Sweden. Dr Follin has over 15 years of experience from the field of endocrinology. She holds particular interests in late complications after childhood cancer and pituitary and hypothalamic disorders. Cecilia is initiator and chair of the Nordic Network of Endocrine Nurses.
In 2010, Dr. Follin was awarded with a PhD degree in endocrinology. The thesis was titled "Late complications of childhood acute lymphoblastic leukemia (ALL), with special reference to hormone secretion,

cardiovascular risk and bone health." In 2010–2012, Cecilia had a postdoc position at the Institution of Clinical Sciences, and currently she has a position as researcher and senior teacher at Lund University. Dr. Follin has published numerous papers.

Christine Yedinak, DNP, FNP-BC, MN, Grad DipEd, RN is a doctor of nursing practice and a board-certified family nurse practitioner. She is an assistant professor at the Northwest Pituitary Center, Oregon Health & Sciences University, Portland, Oregon, USA. Dr. Yedinak completed her undergraduate training in Australia and received her postgraduate diploma in tertiary education at the University of Southern Queensland, Toowoomba. She completed her postgraduate and doctoral studies at Oregon Health & Sciences University, Portland, Oregon. Her ongoing research focus is on quality of life and clinical outcomes for patients with pituitary diseases. Dr. Yedinak is president of the Endocrine Nurses Association (USA) and a board member of the European Society of Endocrinology Nurses' Group. She is co-founder and president of the Federation of International Nurses in Endocrinology (FINE).

Ashley Grossman, BA, BSc, MD, FRCP, FMedSci initially graduated with a BA in psychology and social anthropology from the University of London, then entered University College Hospital Medical School in London, and received the University Gold Medal in 1975. He also obtained a BSc in neuroscience. Professor Grossman joined the Department of Endocrinology at St. Bartholomew's Hospital where he spent most of his career, eventually as professor of neuroendocrinology, but then moved to become professor of endocrinology at the University of Oxford in the Oxford Centre for Diabetes, Endocrinology and Metabolism. Most recently, he has moved to the Royal Free London where he has specialized in neuroendocrine tumors. In 1999, he was appointed a fellow of the Academy of Medical Sciences, and in 2011, he was made a fellow of Green Templeton College at the University of Oxford. Professor Grossman has published more than 900 research

papers and reviews. He has a major interest in tumors of the hypothalamo-pituitary axis, especially Cushing's disease, but his clinical concern and research have expanded increasingly to include broad areas of endocrine oncology, most especially neuroendocrine tumors of all types, including pheochromocytomas, paragangliomas, adrenocortical cancer, medullary thyroid cancer, and hereditary endocrine tumor syndromes. He is past president of the European Neuroendocrine Association (ENEA), past chairman of the UKI Neuroendocrine Tumour Society (UKINETS), and past president of the Society of Endocrinology and the Pituitary Society. He was previously editor of the journal, *Clinical Endocrinology*; is on the editorial board of the major textbook, *Endocrinology*, by De Groot and Jameson; is vice chairman of the major online textbook, *Endotext.org*; and serves on the editorial boards of many journals.

About the Part Editors

Kate Davies, RN(Child) BSc(Hons) MSc PGDip has over 25 years of experience as a children's nurse, with over 18 years in pediatric endocrinology. She has subspecialized in growth and puberty, Cushing's syndrome, multiple endocrine neoplasia in children, neuroendocrine late effects of childhood brain tumors, adrenal disorders, and disorders of sex development. She is currently a senior lecturer in children's nursing and course director of the PGDip/MSc Children's Advanced Nurse Practitioner program at London South Bank University, UK. She has been chair of the Royal College of Nursing Paediatric Endocrine Special Interest Group (2002–2008), a member of the UK Society of Endocrinology Nurse Committee (2012–2017), and is currently secretary of the European Society of Paediatric Endocrine Nurses Group. She was awarded the BSPED Ipsen Paediatric Endocrine Nurse Award in 2014. Kate is a fellow of the Higher Education Academy, a NMC-registered nurse teacher, and a children's advanced nurse practitioner.

Margaret F. Keil, PhD, CRNP is a board-certified pediatric nurse practitioner with 30+ years of experience in pediatric nursing caring for children with chronic medical conditions in a variety of clinical settings. Dr. Keil received her PhD in nursing from the Uniformed Services University of the Health Sciences and is a graduate of the University of Colorado and Georgetown University. Dr. Keil is a clinical researcher at the National Institutes of Health; her research focuses on biobehavioral outcomes of early life adversity and quality of life and other outcomes associated with chronic endocrine disorders in children. Dr. Keil has authored or co-authored numerous articles published in peer-reviewed journals on pediatric endocrine disorders, including Cushing syndrome, quality of life outcomes, congenital adrenal hyperplasia, obesity, and pituitary tumors. She holds leadership positions in the Pediatric Endocrinology Nurses Society and the Cushing Support and Research Foundation and is a member of the European Society of Endocrinology and the Federation of International Nurses in Endocrinology.

Judith P. van Eck is one of the first advanced practice nurses specialized in endocrinology in the Netherlands. Her career in nursing started in 2004 when she received her bachelor degree in nursing science. Afterward, she worked from 2004 to 2008 as a registered nurse on the clinical department of internal medicine at the Erasmus Medical Center in Rotterdam, the Netherlands. From 2008 to 2010, she followed the Master in Advanced Nursing Practice at Rotterdam University of Applied Sciences. From 2010 until 2018, she worked as a nurse practitioner for the Pituitary Center at the Erasmus Medical Center in Rotterdam, the Netherlands. She was also running a nurse-led clinic for patients with radiation induced hypopituitarism. Currently, she works as a nurse practitioner at the department of Pediatric Endocrinology at Erasmus MC- Children's Hospital in Rotterdam, The Netherlands. She also runs a nurse-led clinic for patients with radiation induced hypopituitarism. She has been a member of the ESE nurses working group from 2013 to 2017, and currently, she is a member of the Dutch Endocrine Nurses Group.

Violet Fazal-Sanderson's, RGN, BSc(Hons), MSc, IP nursing career took off in Oxford where she worked for several years as a staff nurse in the intensive care unit at the Oxford University Hospitals NHS Foundation Trust. She graduated with a BSc (hons) in critical care nursing at Oxford Brookes University. From 2000 to 2016, she worked in the endocrine investigations unit as an advanced nurse practitioner at the Oxford Centre for Diabetes, Endocrinology and Metabolism. She developed an interest in acromegaly and thyroid nurse-led clinics and involved herself in 40 research projects from which emerged several published abstracts and 2 nurse awards.

In 2017, she gained an MSc in endocrinology and now works as a senior endocrine clinical specialist nurse at the Royal Berkshire Hospital NHS Foundation Trust, Reading, and continues to work in endocrinology and thyroid virtual nurse-led clinics. Violet is a member of the British Society for Endocrinology Nurse Committee and the UK TEDct.

Gerard S. Conway is a consultant endocrinologist at University College London Hospitals and professor of clinical medicine in the Institute for Women's Heath, University College London. His clinical practice covers general endocrinology including pituitary, adrenal, thyroid, and reproductive endocrinology.

His clinical research interests are in the field of reproductive endocrinology particularly polycystic ovary syndrome, ovarian and testicular function, disorders of sexual development, and Turner syndrome. This research has formed the basis of over 160 academic publications.

Professor Conway qualified from the Royal London Hospital in 1981 and trained in diabetes, endocrinology, and general medicine in several centers in Central London. He has been professor of clinical medicine in the Institute for Women's Health UCL since 2012.

With a major interest in teaching, Professor Conway lectures in reproductive endocrinology, for the Society for Endocrinology, the Royal College of Obstetricians and Gynaecologists, and internationally with the endocrine societies in the USA, Sri Lanka, India, New Zealand, Australia, Japan, and throughout Europe.

Andrew A. Dwyer, PhD, FNP-BC, FNAP is a board-certified family nurse practitioner with 18+ years of experience in reproductive endocrinology and translational research at the Massachusetts General Hospital (MGH) in Boston (USA) and the University Hospital of Lausanne (CHUV) in Switzerland. Professor Dwyer specializes in genetic disorders of growth/puberty and has helped develop and test structured transitional programs for young adults with chronic endocrine conditions. He presents internationally and has authored/co-authored more than 50 articles on these topics. He holds leadership positions in several organizations including the European Society of Endocrinology, Pediatric Endocrine Nursing Society, European Society of Paediatric Endocrine Nursing, International Society of Nurses in Genetics, and Global Genomic Nursing Alliance. In 2018, Professor Dwyer was inducted into the National Academies of Practice (nursing) as a distinguished fellow.

Ann Robinson is an endorsed nurse practitioner (NP) with experience in both public and private sectors. With a background in diabetes and endocrine nursing, her main area of clinical work is now bone health and fracture prevention in high-risk populations. In addition, Ann sits on the governing board of the SOS Fracture Alliance and is past president of the Endocrine Nurses Society of Australasia. Ann works at Gold Coast Health as a nurse practitioner collaborating between hospital and community services to improve osteoporosis awareness and reduce the burden of osteoporotic fractures. She collaborates with the orthopedic teams and has an interest in when to commence treatment, for how long, and when, if ever to stop treatment.

Phillip Yeoh, RN, BSc, MSc, PhD(c) completed registered nurse training in London, BSc from the University of Manchester, and MSc from Brunel University. Philip is currently doing a PhD in Nursing at King's College in London. He is consultant nurse in endocrinology and manager for Endocrine and Diabetes Department within the London Clinic, providing inpatient and outpatient care. His interests in endocrinology focus on adrenal diseases, pituitary conditions, Cushing's disease, acromegaly, neuroendocrine conditions, parathyroid diseases, thyroid cancers, Conn's syndrome, endocrine malignancy such as adrenocortical carcinoma, endocrine testing, endocrine nurse clinical roles, and endocrine nurse educations. He is co-author of *Competency Framework for Adult Endocrine Nursing (Society for Endocrinology)* editions I and II. Currently, he is involved in various research projects looking at dynamic function tests and endocrine nurse role in continuous subcutaneous hydrocortisone infusion pump for patients with adrenal insufficiency. He is coordinator for Federation of International Nurses in Endocrinology. He was a nurse committee member for European Society of Endocrinology and Society for Endocrinology. He is also a trustee for Addison's Disease Self-Help Group UK.

Anne Marland, RGN, INP, BSc, MSc, PhD(c) is advanced nurse practitioner in adult endocrinology and independent nurse prescriber (INP) at the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) in the UK. Anne worked in the Neuroscience Department in Oxford, and in 1998, she took on a senior research nurse role in OCDEM and, following this, advanced nurse practitioner. Anne has a keen interest in the clinical area of "late effects in endocrinology" and is currently studying for a PhD in this area. She is the patient and public involvement representative for the NIHR

for endocrinology and rare disease in the UK. Anne has a keen interest in education and regularly lectures worldwide. She chairs the working party which developed the Society for Endocrinology MSc in Adult Endocrine Nursing in collaboration with Oxford Brookes University in the UK. Anne is the current chair for the British Society for Endocrinology Nurse Committee and member of the Public Engagement Committee.

Mike Tadman is a cancer nurse specialist with over 20 years of experience both in practice and education, mainly within Oxford, but has also practiced in Edinburgh and briefly in Melbourne. He set up the Neuroendocrine Tumours Specialist Nursing Service at the Oxford University Hospitals NHS Foundation Trust in 2013. He is an active member of UKINETs and ENETs and has presented regularly at national and international conferences on NETs. He has completed a survey of how centers commence and he has recently published research into the use of somatostatin analogue test dosing and urine 5HIAA testing. He is author of the *OUP Cancer Nursing Handbook*, having just completed editing its 2nd edition.

Contributors

Daphne T. Adelman Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Bushra Ahmad Bristol Royal Infirmary, University of Bristol, Bristol, UK

Clare Akers Urology Department, Westmorland Street Hospital, University College London Hospitals NHS Foundation Trust, London, UK

Ahmed Al Sajwani Department of Endocrinology, Tallaght Hospital, Dublin and Trinity College, Dublin, Ireland

Susie Aldiss Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK

Wiebke Arlt Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Miriam Asia Department of Endocrinology, Birmingham University Hospital, Birmingham, UK

Margaret G. Au Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Theingi Aung Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK

Lesley Baillie School of Health, Wellbeing and Social Care Nursing, The Open University, Milton Keynes, UK

Stephanie E. Baldeweg Department of Diabetes and Endocrinology, University College London Hospitals, London, UK

Kelly Mullholand Behm Orlando, FL, USA

Sarah Benzo Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Jérôme Bertherat Service d'Endocrinologie, Hôpital Cochin, Paris, France

Beth Brillante National Institutes of Health, National Institute of Dental and Craniofacial Research, Craniofacial and Skeletal Diseases Branch, SCSU, Bethesda, MD, USA

Chloe Broughton North Bristol NHS Trust, Bristol, UK

Adrian Brown Imperial College London, London, UK

Debbie Carrick-Sen School of Nursing, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Paul V. Carroll Department of Endocrinology, Guy's & St. Thomas' NHS Foundation Trust, DEDC 3rd Floor Lambeth Wing, St. Thomas' Hospital, London, UK

Harvinder Chahal Imperial Weight Centre, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

Yuk Fun Chan Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia

Kathryn Clark University of Michigan Hospital, Ann Arbor, MI, USA

Sharron Close Emory School of Medicine, Emory University School of Nursing, The eXtraordinarY Clinic at Emory, Atlanta, GA, USA

Arthur D. Conigrave Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Gerard S. Conway Institute for Women's Health, University College London, London, UK

Sherwin Criseno University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Rachel Crowley St. Vincent's University Hospital and University, College Dublin, Dublin, Ireland

Marina Cunha-Silva Disciplina de Endocrinologia e Metabologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil, São Paulo, Brazil

Christine Davies Children's Hospital for Wales, Cardiff and Vale UHB University Hospital of Wales (UHW), Cardiff, UK

Kate Davies Department of Advanced and Integrated Practice, London South Bank University, London, UK

Philippa Davies NET Unit, Royal Free London NHS Foundation Trust, London, UK

Andrew P. Demidowich National Institutes of Health, Bethesda, MDUSA

Louise Doodson Great Ormond Street Hospital for Children NHS Trust, London, UK

Andrew A. Dwyer William F. Connell School of Nursing, Boston College, Chesnut Hill, MA, USA

Margaret Eckert-Norton SUNY Downstate, Brooklyn, NY, USA

Anne L. Ersig UW-Madison School of Nursing, UW Health American Family Children's Hospital, Madison, WI, USA

Violet Fazal-Sanderson Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK

Chona Feliciano Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Cecilia Follin Department of Endocrinology, Skane University Hospital, Lund, Sweden

Rebecca Ford Bristol Eye Hospital, University Hospitals Bristol NHS Trust, Bristol, UK

Kirtan Ganda Concord Hospital, Sydney, NSW, Australia

Rhonda Garad Monash Centre for Health Research and Implementation (MCHRI), Monash University, Clayton, VIC, Australia

Claire Gilbert Great Ormond Street Hospital for Children NHS Trust, London, UK

Helena Gleeson Department of Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Clare Grace Relish Nutrition Consultancy, North Yorkshire, UK

Ashley Grossmann Royal Free Hospital, London, UK

Green Templeton College, University of Oxford, Oxford, UK

Barts and the London School of Medicine, London, UK

Lori Guthrie National Institutes of Health, National Institute of Dental and Craniofacial Research, Craniofacial and Skeletal Diseases Branch, SCSU, Bethesda, MD, USA

Saira Hameed Imperial Weight Centre, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

Geraldine Hamilton Macmillan Support Line, Macmillan Cancer Support, Glasgow, UK

Ingrid Haupt-Schott Velindre NHS Trust, Velindre Cancer Centre, Cardiff, UK

Christina Hayes Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Frances J. Hayes Endocrine Division, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Saundra Hendricks Department of Medicine, Center of Bioenergetics, Houston Methodist Hospital, Houston, TX, USA

Fiona Holden Urology Department, Westmorland Street Hospital, University College London Hospitals NHS Foundation Trust, London, UK

Jürgen Honegger Department of Neurosurgery, University of Tuebingen, Tuebingen, Germany

Irena R. Hozjan Endocrine Program, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada

Khalid Hussain Great Ormond Street Hospital for Children NHS Trust, London, UK

Sue Jackson Psychology Department, University of the West of England, Bristol, UK

Channa Jayasena Reproductive Endocrinology and Andrology, Imperial College and Hammersmith Hospital, London, UK

Peggy Kalancha Clinical Resource, Pediatric Endocrine and Gynecology Clinics, Alberta Children's Hospital, Calgary, AB, Canada

Niki Karavitaki Institute of Metabolism and Systems Research, University of Birmingham and Queen Elizabeth Hospital, Birmingham, UK

Margaret F. Keil Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

Dev A. Kevat Monash Health and Western Health, Melbourne, VIC, Australia

Nicole Kirouac St. Amant Inc., Winnipeg, MB, Canada

Kathryn Evans Kreider Duke University School of Nursing and Duke University Medical Center, Durham, NC, USA

Ana Claudia Latronico Disciplina de Endocrinologia e Metabologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil, São Paulo, Brazil

Megan K. Lessig Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Karen J. P. Liebert Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA

Terri H. Lipman Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Sofia Llahana School of Health Sciences, City, University of London, London, UK

Lucy Mackillop Nuffield Department of Women's and Reproductive Health, University of Oxford, Level 6, Women's Centre, John Radcliffe Hospital, Oxford, UK

Anne Marland Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

Lee Martin Barts Health NHS Trust, The Royal London Hospital, London, UK

Raven McGlotten National Institutes of Health, Bethesda, MD, USA

Gisela Michel Department of Health Sciences and Health Policy, University of Lucerne, Luzern, Switzerland

Radu Mihai Department of Endocrine Surgery, Churchill Cancer Centre, Oxford University Hospitals Foundation Trust, Oxford, UK

Kerry-Lee Milner Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia

Irene Mitchelhil Department of Endocrinology, Sydney Children's Hospital (SCHN), Randwick, NSW, Australia

Bin Moore The Children's Hospital, Westmead, NSW, Australia

Kate Morgan Great Ormond Street Hospital for Children NHS Trust, London, UK

Amy Mundy McGuire Veterans Medical Center, Richmond, VA, USA

Pauline Musson Southampton Children's Hospital, Southampton, UK

Sebastian J.C.M.M. Neggers Department of Medicine, Section Endocrinology, Erasmus Medical Centre, Rotterdam, The Netherlands

Milla Pantovic Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center Serbia, Belgrade, Serbia

Petro Perros Newcastle upon Tyne Hospitals NHS Foundation Trust and Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

Catalina Poiana Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Vera Popovic Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center Serbia, Belgrade, Serbia

Alison Pottle Royal Brompton and Harefield NHS Foundation Trust, London, UK

Alessandro Prete Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Eileen Pyra Alberta Children's Hospital, Endocrine Clinic, Calgary, AB, Canada

Marcus Quinkler Department of Medicine for Endocrinology, Diabetes and Nutrition Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany

Richard Quinton Newcastle-upon-Tyne Hospitals Foundation NHS Trust (Royal Victoria Infirmary), Newcastle-upon-Tyne, UK

Rabia Arfan Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK

Ann Robinson Gold Coast University Hospital, Parkwood, Queensland, Australia

Katharina Roser Department of Health Sciences and Health Policy, University of Lucerne, Luzern, Switzerland

Elisabeth Rutten Department of Endocrinology, Ghent University Hospital, Ghent, Belgium

Katrin Scheinemann Division of Hematology/Oncology, University Children's Hospital Basel (UKBB), Basel, Switzerland

Wendy Schwarz Alberta Children's Hospital, Endocrine Clinic, Calgary, AB, Canada

Mark Sherlock Department of Endocrinology, Tallaght Hospital, Dublin and Trinity College, Dublin, Ireland

Soulmaz Shorakae Monash Centre for Health Research and Implementation (MCHRI), Monash University, Clayton, VIC, Australia

Klaus Sommer Concord Hospital, Sydney, NSW, Australia

Victoria J. Stokes Endocrinology and Metabolism, Oxford Radcliffe Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, UK

Mike Tadman Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Helena Teede Monash Centre for Health Research and Implementation (MCHRI), Monash University, Clayton, VIC, Australia

Raluca-Alexandra Trifanescu Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Helen E. Turner The Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford, UK

Suma Uday University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Tanya L. Urquhart Sheffield Hallam University, Sheffield, UK

Judith P. van Eck Department of Medicine, Section Endocrinology, Erasmus Medical Centre, Rotterdam, The Netherlands

Marsha M. van Oostwaard Department of Internal Medicine and Endocrinology, Veldhoven, The Netherlands

Artemis Vogazianou Department of Diabetes and Endocrinology, University College Hospital, London, UK

Jerry K. Wales Lady Cilento Children's Hospital, Brisbane, QLD, Australia

Chris White Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia

Amanda Whitehead Leeds Children's Hospital, Leeds General Infirmary, Leeds, UK

Tara Whyand NET Unit, Royal Free London NHS Foundation Trust, London, UK

Elizabeth Williamson Reproductive Medicine Unit, University College London Hospitals, London, UK

Christine Yedinak Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA

Phillip Yeoh Department of Diabetes and Endocrinology, The London Clinic, London, UK

Kathrin Zopf Department of Medicine for Endocrinology, Diabetes and Nutrition Medicine, Charité Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

Part I

Growth and Development

Kate Davies and Margaret F. Keil

The Importance of Auxology for Growth Assessment

1

Terri H. Lipman and Megan K. Lessig

Contents

1.1 **Importance of Growth Monitoring** ... 4
1.2 **Stages of Growth and Growth Rates by Age** ... 4
1.3 **Measurements Used in Evaluation of Growth** ... 5
1.3.1 Growth Parameters ... 5
1.4 **Growth Charts** ... 8
1.5 **Tools for Adult Height Prediction** ... 10
1.5.1 Bone Age X-Ray ... 10
1.5.2 Midparental Height ... 10
1.6 **Conclusions** ... 10
References ... 10

Abstract

Auxology is the basis of a proper growth evaluation. It is through the history, physical exam, and auxology that we are able to properly assess a child's growth. Auxology enables us to establish a child's growth patterns and determine if growth is indeed normal. An accurate and reliable measurement, along with appropriate and accurate charting, is critical for a proper growth evaluation.

Keywords

Auxology · Growth chart · Measurement

Abbreviations

BMI	Body mass index
CDC	Center for Disease Control
cm	Centimeter
in	Inch
kg	Kilogram
lb	Pound

T. H. Lipman (✉)
University of Pennsylvania School of Nursing, Philadelphia, PA, USA

Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: lipman@nursing.upenn.edu

M. K. Lessig
Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: LESSIGM@email.chop.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_1

LGA	Large for gestational age
m	Meter
MPH	Midparental height
MUC	Mid upper arm circumference
NHANES	National Health and Nutrition Survey
oz	Ounce
SD	Standard deviation
SGA	Small for gestational age
WHO	World Health Organization

Key Terms

- **Auxology:** Science of human growth and development.
- **Accuracy:** A measure of how close the measurement is to the actual measurement.
- **Diurnal variation:** Normal fluctuations that occur over the course of a day.
- **Frankfort plane:** Eye ear plane which is a standard horizontal cephalometric reference.
- **LGA (large for gestational age):** Refers to infants who have birthweights greater than the 90th percentile for babies of the same gestational age.
- **Measurement error:** Difference between a measured quantity (e.g., height) and its true value (e.g., actual height).
- **Reliability:** This is the quality of the measurement. It predicts how likely a repeat measurement will be the same when repeated. Expressed in a percentage.
- **SGA (small for gestational age):** Refers to infants who have birth weights below the 10th percentile for babies of the same gestational age.

Key Points

- Learners will be able to properly identify and obtain proper measurements for a growth evaluation.
- Learners will be able to accurately interpret meaning of these measurements though proper charting.

1.1 Importance of Growth Monitoring

Linear growth is the single most important indication of the health of a child (Tanner 1986). Since healthy infants and children have predictable patterns of linear growth (length/height), normal growth is used as a standard for assessing child health and well-being. Children with growth pattern deviations (e.g., unexplained short or tall stature, growth failure, unexpected growth acceleration) should be evaluated to differentiate between normal growth variants and pathologic conditions. Growth is such a sensitive indicator of health that abnormal growth may be the earliest sign of pathology (Craig et al. 2011; Haymond et al. 2013). Pathological growth may result from nutritional disease, a genetic disorder, an endocrine cause, psychosocial problems, intrauterine growth retardation, or systemic disease and/or disease progression or exacerbation. (Haymond et al. 2013; Rogol and Hayden 2014; Richmond and Rogol 2014).

1.2 Stages of Growth and Growth Rates by Age

From infancy through adolescence, both cell number and cell size increase and body composition changes significantly in terms of absolute and relative changes in the amount of lipid, protein, water, and minerals (Beker 2006). Growth during childhood is tightly regulated and depends on the proper functioning of multiple systems including maternal nutrition and uterine size; genetic growth potential inherited from parents; and nutrition. Growth also is affected by the interaction of multiple hormones, including growth hormone (GH), thyroid hormone, insulin, and sex hormones, all of which effect growth at different points in development.

Child growth generally is divided into six periods: (1) conception to birth, (2) infancy (birth to 1 year of age), (3) toddlerhood (1–3 years of age), (4) early childhood (3–6 years), (5) school-age (6–12 years), and (6) adolescence (12–18 years) (Weintraub 2011).

1.3 Measurements Used in Evaluation of Growth

1.3.1 Growth Parameters

1.3.1.1 Length or Height

Accurate measurement of linear growth is paramount when evaluating pediatric growth. (Foote et al. 2015) A multicenter study in eight cities in the United States demonstrated that only 30% of children in primary care practices were measured accurately (Lipman et al. 2004).

To ensure accuracy, children younger than 24 months must be measured supine and have growth plotted on a length growth chart. When incorrectly obtaining a standing height on a child who is younger than 24 months, the measurement must be plotted on length growth chart—as the height growth chart begins at age 2. A supine measurement is greater than a standing measurement—particularly in children under two who stand with a marked lordosis. Therefore, a child who is measured standing before age 2, and plotted on a length chart, will appear to have linear deceleration which may result in an inappropriate referral for a growth evaluation. Children 24 months and younger should be measured, on a firm platform with a yardstick attached, a fixed head plate, and a moveable footplate (e.g., recumbent measuring board) (Rosenfeld and Arnold 1993; Wales et al. 2003) (Fig. 1.1). Due to slight changes in a child's posture with each measurement it is recommended that three consecutive linear measurements be obtained on each child. All children must be measured in centimeters rounded to the closest millimeter. The average of the three measurements is considered to be closer to the true height of the child (Voss and Bailey 1994; Foote et al. 2009).

All children older than age 3 should be measured standing. Patients that are between 24 and 36 months can be measured either standing or supine. However, it is important that these children are then plotted on the correct growth chart. When obtaining height, children should be measured while standing against a wall mounted device (e.g., stadiometer) with a fixed right angle at the head (Foote et al. 2009). The child's head, shoulders, buttocks, and heels should be against the wall and feet should be forward facing and together. Gentle traction should be placed under the child's jaw to accurately position the head forward and the head plate should touch the child's scalp, potentially causing hair accessories to be removed or hair styling to be flattened (Foote et al. 2009) (Fig. 1.2). All measurements should be obtained by personnel who have proper and regular training (Foote et al. 2009). Ideally, serial measurements should be taken at the same time of day due to diurnal variation. Studies have shown that there is minimal height loss that can range from 0.47 to 2.8 cm when children are measured in the afternoon versus the morning (Foote et al. 2009).

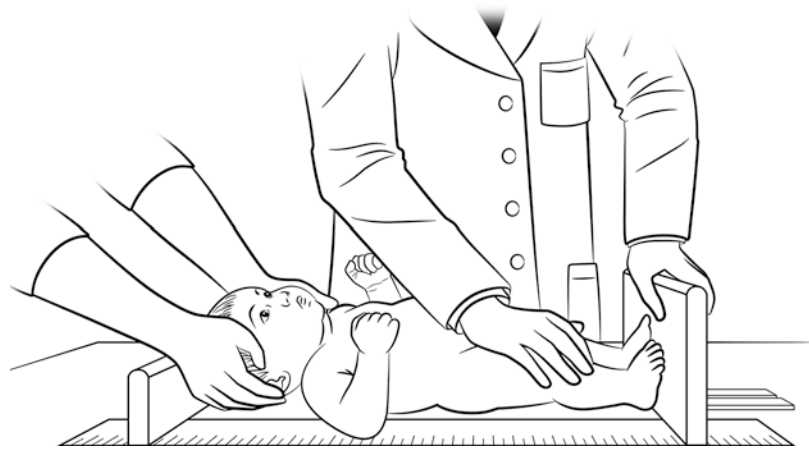


Fig. 1.1 Measurement of infant length

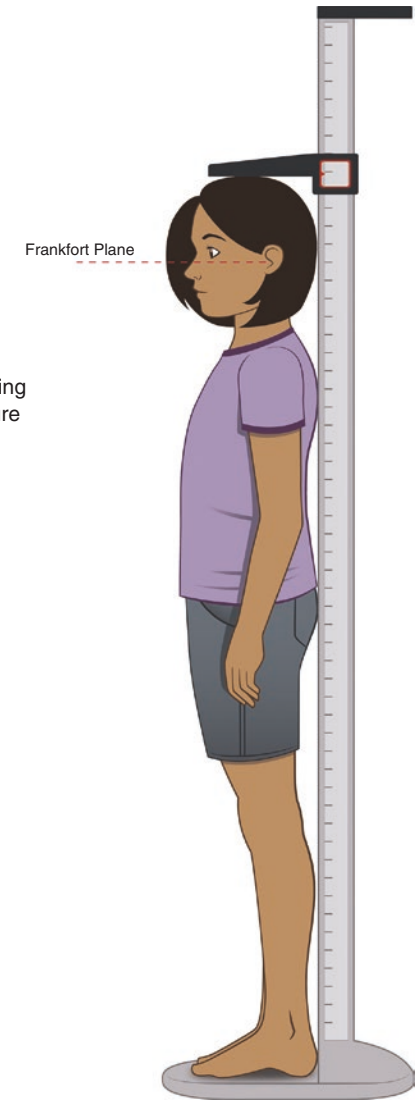


Fig. 1.2 Correct technique for measuring linear height. Reprinted with permission of Nichole Jonas, Graphic Designer. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD USA

1.3.1.2 Calibration of Measuring Devices

Instruments must be calibrated at least monthly. Calibration should be more frequent if variance is noted or if recommended by the manufacturer (Voss 2000). A rod of known and fixed height/length can be used to check the calibration of instruments (Foote et al. 2009).

1.3.1.3 Segment Measurements

If full body recumbent length is measured in a child with spasticity, contractures, and/or other musculoskeletal abnormalities, measure the side of the body that is unaffected or less affected and that can be extended the fullest. Record the side measured and the presence of spasticity, joint contractures, and/or other musculoskeletal issues. Alternative measurements, such as arm span, crown-rump length, sitting height, knee height, and other segmental lengths, may be taken to assess growth (Foote et al. 2009).

1.3.1.4 Arm Span

Arm span, after 10 years of age, approximates height in normally proportioned children. It is obtained when it is not possible to obtain a standing height or when a child appears disproportionate. Arm span is the physical measurement of the

length from one end of an individual's arms (measured at the fingertips) to the other when raised parallel to the ground at shoulder height at a 90° angle. The patient should be placed with the back to the wall and feet together. The measurer should stretch a measuring tape from the tip of the middle finger on one hand to the tip of the middle finger on the other hand. Measurements of arm span should be obtained in centimeters and rounded to the closest millimeter.

1.3.1.5 Sitting Height

Sitting height should be measured by bringing the fixed right angle of a measuring device to the most superior midline of the head while the child is sitting in an erect position on a flat surface. Arching of the back should be avoided by applying upward pressure to the mastoid processes while the child breathes deeply and holds breath during the measurement (Fredriks et al. 2005).

1.3.1.6 Head Circumference

Head circumference should be measured in all children under the age of 36 months and plotted on a head circumference growth chart to evaluate head growth over time. Two measurers are needed to obtain this measurement and it should be obtained with a tape measure that does not stretch. The tape is positioned across two land marks—the supraorbital ridge and the occiput. Measurements of head circumference should be obtained in centimeters and rounded to the closest millimeter. These measurements are so important in the early months of life, as these measurements are a reflection of intracranial volume and brain growth (Hall et al. 1989). Identification of abnormal growth patterns can lead to early diagnosis of treatable conditions, such as hydrocephalous (Nellhaus 1968).

1.3.1.7 Weight

Younger infants should be weighed nude or in a clean diaper on a calibrated beam or electronic scale. Weigh older infants in a clean, disposable diaper. Position the infant in the center of the scale tray. It is preferable to have two people when weighing an infant. One measurer weighs the infant and protects the child from falling and reads the weight as it is obtained. The other measurer notes the measurement in the infant's chart. Weigh the infant to the nearest 0.01 kilogram (kg) or 1/2 ounce (oz).

A child older than 36 months who can stand without assistance should be weighed using a calibrated beam balance or electronic scale wearing only lightweight clothes or a gown. It is important to stand on the center of the platform of the scale. Children should be weighed to the closed 0.01 kg or ½ oz (Tanski et al. 2007).

1.3.1.8 BMI

The body mass index (BMI) is utilized to quantify the amount of tissue mass in an individual and then categorize that person as underweight, normal weight, overweight, or obese. BMI is used to determine childhood overweight and obesity. Overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile for children and teens of the same age and sex. BMI can be calculated using the following formulas:

$$\text{English}: \left(\text{Weight}\left(\text{pound}\left(\text{lb}\right).\right) / \left[\text{height inch}\left(\text{in}\right) \times \text{height}\left(\text{in}\right)\right]\right) \times 703$$

$$\text{Metric}: \text{Weight}\left(\text{kg}\right) / \left[\text{height meter}\left(\text{m}\right) \times \text{height}\left(\text{m}\right)\right]$$

BMI is then plotted on growth chart for age and sex to determine BMI percentile (Tanski et al. 2007).

1.3.1.9 Waist Circumference

Waist circumference is a useful measurement when evaluating a child for obesity or overnutrition. The measurement is obtained by measuring a child between the lower ribs and the ischial ridge at the level of the umbilicus at the end of a normal expiration (Tanski et al. 2007). Skinfold measurements, described in more detail below, can also be used when evaluating a child for weight concerns, as these measurements allow the practitioner to better estimate fat distribution. These measurements become more valuable clinically when used serially to establish a potential improvement from a clinical intervention. To obtain a waist cir-

cumference, have the child hold his gown above the waist, cross his arms, and then place hands on opposite shoulders, as if he is giving himself a hug. Next, mark the measurement site. To do this, the measurer should stand on the right side of the child, palpate the hip area to locate the right ilium of the pelvis, and with a cosmetic pencil draw a horizontal line just above the uppermost lateral border of the right ilium. It is important that the measurer ensures that this line crosses the midaxillary line, which is the line that extends from the armpit to the down the side of the torso. To obtain the actual measurement, the measurer should extend the measuring tape around the waist. The measuring tape should be positioned in horizontal plane at the same level as the measurement mark and the zero end of the tape should be positioned below the part of the tape containing the measurement value. The measurement tape should fit snug but should not compress the skin. The measurement should be measured to the nearest 0.1 cm at the end of a normal expiration. The National Health and Nutrition Survey (NHANES) and the Center for Disease Control (CDC) provide a table of ranges of waist circumferences based on age, race, and weight. This enables us to better interpret and use the data (https://www.cdc.gov/nchs/data/series/sr_11/sr11_252.pdf).

1.3.1.10 Skinfolds

Skinfold thickness is another measurement that can be used in conjunction with the waist circumference when evaluating an overweight child. Although four sites can be used, including the triceps, subscapular, biceps and suprailiac, the current National Health and Nutrition Examination Survey (NHANES) anthropology protocol recommends the triceps and subscapular skinfold measurements for patients 2 months of age and older (CDC 2007). In order to accurately obtain this measurement, a skinfold caliper must be used. THE NHANES recommends the Holtain skinfold caliper. Regardless of site, the skinfold measured must contain a double thickness of skin and underlying adipose tissue. To obtain the triceps skinfold, use the thumb and index finger to grasp a fold of skin and subcutaneous tissue at the midpoint of the dorsum of the upper arm. The tips of the caliper jaws are then placed over the complete skinfold. Release the caliper handle to apply full tension while continuing to hold the skinfold in place so the measurement will register accurately. This should be held for approximately 3 seconds before the measurement is read and recorded. For the subscapular skinfold, the measurement is taken at the inferior angle of the right scapula while arms are in the relaxed position. It is important to not hold the caliper more than 3 seconds or repeat the measurement too frequently at the same spot, as the tissue can be compressed, and ultimately the measurement is falsely low (Hall et al. 1989). Just as in waist circumference, there are charts for normative values for skinfolds (CDC 2007, 2012).

https://www.cdc.gov/nchs/data/series/sr_11/sr11_252.pdf

1.3.1.11 Mid Upper Arm Circumference

A mid upper arm circumference (MUAC) is a measurement that can be utilized when evaluating a child that is undernourished. This measurement is obtained using a flexible nonstretch tape measure. The tape measure is placed mid-way between the elbow and shoulder. The World Health Organization provides standards for arm circumference (http://www.who.int/childgrowth/standards/ac_for_age/en/).

1.4 Growth Charts

To assess if a child's growth pattern is normal, it is crucial that the length or height is plotted on a growth chart with established standards, plotted correctly, and plotted on the correct growth chart. To plot an infant or child, the correct growth chart needs to be identified (i.e., length chart for <36 months and height chart for all children older than 36 months of age). To actually plot the child or infant on the growth chart, the correct age needs to be determined and located on the x-axis of the growth chart. For infants, the age should be calculated to the nearest week. For a child over 36 months of age, the age should be calculated to the nearest month. Once this age is determined,

draw a vertical line using a straight edge. Next, on the y-axis, identify the child's height or length. Similarly, a horizontal line should be drawn at this exact measurement. The height or length for age is the intersection of the two lines.

The actual growth charts utilized vary among countries. Internationally, the World Health Organization's growth charts are most frequently used. These growth charts are based on measurements of 8400 infants and children from varying countries of different ethnic backgrounds that were in environments to support optimal growth and were obtained between 1997 and 2003 as part of the Multicentre Growth Reference Study (World Health Organization). The study included two components, longitudinal data for infants to 2 years of age as well as cross-sectional data for those children 18–71 months. The similarities between the data in the six different countries made a case for pooling the data and making an international growth chart (WHO Multicentre Growth Reference Study Group 2006).

The Centers for Disease Control and Prevention's growth charts are most used by practitioners in the United States (Koren and Grimberg 2011). However, for infants to 2 years of age, the CDC recommends utilizing the WHO growth chart, as these charts better illustrate how infants should grow under optimal conditions, rather than how a select group of children in the United States did grow (CDC). The CDC growth charts are based on cross-sectional data provided by the National Center for Health Sciences (NCHS), which is now a part of the CDC (Rosenfeld and Cohen 2002). These charts are particularly helpful for plotting children between the 3rd or 5th, 10th, 25th, 50th, 75th, 90th, and 95th–97th percentile, but unfortunately are limited, as they do not define growth rates for children below the 3rd percentile or above the 97th percentile. The data from these growth charts do, however, allow standard deviation scores (SD) to be calculated. These SD scores (or Z scores) can better describe children's growth rates who are at one spectrum or the other (Rosenfeld and Cohen 2002). For example, a child can be described as having a growth rate that is −4.5 or −2.2 SD from normal. This cross-sectional data is quite helpful during infancy and childhood, but during puberty, when there is a normal variation of the timing of pubertal growth spurts, it may pose a challenge due to the fact that children begin puberty and the increase in growth velocity that accompanies puberty subsequently occurs at varying ages. For this reason, Tanner and colleagues established longitudinal growth charts that take into the consideration the varying ages for the activation of puberty (Rosenfeld and Cohen 2002).

There can be considerable difference in heights of children of the same ages. Because of this, the growth velocity, especially between the age of 2 years and prepubertal years, should be more consistent around 2–3 in per year. When a child crosses percentiles during these ages, further evaluation is warranted.

It is important that children are plotted on the correct growth chart. Because children between the ages of 2 and 3 years can be measured either supine or standing, it is crucial that the type of measurement is then plotted on the appropriate growth chart. Length is the measurement obtained when a child is laying down, as height is obtained while a child is standing. If a 26-month-old child is measured standing up and then plotted on a length growth chart, it will appear that the growth has decelerated. For this reason, the 26-month-old should be plotted on a height chart in order to obtain a true growth trend. Similarly, if this same 26-month-old was measured supine, the measurement should be plotted on a length chart.

In addition to the standard growth charts established by WHO and the CDC, there are specialized growth charts available. For instance, patients with Turner Syndrome, SGA, Russell Silver Syndrome, and Down syndrome have been established in order to better define normative values for these more specialized populations.

The American Academy of Pediatrics recommends that infants and children routinely get measured and weighed as part of their well visit care. The recommended timing of both length/height and weight is as a newborn, 3–5 days, by 1 month, 2 months, 4 months, 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 30 months, 3 years, and then annually for subsequent years at well child visits (AAP

2017). Insofar as children may only visit the primary care practitioner when ill, and that children with chronic disorders are most often seen at specialty visits, it is critical that children also be measured at sick visits and during evaluation by specialty care (Lipman et al. 2000).

1.5 Tools for Adult Height Prediction

1.5.1 Bone Age X-Ray

A bone age is a radiograph of the left wrist and hand. As a child ages, the ossification centers in the skeleton appear and progress in predictable fashion. When compared with normal age related standards, a child's bone age can be determined. Gruelich and Pyle established such standards for a child's left hand and wrist to determine a child's bone age (Brook and Dattani 2012; Greulich and Pyle 1999). A bone age is the only quantitative indicator of somatic maturation, and allows the practitioner to assess the remaining growth potential of a child (Koren and Grimberg 2011). The bone age can then be utilized to predict a child's adult height. The classic method for predicting adult height is based on Greulich and Pyle's Radiographic Atlas of Skeletal Development, and was developed by Bayley and Pinneau (Greulich and Pyle 1999). This method uses a child's bone age and height at the time bone age was completed (Rosenfeld and Cohen 2002). Using the bone age, a height prediction can be made. Since Bayley and Pinneau, there have been other variations of this height prediction formula that includes further information such as midparental height, and weight. It is important to note that all of these methods for predicting adult height are based on normal children and would not be applicable to children with growth abnormalities, such as achondroplasia.

1.5.2 Midparental Height

When completing a growth evaluation, it is important to determine one's height potential based on his family's genetics. A child's parental target height is within 2 SD (approximately ±10 cm) of the child's midparental height (MPH). MPH is a simple calculation that is gender adjusted and utilizes the heights of the child's parents. A gender adjusted midparental height for a boy can be calculated by adding the father's height and the mother's height plus 5 in (or 13 cm) divided by 2. Similarly for a girl, this can be calculated by adding the mother's height and the father's height minus 5 in (or 13 cm) divided by 2. As more practices move toward electronic health records (EHR), it is imperative that these EHR in pediatric practices support pediatric functions, such as midparental height. A study completed in 2015 that implemented a midparental height auto-calculator in electronic health records in pediatric practices proved to change PCP decision making, both prompting and preventing unnecessary endocrine referrals (Lipman et al. 2016). Therefore, when a child's current height deviates more than 2 SD from their midparental height, one must consider a pathologic process and consider referral.

1.6 Conclusions

Linear growth is the single most important indication of the health of a child (Tanner 1986).

Determination of proper linear growth requires a trained clinician to not only properly obtain the various growth measurements, but also to document and interpret these measurements correctly. It is essential for pediatric health care providers to understand basic auxology of growth. The understanding of normal growth patterns leads to better care of a child and ultimately appropriate endocrine referrals.

References

AAP. Recommendations for preventive pediatric care. bright futures: guidelines for health supervision of infants, children, and adolescents. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017.

Beker L. Principles of growth assessment. Pediatr Rev. 2006;27(5):196.

Brook CGD, Dattani MT. Handbook of clinical pediatric endocrinology. 2nd ed. West Sussex: Wiley Blackwell; 2012.

CDC. Safer healthier people. National Health and Nutrition Examination Survery. Anthropology procedures manual. 2007.

CDC. Anthropometric reference data for children and adults: United States, 2007–2010. 2012.

Craig D, Fayter D, Stirk L, Crott R. Growth monitoring for short stature: Update of a systematic review and economic model. Health Technol Assess. 2011;15(11):1–64. https://doi.org/10.3310/hta15110.

Foote J, Brady LH, Burke AL, Cook JS, Dutcher ME, Gradoville K M, et al. Evidence based clinical practice guideline on linear growth measurement of children. 2009.

Foote JM, Kirouac N, Lipman TH. PENS position statement on linear growth measurement of children. J Pediatr Nurs. 2015;30(2):425–6.

Fredriks A, van Buuren S, Dijkman-Neerinex RHM, Verloove-Vanjorick SP, Wit JM. Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders. Arch Dis Child. 2005;90(8):807–12. https://doi.org/10.1136/adc.2004.050799.

Greulich W, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. Palo Alto, CA: Stanford University Press; 1999.

Hall J, Froster-Iskenius UG, Allanson JE. Handbook of normal physical measurements. Oxford: Oxford University Press; 1989.

Haymond M, Kappelgaard A, Czernichow P, Biller BMK, Takano K, Kiess W. Early recognition of growth abnormalities permitting early intervention. Acta Paediatr. 2013;102:787–96. https://doi.org/10.1111/apa.12266.

Koren D, Grimberg A. Disorders of the endocrine system: disorders of growth. In: Florin T, Ludwig S, editors. Netter's pediatrics. Philadelphia, PA: Elsevier Saunders; 2011. p. 457–64.

Lipman TH, Hench K, Logan JD, DiFazio DA, Hale PM, Singer-Granick C. Assessment of growth by primary health care providers. J Pediatr Health Care. 2000;14:166–71. https://doi.org/10.1067/mph.2000.104538.

Lipman TH, Hench KD, Benyi T, Delaune J, Gilluly K, Johnson L, Johnson MG, McKnight-Menci H, Shorkey D, Shults J, Waite FL, Weber C. A multicentre randomized controlled trial of an intervention to improve the accuracy of linear growth assessment. Arch Dis Child. 2004;89:342–6.

Lipman TH, Cousounis P, Grundmeier RW, Massey J, Cucchiara AJ, Stallings VA, Grimberg A. Electronic health record mid-parental height auto-calculator for growth assessment in primary care. Clin Pediatr. 2016;55(12):1100–6. https://doi.org/10.1177/0009922815614352.

Nellhaus G. Head circumference from birth to eighteen years: Practical composite international and interracial graphs. Pediatrics. 1968;41:106–14.

Richmond EJ, Rogol AD. The child with tall stature and/or abnormally rapid growth. The child with tall stature and or abnormally rapid growth? [Internet]. 2014. https://www.uptodate.com/contents/search?search=the&sp=&searchType=PLAIN_TEXT&source=USER_INPUT&searchControl=TOP_PULLDOWN&searchOffset=1&autoComplete=false&language=&max=0&index=&autoCompleteTerm=

Rogol AD, Hayden GF. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr. 2014;164:S1–S14. https://doi.org/10.1016/j.jpeds.2014.02.027.

Rosenfeld R, Cohen P. Disorders of growth hormone/insulin-like growth factor secretion and action. In: Sperling M, editor. Pediatric endocrinology. Philadelphia, PA: Saunders; 2002. p. 212–7.

Rosenfeld RG, Conte F, Arnold M. Diagnosis and monitoring of growth disorders. Califon, NJ: Gardiner-Caldwell SynerMed; 1993.

Tanner J. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986;15:411–51. https://doi.org/10.1016/S0300-595X(86)80005-6.

Tanski S, Lynn C, Garfunkel LC. Assessing growth and nutrition in bright futures. Performing preventive services: A bright futures handbook; 2007. p. 51–6.

Voss L. Standardised technique for height measurement. Arch Dis Child. 2000;82(1):14–5.

Voss LD, Bailey BJR. Equipping the community to measure children's height: the reliability of portable instruments. Arch Dis Chad. 1994;70:469–71.

Wales JKH, Wit JM, Rogol AD. Pediatric endocrinology and growth. 2nd ed. Philadelphia, PA: Saunders Elsevier; 2003. p. 1–7.

Weintraub B. Growth. Pediatr Rev. 2011;32(9):404. https://doi.org/10.1542/pir.32-9-404.

WHO Multicentre Growth Reference Study Group. Assessment of difference in linear growth among populations in the WHO Multicentre Growth Reference Study. Acta Pediatr Suppl. 2006;450:56–65.

2 Short Stature, Growth Hormone Deficiency, and Primary IGF-1 Deficiency

Bin Moore, Amanda Whitehead, and Kate Davies

Contents

2.1 **Short Stature: Definition of Short Stature** 15
2.1.1 Short Stature or Slow Growth 15
2.1.2 Why Might a Child Be Short? 15
2.1.3 Why Should Short Stature Be Investigated? 17

2.2 **Growth Hormone Deficiency? (GHD)** 17

2.3 **Pathophysiology of GHD** 18
2.3.1 Signs and Symptoms 20

2.4 **Clinical Characteristics** 21
2.4.1 Clinical Investigations 21
2.4.2 Bone Age Assessment 21

2.5 **Investigations and Diagnosis** 22

2.6 **Treatment** 23
2.6.1 Compliance and Growth Hormone Device Choice 25

2.7 **Nursing Considerations** 25
2.7.1 Emotional and Social Elements 27

2.8 **Primary IGF-1 Deficiency/Growth Hormone Insensitivity Syndrome** 27

2.9 **Pathophysiology** 27

2.10 **Clinical Characteristics** 28

2.11 **Diagnosis** 29

B. Moore
The Children's Hospital, Westmead, NSW, Australia
e-mail: bin.moore@health.nsw.gov.au

A. Whitehead
Leeds Children's Hospital, Leeds General Infirmary, Leeds, UK
e-mail: Amanda.whitehead3@nhs.net

K. Davies (✉)
Department of Advanced and Integrated Practice, London South Bank University, London, UK
e-mail: kate.davies@lsbu.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_2

2.12 **Treatment** 30
2.12.1 Initiating Therapy 30
2.12.2 Maintenance of Therapy 31
2.13 **The Multidisciplinary Team (MDT)** 32
2.13.1 Psychology 32
2.13.2 School 32
2.13.3 Community/Home Support Nurses 32
2.13.4 PENS 32
2.14 **Nursing Considerations** 32
2.15 **Patient Support Groups and Useful Websites** 33
2.16 **Useful Websites** 34
2.17 **Conclusions** 35
Appendix: GH Stimulation Test Information Sheet 35
References 36

Abstract

Regular monitoring of a child's growth, using height and weight measurements, is an essential part of the nursing role, as outlined in a previous chapter.

Sequential measurements provide information regarding a child's general health and are invaluable in assessing whether there is a concern regarding their growth pattern. Body proportions, general health, and parental heights will give an indication as to whether the child fits their family pattern or has a growth problem. Review of sequential measurements can help establish whether they have familial or idiopathic short stature, or if they may have a growth and/or other hormone deficiencies.

Growth hormone deficiency (GHD) affects approximately 1:4000 children (Davies, Assessment of growth failure in children: MIMS for Nurses Pocket Guide, 2004).

It can be classified into congenital or genetically associated conditions, or may be acquired due to insult or injury. It may be an isolated deficiency or part of a more complex condition of multiple pituitary hormone deficiencies. Isolated growth hormone deficiency (GHD) is primarily a clinical diagnosis, based upon auxological features, and confirmed by biochemical testing. Once a cause for short stature or GHD is established, treatment can be initiated, which requires daily injections of growth hormone. Growth hormone insensitivity syndrome (GHIS) is rare and requires twice daily injections of insulin-like growth factor 1 (IGF-1).

A long-term commitment to treatment is required by both the patient and their family for best results. A good understanding of the condition and ongoing education is essential to ensure the maximum benefits of treatment are attained.

Growth is a slow process, and often it is easy for families to become complacent or discouraged with treatment regimes. By examining patient behaviour and any concerns they may have regarding their stature, we are in a position to encourage compliance with treatment by recognising that short-term pain (of injections) leads to long-term gain, once final height is reached.

This chapter explores the pathophysiology, clinical characteristics, investigations, and management of children with growth hormone deficiency and growth hormone insensitivity, the treatment required, and nursing considerations needed to manage these children through the ages. The role of the multidisciplinary team will be discussed with emphasis on the role of the Paediatric Endocrine Nurse Specialist in supporting these children and families through many years of treatment.

Keywords
Short stature · Growth hormone deficiency
Multiple pituitary hormone deficiencies
Hypoglycaemia · Growth hormone insensitivity syndrome · Insulin-like growth factor 1

Abbreviations

BG	Blood glucose
BSPED	British Society for Paediatric Endocrinology and Diabetes
CDGP	Constitutional delay of growth and puberty
CPG	Capillary blood glucose
ENT	Ear, nose, and throat
EU	European Union
GH	Growth hormone
GHD	Growth hormone deficiency
GHIS	Growth hormone insensitivity syndrome
GHR	Growth hormone receptor
GHRH	Growth hormone-releasing hormone
IGF-1	Insulin-like growth factor 1
IGHD	Isolated growth hormone deficiency
MDT	Multidisciplinary team
MPHD	Multiple pituitary hormone deficiencies
PENS	Paediatric Endocrine Nurse Specialist
rhGH	Recombinant human growth hormone
rhIGF-1	Recombinant insulin-like growth factor 1
SPIGFD	Severe primary IGF-1 deficiency
SS	Short stature
STAT5b	Signal transducer and activator of transcription 5b
UK	United Kingdom
USA	United States of America

Key Terms

- **Short Stature:** When a child is considered to be shorter than appropriate for their age, sex and genetic background.
- **Diagnostic pathway:** A series of growth measurements, bone age assessment, physical examination, and dynamic GH testing that leads to a diagnosis of growth hormone deficiency or (more rarely) GH insensitivity syndrome.
- **GH therapy treatment indications:** A group of diagnosis where children are eligible to be prescribed GH therapy or IGF-1 treatment.
- **GH devices:** A group of medical injection devices for administering GH injections.

Key Points

- Ongoing monitoring of a child's growth is essential if determination of a growth problem is to be identified.
- Growth hormone deficiency (GHD) is a rare condition: Growth hormone insensitivity syndrome (GHIS) is even more rare.
- Treatment involves daily growth hormone injections, twice daily for GHIS.
- The psychosocial aspects of extreme short stature need to be considered.
- Children should always be treated according to their age, not height.

2.1 Short Stature: Definition of Short Stature

Short stature is defined as a height less than −2.0 SDS or more below the mean height for children of the same chronological age and sex (below the 2.3 centile) and with a height velocity of less than −1 SDS.

2.1.1 Short Stature or Slow Growth

At any age, there can be a number of reasons for short stature (SS) or slow growth, and sometimes a cause is never found.

2.1.2 Why Might a Child Be Short?

The causes of short stature can be many and varied. They can range from *normal variants* to *pathological conditions.*

Familial short stature is one of the commonest reasons in otherwise healthy children, meaning that if the child's parents are short, then it is more likely for the child to be short also. However, this may not indicate that the family's short stature is considered to be "normal": (1) there may be an identified growth disorder that runs in the family (2) ethnic and racial growth patterns also need to be considered.

Delayed growth can present at any age and is often seen in teenagers with a delayed puberty and/or growth spurt. *Constitutional delay of growth and puberty* (CDGP) is more commonly seen in boys in comparison to girls and may require endocrine intervention. Criteria for this would include short stature, delayed secondary sexual characteristics, and psychological distress. Psychological distress should not be discounted and can cover a multitude of representations, such as depression, school refusal due to bullying, poor self-image, and the difficulty in being admitted to age appropriate past times (i.e. the cinema or fairground rides) (Raine et al. 2011).

Intrauterine growth retardation or babies born small for gestational age can cause abnormal programming of growth from birth, resulting in babies weighing at least 2 standard deviations (SD) below the mean for the infant's gestational age (Lee et al. 2003).

Genetic conditions can also cause abnormal growth patterns and a karyotype should be done in all children suspected of any genetic condition or if there is no known cause for the abnormal growth pattern. Such conditions can include Turner syndrome (see Chap. 40), Prader-Willi syndrome (see Chap. 9), Down syndrome, or Noonan syndrome (Romano et al. 2010), or if a child appears to have a skeletal dysplasia.

In children with Noonan syndrome, the diagnosis is not usually confirmed with a genetic diagnosis, but on clinical grounds, although there are some defined gene mutations. The condition is characterised by distinctive facial features, such as hypertelorism (where the distance between the inner eye corners is greater than normal), ptosis, and low set prominent ears. The child will often have a cardiac defect, usually pulmonary stenosis, and also have skeletal problems, including short stature, scoliosis, pectus excavatum, and cubitus valgus.

Other endocrine factors to consider would be gonadal problems: most boys have cryptorchidism and also delayed puberty. There may also be a degree of mild learning difficulty (Lee et al. 2003; Skuse et al. 1996).

Nutritional problems, chronic illness or unexplained (idiopathic) reasons despite investigation, are also reasons for concern in families. It is well documented in the literature that chronic illness has an impact on linear growth (Raine et al. 2011) due to the disease process, or its treatment (e.g. systemic corticosteroids)—this is commonly seen in children with asthma, inflammatory bowel disease, renal failure, and children with a decrease in calorie intake, such as cystic fibrosis, coeliac, and Crohn's disease.

2.1.2.1 Psychosocial Short Stature

Although seen less often, another cause for isolated GHD may be due to social deprivation (Skuse et al. 1996; Albanese et al. 1994). Growth failure observed without organic aetiology, but associated with behavioural disturbance and psychosocial stress, has been termed psychosocial short stature.

Children exposed to social deprivation, abuse or neglect, may exhibit signs of social withdrawal, bizarre eating habits, hyperphagia compulsive eating disorders, vomiting, and polydipsia. It has long been recognised that children who are exposed to psychological or physical abuse may present with signs similar to those of a child with isolated GHD. This condition encompasses failure to thrive, stunting secondary to chronic malnutrition, and idiopathic hypopituitarism.

Some children show spontaneous catch-up growth when removed from the source of stress without further treatment, but for some, GHD persists and there are some indications that a possible genetic predisposition may exist. These tend to resolve when the situation is addressed.

2.1.2.2 Idiopathic Short Stature

This is defined as short stature due to an unknown diagnosis or physiological variants. Height is below −2 SDS but the children have a normal birth weight and are GH sufficient. They usually have no finding of any disease when examined by a paediatric endocrinologist, and no identified

Table 2.1 Causes of short stature (Maguire et al. 2013)

Normal Variants	Maturational delay Familial short stature Idiopathic short stature	
Pathological Conditions	**Dysmorphic Syndromes** Chromosomal Other syndromes Non-specific conditions	Turner and Down Syndrome Noonan's or Russell-Silver syndrome Those associated with birth defects/mental retardation
	Intrauterine growth retardation (IUGR)	
	Skeletal disorders	Achondroplasia/hypochondroplasia Chondrodystrophies e.g. Leri-Weill SHOX Rickets/vitamin D deficiency
	Psychosocial deprivation	
	Medication side effects	Glucocorticoids High dose oestrogen or androgens Methylphenidate Dexamphetamines
	Nutritional	Insufficient caloric intake Malabsorption Chronic inflammatory bowel disease Coeliac disease
Endocrine	Isolated GHD Multiple pituitary hormone deficiencies Hypothyroidism Cushing syndrome Consequences of untreated precocious puberty Consequences of childhood cancer treatments—radiotherapy/chemotherapy	

cause for their short stature. Familial short stature and CDGP are commonly included under the umbrella of idiopathic short stature (Cohen et al. 2008).

Hormonal deficiencies, particularly those with thyroid and growth hormone deficiency can present during infancy or at any age, and can have an impact on linear growth. Ongoing monitoring of a child's growth using height and weight measurements is essential if determination of a growth problem is to be identified. Regular sequential measurements provide information regarding a child's general health and are essential in assessing a child's growth pattern (See Chap. 1) (See Table 2.1 (Maguire et al. 2013)).

2.1.3 Why Should Short Stature Be Investigated?

Although short stature is the most common reason why a child is referred to a paediatric endocrine clinic, it is essential that it should be investigated, as there is a multitude of aetiologies that can be the cause (Maghnie et al. 2017). As well as the obvious psychological impact short stature has on the child or young person, it is important to determine the reason, if any, as the pathological cause could be masking other underlying disease. Therefore, once idiopathic, clinical, or other endocrine causes for short stature have been eliminated, then the diagnosis of growth hormone deficiency needs to be considered.

2.2 Growth Hormone Deficiency? (GHD)

See Table 2.2 for causes for GHD (Davies 2004; Raine et al. 2011).

GH deficiency occurs when the pituitary gland fails to produce sufficient levels of hormones, the chemical signals that regulate important biological functions, including growth. It may be an isolated deficiency or part of a condition known as

multiple pituitary hormone deficiencies (MPHD). It is rare to have a complete lack of growth hormone but insufficient amounts will lead to poor growth.

The diagnosis of isolated growth hormone deficiency can often be missed in early childhood as the child may be healthy, apart from being smaller than other children their age. It may not be until a child starts school (or prior to starting at senior school) that the diagnosis is made as the size difference is noticeable compared to peers.

Table 2.2 Causes of growth hormone deficiency

Congenital	– Intrauterine infections – Pituitary absence or hypoplasia – Structural abnormality such as septo-optic dysplasia – GHRH deficiency
Acquired	– Central nervous system tumours such as craniopharyngiomas or optic gliomas – Cranial irradiation or total body irradiation – Chemotherapy – Langerhans cell histiocytosis – Traumatic head injury – Inflammatory disease
Transient	– Hypothyroidism – Delayed puberty – Psychosocial deprivation – Prepubertal
Genetic	– GH-1 mutations – GHRH receptor mutations – Pit-1/Prop-1 mutations

2.3 Pathophysiology of GHD

The pituitary gland includes the anterior and intermediate lobes (adenohypophysis) and a posterior lobe (neurohypophysis) and produces a number of hormones, including GH. The release of GH-releasing hormone (GHRH) from the hypothalamus stimulates the release of GH, and somatostatin inhibits the release of GH.

Growth hormone (GH) is secreted from the pituitary gland in a pulsatile fashion, with an increase in the frequency and amplitude of pulses at night (See Fig. 2.1) (Brook et al. 2008).

Its secretion is controlled by the hypothalamus through an interaction between releasing hormones (GHRH and ghrelin) and the inhibitory hormone somatostatin. It binds to receptors and activates the production of insulin-like growth factor 1 (IGF-1). This in turn mediates the various growth-promoting actions of GH.

Concentrations of IGF-1 correlate well with those of GH, but, low IGF-1 levels may also be observed in many conditions (hypothyroidism, malnutrition, poorly controlled diabetes) and chronic disease.

The vascular network of the hypothalamus and pituitary and the structure of the pituitary stalk make them susceptible to the effects of trauma or any other insult to the hypothalamic-pituitary region. Tumours in the hypothalamic-pituitary area may cause endocrine disturbance, either directly or secondary to treatment (surgery,

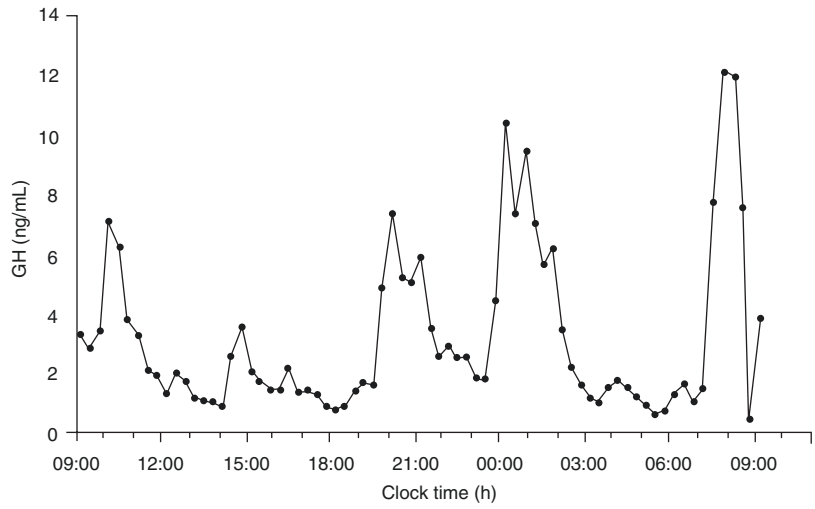


Fig. 2.1 Growth hormone pulsatile secretion (Brook et al. 2008)

radiotherapy), and early signs of endocrine dysfunction or GHD can be seen if there is growth failure.

Therefore, GHD can be classified into *congenital or genetically associated* familial conditions or may be *acquired* due to an insult or injury.

It may be an *isolated deficiency*, or part of a more complex condition of *multiple pituitary hormone deficiencies.*

The single most important clinical indicator of GHD is growth failure. Multiple pituitary deficiencies (MPHD or pan-hypopituitarism) tend to be identified earlier in life, especially if hypoglycaemia is present, but in some cases of congenital isolated GHD, the growth failure may not be established until later in childhood.

Most commonly, patients with IGHD present in late infancy or early childhood, typically with a low growth velocity and short stature. Most cases are idiopathic in origin (See case study 1 in Box 2.1).

Box 2.1 Case Study 1

A young male presents at the age of 4.3 years with a history of slow growth since the age of 2 years. Born at 42 weeks gestation at a birth weight of 3700 g, he had the cord around his neck, but no other neonatal issues. It was noted that he had had an undescended testis, and an inguinal hernia, but the rest of his development was normal.

At presentation parents' height was obtained with mum being 168.4 cm (72 centile) and dad measuring 181 cm (78th centile). This gave him a mid-parental height (MPH) of 181.2 cm (approximately 73rd centile).

On examination, it was noted that he was a small, healthy, non-dysmorphic, proportionate male with a height of 97.0 cm (fourth percentile) and a weight of 14.6 kg (10th percentile) (See Fig. 2.2). He had 2 ml testes, now descended, and normal genitalia. Neurological and thyroid examination were normal, and no other body system abnormalities were detected on examination.

Baseline investigations included FBC, ESR, biochemistry—all normal, a coeliac screen which was negative, TSH 2.3 mIU/l (0.4–5), FT4: 14.6 pmol/l (10–20), IGF-1: 1.5 nmol/l (6–25), prolactin normal. Parents were provided with information regarding GH stimulation tests and had the opportunity to ask questions before proceeding with the glucagon/arginine stimulation test. GH peaks to both stimulation tests showed a blunted response of 3.9 and 4.1 mIU/l (N > 20). An appropriate cortisol peak of 621 nmol/l (>500) was obtained. Bone age was delayed, being 3.5 years at a chronological age of 4.5 years.

A diagnosis of isolated GH deficiency was declared and treatment with GH commenced at a dose of 4.5–6 mg/m^2/week. This dose was reviewed 6 monthly (as per Australian guidelines) and adjusted according to increasing body surface area (BSA).

Long-term progress has shown that no other pituitary deficiencies have evolved. At age 12.9 years, he had 4 ml testes and by 14.1 years has 8 ml testes, PH3, G3, and will continue on GH therapy until he reaches a bone age of 15.5 years or his growth has slowed down to be <2 cms/year.

This will indicate that he has completed approximately 97% of his childhood growth.

Key points to consider when assessing a child with short stature include considering a child's height and EMH in the family context. Any child tracking below, or with EMH below target height range, warrants investigation. Evaluating growth velocity is a valuable indicator and doesn't even require plotting on a growth velocity chart, as a falling height percentile or SD is the same.

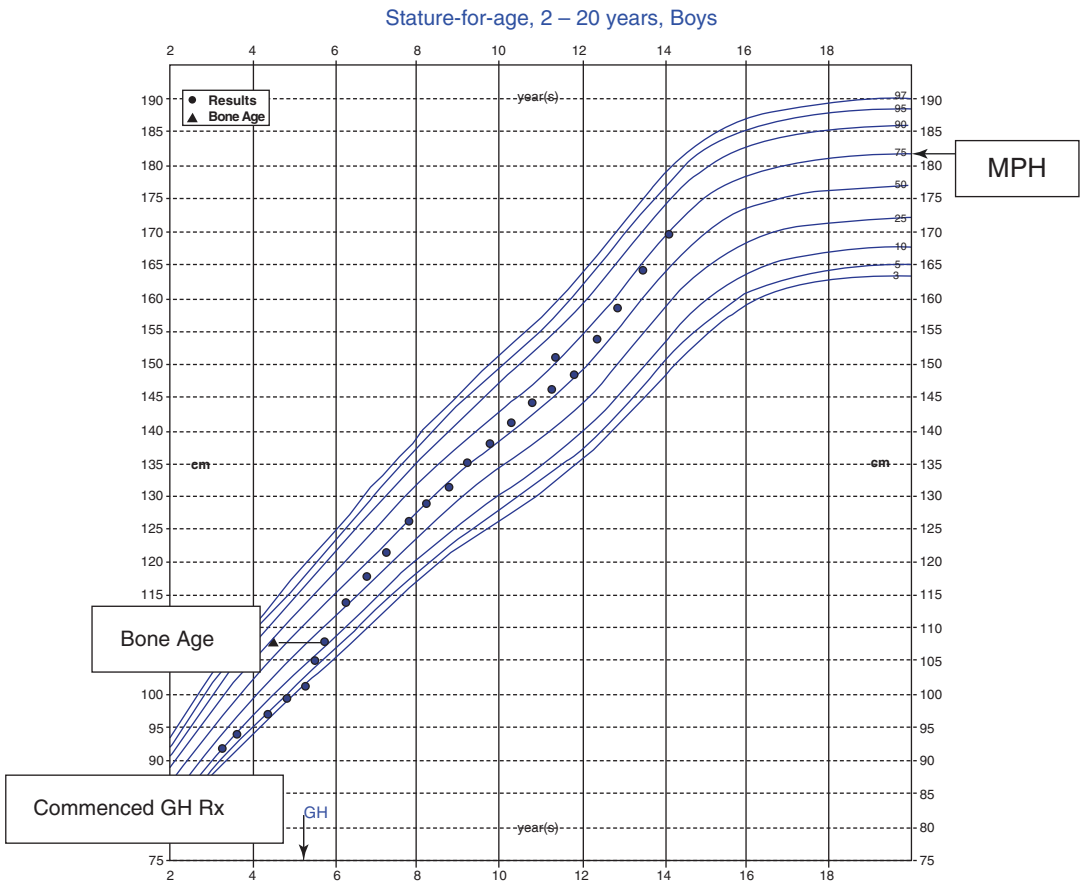


Fig. 2.2 Case study growth chart

Untreated, children with GHD will be short and have delayed puberty, decreased pubertal growth spurt, and a final height standard deviation score (SDS) of −4 to −6, much lower than the general population (Ranke et al. 1997; Wit et al. 1996)

2.3.1 Signs and Symptoms

Hypopituitarism or multiple pituitary insufficiencies can cause a range of symptoms. Abnormalities in the development of the hypothalamus/pituitary access mean that presentation in the neonatal or early infancy period is common.

- Hypoglycaemia
- Prolonged jaundice
- Micro phallus (in boys)
- Impaired vision
- Facial or midline defects such as cleft lip or palate or single central incisor
- Defects in genes associated with the development and function of the pituitary gland can also lead to a diagnosis of isolated GHD (Alatzoglou et al. 2014).

These signs are more common in children with multiple pituitary hormone deficiencies diagnosed in the neonatal period, but may be present as isolated GHD with other deficiencies evolving over time. Recent data suggest that childhood IGHD may have a wider impact on the health and neurodevelopment of children, but it is yet unknown to what extent treatment with recombinant human growth hormone can reverse this effect (Rosenfeld et al. 1995)

Acquired GHD can be due to a variety of causes including tumours in the hypothalamic-pituitary region. These may be benign or malig-

nant, cystic or solid, and may present as a craniopharyngioma, germinoma, or teratoma. GHD may arise due to the tumour, as a result of surgery, or, more commonly, after radiotherapy. If cranial irradiation of the pituitary gland has been indicated for a condition such as leukaemia, medulloblastoma, glioma/astrocytoma, or rhabdomyosarcoma, this can also result in impaired function of growth hormone and other hormones further along in life (See Chaps. 58 and 59).

Whatever the cause of GHD, abnormalities in the growth pattern should be investigated.

2.4 Clinical Characteristics

Children with GHD are small compared to other children of their age but they will have normal proportions. In the first year of life, growth is more dependent on nutrition than on growth hormone secretion, and may be normal, even if growth hormone deficiency is present from birth.

They often have a characteristic facial appearance including, mid-facial hypoplasia, classic "cherubic" appearance, with chubby cheeks and increased truncal adiposity with dimpling of fat. Delayed dentition, single central incisor, and frontal bossing may also be present. Both puberty and bone age may be delayed.

It is worth noting that the condition is highly variable in its clinical presentation so evaluation in reference to other family members, including siblings should also be included.

In acquired GHD, there can be a variety of presentations. Growth failure or a decline in height velocity is sometimes only noticed when shoe or clothing size does not increase over a period of time. Increasing lethargy, vomiting, visual impairment, or photophobia may all be reasons for initial presentation. Continuing visual impairment (of varying severity) can often be seen in patients after the removal of a suprasellar tumour (e.g. craniopharyngioma or optic glioma).

Any child with a history of cranial irradiation, with decelerating growth, even if the height is within the normal range, should be evaluated (Urquhart and Collin 2016) (See Chap. 58).

2.4.1 Clinical Investigations

Any child with severe short stature (3 standard deviation scores [SDS] below mean for population) should be referred to an endocrinologist for evaluation to establish a cause.

The diagnosis of GHD is a stepped process. It is based on a combination of auxological data, the clinical phenotype, dynamic GH testing (See Chap. 64), insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP3) levels, bone age X-ray, and other radiological findings including an MRI of the hypothalamic-pituitary area.

2.4.2 Bone Age Assessment

The bone age is assessed by taking an X-ray of the non-dominant hand and wrist. Comparison is made to a photographic standardised set of X-rays for a child of the same age using the Greulich and Pyle, or Tanner-Whitehouse methods.

This provides an estimation of the skeletal maturation of the bones (Greulich and Pyle 1959; Tanner et al. 2001; Satoh 2015).

A bone age assessment (See Fig. 2.3) can help determine the amount of growth left and give an estimation of what final height will be achieved.

In girls, the epiphyses usually close around the age of 13.5 years, whereas in boys their epiphyses close around the age of 15.5 years. The further behind the bone age is delayed behind the chronological age, the longer the growing period. As long as the growth plates remain open, there is potential for continued growth. Once the bones reach the ages noted above, most of a child's growth is complete.

A thorough medical history should be taken and physical examination done to assess if there is any other cause for growth failure. See Table 2.3 for the diagnostic approach to short stature (Savage et al. 2016)

Fig. 2.3 Bone age assessment—Photo from authors collection

Table 2.3 Diagnostic approach to short stature

Take a full history:
• Birth history including weight length gestation
• Heights of parents, siblings, and any other relevant family members
• Parental consanguinity?
• Origin of short stature, nutrition, psychological disturbance
• Appetite, gastrointestinal symptoms, stool frequency/features, abdominal pain, mouth ulcers
• Hypoglycaemia, chronic infections
• Respiratory symptoms, urological symptoms
• Motor skills, intellectual development, milestones, school performance, learning difficulties
• Headache, visual disturbances
Examine the patient standing in front of you:
• Look directly face to face, and look at the head, limbs, hands, fingers, and toes.
• Full systemic examination: Neurological, musculoskeletal, abdominal, respiratory, cardiac, dermatology, and pubertal examination
• Exclude any dysmorphic features Dysmorphic features are a difference of body structure. They can be an isolated finding in an otherwise normal individual or can be related to a congenital disorder, genetic syndrome, or birth defect
• General baseline investigations
• Endocrine-specific investigations

Family history should be taken to determine if there is any heritable condition or any other systemic concern. Parental heights should be plotted on the growth chart to determine the mid-parental height (MPH) (or target height) and establish if the child's growth is out of keeping with other family member's stature.

Pituitary hormone deficiencies can evolve with time, so regular monitoring of clinical as well as biochemical investigations is considered good practice.

Height more than 2 SDs below the mean and a growth velocity over 1 year of more than 1 SDs below the mean should be investigated.

A decreasing height velocity in the absence of short stature should also be evaluated if:

- There is a decrease in the height SDS of more than 0.5 SDS over 1 year in children over 2 years,
- There is a decrease in height velocity of more than 1 SDS over the year in children aged over 2 years,
- The height SDS is more than 1.5 SDS below target height SDS,

The height velocity is >2 SDS below the mean over 1 year or more than 1.5 SDS over a 2-year period. All of these variations should be evaluated when assessing a child's growth pattern (Growth Hormone Research Society 2000; Cook et al. 2009).

2.5 Investigations and Diagnosis

Baseline investigations will help determine the likelihood of GHD which can effectively be excluded in children with a normal bone age and height velocity.

Baseline investigations should include (Cook et al. 2009):

- A full blood count
- Blood chemistry, including thyroid stimulating hormone and free thyroxine level
- Coeliac screen and IgA (Immunoglobulin A) levels
- 25-OH Vitamin D level
- Karyotype in all girls and boys with dysmorphism
- IGF-1

More detailed laboratory evaluation for causes of growth failure may be carried out by a specialist once the initial evaluation is complete. IGF binding protein, hormones to evaluate puberty including luteinising hormone, follicle stimulating hormone, oestradiol, testosterone, and prolactin levels if concerned about pubertal delay should all be measured. Molecular testing or comparative genomic microarray for various genetic conditions may be considered.

GH stimulation testing should be considered if the clinical criteria is insufficient to make the diagnosis of GHD (Chesover and Dattani 2016). Those with a known pituitary abnormality or deficiency of at least one other pituitary hormone, and with obvious growth failure, may not need testing. If there is enough information to determine the cause of growth failure, provocative testing for GHD may not be required (Grimberg et al. 2016).

The most common test to assess GHD is a dynamic GH stimulation test (See Chap. 15). As GH is produced in a pulsatile fashion, it is able to be stimulated to assess pituitary function. A variety of tests are available using pharmacological stimuli and two stimuli are best used to capture the peak levels of GH produced. Provocative agents such as insulin, glucagon, arginine, and clonidine can all be used to assess GH levels. Various cut-off levels have been used, but GHD is generally defined as a value of <10 μg/L (or 3 ng/mL) on two occasions (Butler and Kirk 2011).

Testing should be done after an overnight fast, and in older children (girls>10 years and boys >11 years) is often done after priming with sex steroids for a few days prior to testing. This is done to lessen the chance of a false diagnosis, but there is still some discussion as to whether this is necessary and so is not mandatory (Chesover and Dattani 2016; Rosenbloom 2011).

Testing should be in a recognised testing facility by trained nurses due to the risk of hypoglycaemia associated with many of the stimulation tests.

Finally, an MRI of the brain/pituitary gland will establish if there are any midline defects, structural abnormalities, or evidence of a tumour or cystic mass.

2.6 Treatment

Children with GHD are unlikely to reach their adult potential without treatment. Recombinant human growth hormone is the only treatment that can improve final height but can only influence the active growth phase whilst the bone epiphyses remain open.

In many countries, GH treatment is commonly approved for those not only with GHD but other conditions of short stature as well, such as:

- TS—Turner syndrome
- SGA—Small for gestational age
- PWS—Prader-Willi syndrome
- CRI—Chronic renal insufficiency
- SHOX—Short stature homeobox-containing gene deficiency disorder
- AGHD—Adult growth hormone deficiency
- ISS—Idiopathic short stature (Raine et al. 2011)

More recently, GH has become available in some countries for use in adults with established GHD.

Treatment involves daily subcutaneous injections of recombinant human growth hormone (rhGH), also known as somatropin. Prior to 1985 hGH (human growth hormone) was only used in those with severe GHD, but was withdrawn when concerns regarding its association with Creutzfeldt-Jakob disease (CJD) arose (Buchanan et al. 1991; Boyd et al. 2010).

Treatment today uses a variety of recombinant human growth hormone products. Some products are a liquid formulation, whilst others require

powder and diluent to be mixed to maintain product stability. Doses are based on either patient's weight or body surface area depending on which country they reside in, and the clinical indication they are being prescribed for. There are a number of different devices designed for giving injections, with some that can actually hide the needle tip, but as the needles used are small, they are in most cases well tolerated. Each company has a device designed specifically for their product, so they are not interchangeable.

Subcutaneous injections are given daily usually in the evening prior to bed as GH is released in pulses during the night (See Fig. 2.1) and at a similar time each day where possible. Arms, legs, abdomen, and buttocks are used as injection sites, and the 4–6 mm needles used can usually be accommodated in most of these spots.

Current practice is to use each area for approximately one week, rotating on a regular cycle.

Families, parents, and older children are instructed on injection technique at the time GH injections are commenced, but regular review of technique should be encouraged to uncover any problems parents may be having that may impact on compliance.

Adolescents giving their own injections should *always* be supervised by a parent.

Assessment of the families understanding of *why* the treatment is being given should be part of the ongoing review at appointments.

It is sometimes worthwhile reminding families that if injections are regularly missed the benefits of treatment may be compromised.

Side effects with rhGH are uncommon but should be clearly explained at the time of commencement of injections. Usually, rhGH is safe and well tolerated (Quigley et al. 2005; Quigley et al. 2017; Carel et al. 2012). Minor adverse effects such as bruising at injection sites usually diminish once treatment is established and parents become more confident at injecting their child.

Occasionally, in the early stages of treatment some children may retain excess fluid and salt, causing headaches with some blurring of vision (benign intracranial hypertension). It is not commonly seen and usually disappears when the GH is ceased for a few days, and reintroduced at a lower dose, gradually increasing over time. If it does occur, referral to an ophthalmologist should be made for ongoing assessment in the first few months of treatment.

Slipped capital femoral epiphysis (SCFE) has also been reported to be slightly more common in children receiving GH treatment (Rappaport and Fife 1985). This may cause pain in the hip and knee joints and appears to mostly occur in those with other risk factors such as obesity, trauma, other endocrine conditions, or those who have had previous radiation therapy, or very rapid growth.

Scoliosis has also been observed in some children treated (Clayton and Cowell 2000), but is more the result of an increase in height velocity unmasking the tendency to a curved spine, than the GH itself.

Depending on family history, there may be an increased risk of developing type 2 diabetes mellitus, but as the doses of GH prescribed are mostly physiological the risk is relatively low.

Markedly elevated IGF-1 concentrations have been associated with colon, breast, and prostatic cancer: However, there is no evidence to suggest an increased risk of malignancies using the current dosage recommendations for rhGH. In general, GH should not be given with an active malignant condition. The absence of tumour growth or recurrence should be documented for 12 months before commencing treatment. The long-term safety of GH treatment is, however, uncertain.

The most common questions asked by patients and parents alike when starting treatment is, how much will I grow, and how long will I need to take GH for?

Rapid short-term growth is usually followed by normalisation of long-term growth.

Treatment should be continued until final height or epiphyseal closure is achieved (Clayton

et al. 2005). For girls this is when the bone age is around 13.5 years and for boys around 15.5 years.

A good predictor of response to treatment is the height gain attained in the first year of treatment. Other factors that can impact on the response to treatment include age and height at the start of treatment, duration of treatment, and, in patients with isolated GHD, the pre-pubertal growth available when receiving treatment.

Long-term monitoring of treatment is essential and should include:

- Regular measurements, plotted on an age- and sex-appropriate growth chart.

On average, puberty contributes 20–25 cm of height in females and 25–30 cm in males, and this is dependent on adequate GH and insulin-like growth factor 1 (IGF-1) concentrations.

- Frequency of monitoring patients with an acquired cause of GHD (e.g. tumours, radiation) will depend on the individual condition.
- All patients on GH should continue receiving treatment until final height or epiphyseal closure is achieved.
- Prior to transition to an adult endocrinologist, reassessment of IGF-1 levels and possibly of GH levels should be undertaken.
- If after ceasing treatment the IGF-1 level remains in the normal range, GH stimulation testing should be undertaken to establish if the young persons' GH levels have normalised or remain low.

This will assist in determining whether after completion of growth and puberty patients with idiopathic isolated GHD are at risk of ongoing GHD and will ascertain the need for adult GH replacement (See Chap. 6).

In many patients (25–75%), when testing is repeated, the GH response is in the normal range (Cook et al. 2009). The reason for this reversal of GHD is unclear. Pituitary hormone deficiencies can evolve with time, so regular monitoring, both clinically and with regular biochemical investigations, is recommended.

2.6.1 Compliance and Growth Hormone Device Choice

Growth hormone treatment involves a daily injection. For some families, the thought of injecting their child on a daily basis is confronting, and the emotional factors and anxiety around administration can overwhelm them (or their child). There are a number of devices for giving GH available but nearly all require a needle to be inserted into the subcutaneous fat. Many devices can hide the site of the actual needle if required, and for most children the procedure becomes easier over time. In some countries, allowing families some choice in the decision-making around which device to use, compliance can be shown to be improved. Compliance often waivers especially in the adolescent years, as growth is slow, an immediate response cannot be seen, and the idea of having to remember to give an injection each night does not always sit easily in an adolescents life! Feedback regarding the devices assists in compliance as the family or young person feels they have contributed to their treatment in some way. This along with ongoing positive support from nursing staff assists in improving the patient experience (Gau and Takasawa 2017).

2.7 Nursing Considerations

When evaluating a child with short stature, it is important to think about the following questions. Although the causes and clinical presentation of short stature vary by age group, the same questions are relevant for children of any age:

- How short is the child?
- Is the child's height velocity (HV) impaired?
- Are they in keeping with their family pattern?
- What is the child's likely adult height?

By using these questions as a baseline for assessment, the health care professional can

determine if there is a growth problem and evaluate how concerned are they about their height.

When assessing a child's growth, there are four main aims:

- To determine if the growth pattern is normal or as expected for the child's family background.
- To attempt to predict future growth and final adult height.
- To determine if there are any modifiable medical or other issues that will improve growth.
- To consider if there are any specific treatments that are possible and appropriate to improve growth.

The most important assessment of growth is reliable, reproducible, and regular measurements, done at 3–6 monthly intervals, and plotted on an appropriate growth chart.

Children under the age of 2 years should have their length measured, and between the ages of 2–3 years all children should be assessed in a lying and standing position, as this is the age that they are usually least cooperative.

This will provide the most accurate assessment, as long as that the same piece of equipment is used, it is calibrated regularly, the same the observer takes the measurement, and the growth is plotted on the same growth percentile chart, and once plotted the growth velocity can be calculated.

Growth velocity is one of the most useful parameters when assessing growth as it determines the change in height over time. It should be calculated over *at least* a 6-month period as any less can lead to inaccuracy or misleading results. It is calculated as the difference in height on two different occasions annualised over 1 year and is age and pubertal status dependent.

Height that plots along a given percentile on the growth chart reflects normal growth velocity. Crossing percentiles or a decreasing velocity reflects poor growth velocity.

Plotting the growth is helpful in establishing if a child is just short (compared to his peers) but growing at a consistent rate, or if are they growing at a slower rate than their peers over time. Any child with a growth velocity under the third centile at any time should have further evaluation no matter where they sit on the growth chart.

One of the most important things to remember however is that all children should be treated according to their **AGE** and **NOT** their **SIZE**. It is very common when assessing a child who may look younger and be much smaller than their peers, to speak down to them, or treat them inappropriately for their age, and there is nothing worse for a child. Often on further questioning, or once a relationship begins to develop, you may be able to determine if they are being bullied at school or in the playground, and if this is of concern to them. The issues that children with endocrine conditions may encounter, particularly if they do not fit into the social and emotional norms of their peers, can add to the distress of "being different" and isolate them even further. Children who are shorter than most of their peers may find themselves being excluded from sporting teams or even just play dates as younger children. Some may find that they don't have the energy to keep up with their friends particularly if they are severely growth hormone deficient, making interaction even more difficult. Online or cyber bullying and social media has created a whole new set of issues for those with body image and self-esteem concerns (Cohen and Dwyer 2018). A full social history should always be undertaken in all patients, particularly those who present with poor weight gain and failure to thrive.

If growth hormone production is being assessed using a stimulation test, it is important that both the family and the child have an understanding of what the testing involves and what to expect both during and after the evaluation.

Information sheets regarding the tests should be provided (see Appendix), and the opportunity to ask questions prior to testing, must be considered.

The goal of growth hormone (GH) treatment should be to restore hormone levels as close to healthy levels as possible and allow the child to reach their target adult height potential.

During the initial assessment and monitoring phase, it is important to establish a good relationship with the child and family. This allows time

for consideration of the likelihood of managing daily GH injections when started on treatment, ongoing compliance with treatment, and also gives the opportunity to evaluate if height is of concern to them as an individual, or if it is more of a parental concern.

Results of any tests done should be clearly explained in language that the family will understand to ensure they have a good comprehension of why GH is required.

Once treatment is approved, the family and child should be educated in the day-to-day management of injections, the storage of medication and general information about expectations of treatment, and the importance of compliance.

2.7.1 Emotional and Social Elements

It is important to provide emotional support for the child with GH deficiency and to emphasise the child's many good and valuable characteristics, so that the child's stature does not limit his opportunities. Society (unfortunately) still places an emphasis on height, and children who are short for their age can initially have problems because friends and teachers treat them as though they are *younger* rather than just *smaller*. Parental expectations are often decreased as they feel their child is unable to do the same tasks as other children their age, and in turn children may then not act their age because it is not expected of them. Schools are sometimes unaware of the problems that children who are very small for their age have to deal with such as practical difficulties of being unable to reach a peg or desk or sit on the toilet. Teasing and/or being called names such as "shorty" or "shrimp" or being carried around the playground because they are "cute and doll like" is not helpful in allowing the child to develop to their full potential. Sometimes a frank and open discussion with teachers and classmates may help alleviate some of the problems. Positive role modelling by parents is essential and as with all parenting issues, there must be consistency. Parents must agree on a unified approach to handling any problems. Discussing and role playing hypothetical situations and encouraging practice of these role plays can help children anticipate situations that may develop.

Comments when out shopping or on the sporting field cannot be monitored, but the child can work to control their responses. A "toolkit" of responses is one of the best support mechanisms that can be given to parents and children, and the nurse can suggest that families work with their child to practise responses. The best responses are ones that are polite yet assertive, never rude, easy to remember (even in situations of high anxiety), and comfortable for a child to use. Work with the child and family to come up with a short list of responses that he or she can use in social situations when comments are made about stature.

When commencing GH treatment, it is important that the child and family have realistic expectations. It is important to emphasise that growth takes time and that they are not going to grow overnight. Ongoing reassurance may be needed when the child is not growing as expected. Once there has been an initial response to treatment the possible benefit may include a general increased self-esteem and overall happiness that is gained with the increase in height.

2.8 Primary IGF-1 Deficiency/ Growth Hormone Insensitivity Syndrome

Growth hormone insensitivity syndrome (GHIS) is a rare condition (<1:100,000) whereby the action of growth hormone (GH) is either absent or reduced resulting in extreme short stature (Backeljauw and Underwood 2001).

2.9 Pathophysiology

Childhood growth is regulated via the GH/insulin-like growth factor 1 (IGF-1) axis. Primary insulin-like growth factor 1 (IGF-1) deficiency is characterised by an inadequate production of IGF-1, despite sufficient secretion of growth hormone (Mushtaq 2015). Pituitary-

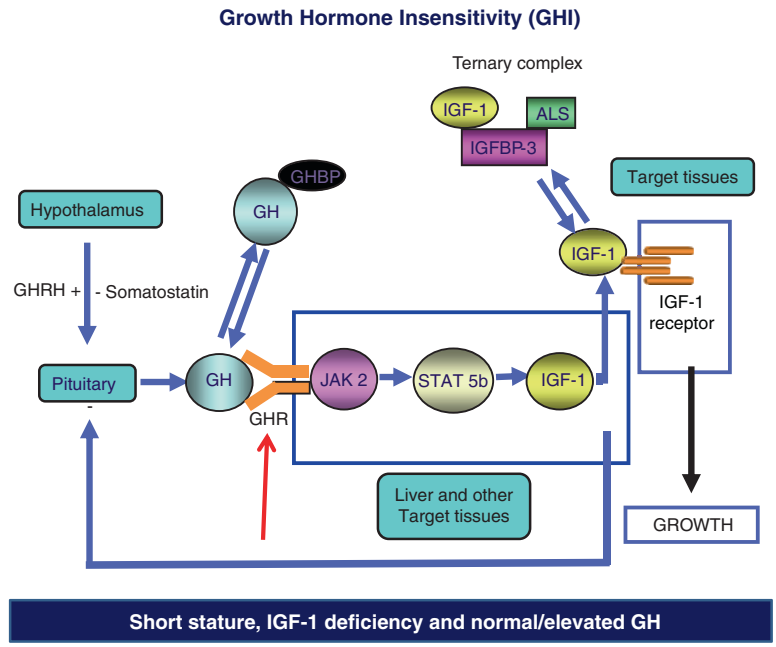


Fig. 2.4 GH-IGF-1 Axis. Courtesy of Professor Martin Savage, Dr. Helen Storr and Dr. Sumana Chatterjee, 2018

derived GH stimulates both the liver production of IGF-1 and augments the actions of locally produced IGF-1, which result in longitudinal growth. Binding of the GH to its receptor results in activation of downstream signalling molecules which ultimately lead to IGF-1 production. Thus, abnormalities along this signalling cascade can cause GH insensitivity. These may include defects in the GH receptor which inhibit GH binding, post-receptor signalling defects such as signal transducer activator of transcription (STAT)-5b or primary defects of IGF-1 synthesis (See Fig. 2.4).

2.10 Clinical Characteristics

The clinical phenotype of primary GH insensitivity in its classic form is identical to severe GH deficiency and was first described by Laron and colleagues in 1966 (Laron 1966). The clinical characteristics include severe post-natal growth failure, mid-facial hypoplasia, adiposity, and hypoglycaemia. It is therefore important to exclude growth hormone deficiency as a cause for these features. Other features associated with the condition may include reduced muscle strength, dental abnormalities including delayed eruption of teeth and reduced number of teeth, distinctive facial features (protruding forehead, a sunken bridge of the nose, and blue sclera) and thin, fragile hair; however, it should be noted that the phenotype can vary even within the same family. Figures 2.5 and 2.6 demonstrate a child with Laron syndrome.

Abnormalities further downstream the GH/IGF-1 axis such as with (STAT)-5b signalling are associated with immune deficiency, whereas IGF-1 mutations have severe intrauterine growth retardation and intellectual delay. The biochemistry shows elevated serum concentrations of GH with low IGF-1 levels due to an abnormal GH receptor.

Recombinant IGF-1 (rhIGF-1) is licenced for use in the United Kingdom (UK), the European Union (EU), the United States (USA), and Canada for children with severe primary IGF-1 deficiency (SPIGFD). This is defined in children as a height less than −3 SDS, low IGF-1 levels (<2.5th percentile for age and gender), and normal GH levels. Secondary forms of IGF-1 deficiency such as malnutrition, hypothyroidism, and use of pharmacological doses of glucocorticoids need to be excluded

Fig. 2.5 Photo of child with Laron Syndrome (front view); note the eyes and orbits characteristic in patients with Laron Syndrome. (Written consent was obtained from the child's parents to use her photo in the book)

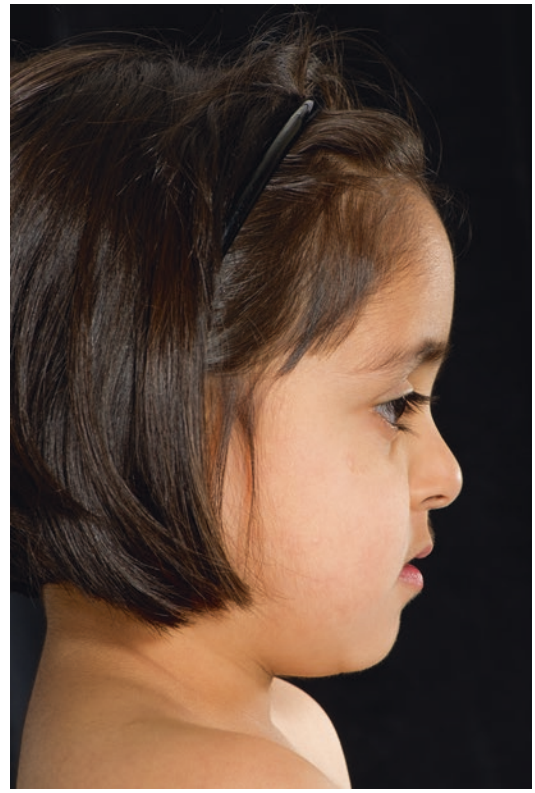


Fig. 2.6 Photo of child with Laron Syndrome (side view); note the eyes and orbits characteristic in patients with Laron Syndrome. (Written consent was obtained from the child's parents to use her photo in the book)

(Grimberg et al. 2016; Mushtaq 2015). It should be borne in mind that although the term GHIS and SPIGFD may be used interchangeably they are distinct entities as the classical Laron's phenotype is not required for the licenced indications.

2.11 Diagnosis

The UK has guidelines formulated by an IGF-1 user's group and endorsed by the British Society for Paediatric Endocrinology and Diabetes (Mushtaq 2015). These state that diagnosis of primary IGF-1 deficiency does not necessarily require either a GH stimulation test or IGF-1 generation test when the presentation is classical. It is recommended that these children have genetic analysis of the growth hormone receptor (GHR) for understanding the condition and to confirm the clinical diagnosis. Those children who do not have the classical features but have abnormal auxology and features of growth failure may need detailed evaluation which should include assessment of the GH-IGF-1 axis. This evaluation should include a GH stimulation test (See Chap. 15).

The guidelines also state that whilst an IGF-1 generation test may also be included in the evaluation, the clinical value of the test in reaching a diagnosis of SPIGFD is unclear. The protocol for the IGF-1 generation test is illustrated in Box 2.2 below (Butler and Kirk 2011) (See Chap. 15).

It is worth noting that some children with classical SPIGFD may present late as the extreme short stature may have previously been diagnosed as failure to thrive or familial short stature.

Box 2.2 Protocol for the IGF-1 Generation Test

Dose:

– 0.033 mg/kg growth hormone daily × 4

Procedure:

– Day 1—Blood sample for IGF-1 (± IGFBP-3) before first injection of GH
  • GH injection
– Day 2—GH injection
– Day 3—GH injection
– Day 4—GH injection
– Day 5—Blood sample for IGF-1 (± IGFBP-3) 12 h after the fourth injection of GH

Table 2.4 Baseline assessment (Storr 2015)

Baseline Assessment	Standard	Optional
Enter patient on registry	+	
Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils	+	
Echocardiography	+	
Bone age	+	
Facial photograph (frontal and lateral)	+	
Dietary advice	+	
First injection as an in-patient		+
Fasting cholesterol (HDL, LDL, and total triglycerides)		+
DXA—whole body and lumbar spine		+
Arrange homecare and nurse support		+

BSPED Guidelines (2015) (Cohen et al. 2008).

2.12 Treatment

Once a diagnosis has been determined the treatment options can then be discussed with the family. The current recommended treatment for SPIGFD in the EU, the UK, the USA and Canada is twice daily injections with recombinant IGF-1 (rhIGF-1) therapy (Grimberg et al. 2016; Mushtaq 2015), and the treatment objective is the long-term improvement of adult height.

2.12.1 Initiating Therapy

Both the UK and US and Canada guidelines advocate these patients be managed by a paediatric endocrinologist with experience of managing children with complex growth disorders. Table 2.4 details baseline procedures and checks both standard and optional that should be considered prior to commencing treatment as advised by the IGF-1 users group in the UK.

The UK guidelines recommend a short admission may be needed, particularly in younger children due to the potential risk of hypoglycaemia following the injection. This may not always be possible but the Paediatric Endocrine Nurse Specialist (PENS) plays a vital role in supporting the family at this time to ensure safe initiation of therapy whether in the hospital setting or at home.

The starting dose of rhIGF-1 as recommended by the manufacturer should be 40 μg/kg (micrograms per kilogram) twice daily. The dose should then be increased at regular intervals with the aim of reaching a maintenance dose of 120 μg/kg twice daily approximately three months after starting treatment (Pharmaceuticals I 2007).

As with GH injections, the family are advised to rotate the injection sites with each injection to prevent lipohypotrophy.

One of the most common side effects of the medication is hypoglycaemia. It is therefore advised that the injection should be given after a meal or snack and if the child has not eaten then the dose should be omitted. An important part of the PENS role is to ensure the family are educated to recognise the signs, symptoms, and treatment of hypoglycaemia.

It is also recommended that with initiation of treatment the capillary blood glucose (CBG) should be measured both prior to the injection and post injection. Subsequently, the family is advised to check pre- and post-dose CBG following any dose increase for at least two days and inform the PENS of any problems. Hypoglycaemia is defined in the UK guidelines as a CBG of less than 3.5 mmol/L (Butler and Kirk 2011).

All patients in the UK are asked to give consent for a web-based surveillance registry.

2.12.2 Maintenance of Therapy

Once the young person has been established on treatment it is important they are monitored at regular intervals. Clinic visits are recommended 3–4 monthly and every patient should have an annual review. Table 2.5 details procedures and checks both standard and optional that should be considered during treatment as advised by the IGF-1 users group in the UK.

Table 2.5 Maintenance of therapy (Storr 2015)

Assessment	Every clinic visit	Annually
Enter data on registry	+	
Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils	+	
Echocardiography		+
Bone age		+
Facial photograph (frontal and lateral)		+
Examination of injection sites		+
DXA—whole body and lumbar spine[a]		+
Audiology[a]		+

BSPED Guidelines (2015) (Cohen et al. 2008).
[a]These investigations are not considered to be standard but may provide objective data on changes in hearing and body composition.

Each clinic visit should consist of auxology, discussion regarding injections and examination of injection sites. Targeted adverse events should also be discussed at each visit and any positive clinical history may require more detailed assessment, e.g. history of sleep disordered breathing may require oximetry/sleep studies and referral to ear, nose, and throat (ENT) services. See Table 2.6 (Storr 2015) for some of the more common adverse events as per the UK guidelines.

As previously discussed, hypoglycaemia is the most common side effect of treatment. It is therefore important to continue to discuss this at clinic visits and check the families understanding of signs, symptoms, and treatment of hypoglycaemia.

Treatment should be reconsidered if the patient has an increase in height velocity of less than 30% of baseline or a change in height SDS score of <0.3 over a 12-month period although there should be documented good compliance over this time period.

UK guidelines state treatment with a Gonadotrophin-releasing hormone (*GnRH*) agonist may be indicated in pubertal children who are extremely short and have not received IGF-1 for a sufficiently long period (Mushtaq 2015).

Table 2.6 Targeted adverse events

Potential adverse event	Monitoring	Actions
Hypoglycaemia	Monitor BG	Give injections after food
Lymphoid hyperplasia	Check at clinic visits for snoring, apnoea	Refer to ENT
Intracranial hypertension	Headaches, visual disturbance, papilloedema.	Discontinue treatment. Recommence once resolved at low dose and gradually increase
Slipped capital femoral epiphysis(SCFE)/scoliosis	Physical examination. Pain/limp	Refer to orthopaedics
Coarsening of facies	Physical examination. Photographs	Resolves once treatment discontinued at end of growth
Allergic reaction	Check injection sites for hypersensitivity, urticaria, pruritus, and erythema	Discontinue treatment. Consider giving anti-histamines. Allergy specialist
Hypoacusis (Hearing loss)	Check at clinic visits	Send to audiology for hearing test
Cardiac hypertrophy	Echocardiography	Refer to cardiology. Consider stopping treatment

2.13 The Multidisciplinary Team (MDT)

Although these children are primarily managed by a Paediatric Endocrinologist and PENS, both their extreme short stature and treatment requiring twice daily injections are challenging for these families. Therefore, the involvement of other services and local teams is vital to their overall well-being.

2.13.1 Psychology

As these children have extreme short stature, they may benefit from input from psychology services. Although the aim of treatment is to improve their adult height, they may still remain below the normal centiles once the treatment has completed, and some of these young people will remain significantly smaller than their peers. Psychology may therefore be a useful service to help the young people discuss their feelings and adapt to the adult world.

2.13.2 School

Due to their extreme short stature, these children face a number of difficulties at school. It is important for the PENS to offer information, advice, and support both the family and school to enable the child to fully participate in school activities. As discussed earlier, issues may arise with bullying (Cohen and Dwyer 2018). Information should also include being aware of the signs and symptoms of hypoglycaemia and how to respond if the child were to become hypoglycaemic. The school nursing service should be approached to assist with supporting the child. This may also require liaison with occupational therapists to discuss any adaptations/equipment which may be needed.

2.13.3 Community/Home Support Nurses

Support nurses where available are a useful addition to the package of care for these families. In the UK, they are able to offer home visits and phone calls over the duration of the treatment. This not only supports the family thereby helping them adhere better to long-term treatment but also offers an adjunct to the service the PENS is able to provide.

2.13.4 PENS

The role of the PENS is extremely important with these children and families. They play a key role in supporting the families through diagnosis and lengthy treatment.

They can act as liaison between the different members of the MDT and are usually the main point of contact for the families.

2.14 Nursing Considerations

The PENS is likely to have been involved with the family during the monitoring and investigations of their short stature.

As with GH therapy, the rhIGF-1 injections are likely to continue for many years until final height is reached. This requires support for the families undertaking this treatment to maximise adherence in order to gain the greatest benefit.

The role of the PENS is multi-faceted and includes acting as an educator, support service, advocate, and liaison for the family throughout the period of both diagnosis and treatment.

It is important from the outset that the PENS is able to assess the family's understanding of the condition and the ability to undertake the treatment in order to individualise the care package to their needs.

Good written information is extremely important but as the family are also learning how to give injections, check CBG, and monitor their child, this needs to be discussed, demonstrated, and taught effectively.

If the child is to be admitted to start treatment, the PENS role is to ensure this is a smooth process thereby reducing the stress on the family. This offers an opportunity for the PENS to meet with the family and teach them all the practicalities around administration, storage, side effects, omit-

ting doses and checking CBG. All the equipment the family will need to give the injections and check CBG can be available on the ward on the day of admission. The PENS can also support the family through the first few injections until they become more accustomed to the procedure. Unlike GH, there is currently no pen device for the rhIGF-1 injections; therefore, the family need to be taught how to draw up and administer the injections using needles and syringes. This can be a daunting prospect for some families. It is therefore extremely important to give the family clear instructions and the time needed for them to become confident with the technique.

This face-to-face interaction and support can be invaluable to the family whilst they are learning and can help to build a trusting relationship between the family and PENS. It is also important to give supporting literature when they are discharged home including all necessary contact details.

If the treatment is to be started at home by a homecare nursing service, it is important that there has been liaison between the homecare nurse and the PENS beforehand.

Over the course of treatment, the PENS continues to play an important role. They will see the family regularly at clinic visits and give ongoing support. Any concerns or problems they may be having can be discussed. Injection sites can be checked and ensuring continuing education and understanding regarding treatment and side effects should be a routine part of the appointment.

2.15 Patient Support Groups and Useful Websites

Patient support groups have been shown to be a highly valuable resource for patients and their families (Bartlett and Coulson 2011), not just as a clinical and supportive tool, but by also enabling empowerment and enriching the relationship between the child and family and their caregivers (van Uden-Kraan et al. 2009). The advent of social media, with websites and online support groups can add to this, although children and families are advised on which are the more useful. Box 2.3 details the American support group MAGIC: **M**ajor **A**spects of **G**rowth **I**n **C**hildren, with a description of how it as set up. Further useful websites are listed below.

Box 2.3 Patient Support Groups

The MAGIC Foundation
4200 Cantera Drive, Suite 106, Warrenville, IL 60555

630–836-8200 / fax 630–836-8181 toll free 800–3 MAGIC 3

www.magicfoundation.org * contactus@magicfoundation.org

It is hard to remember days without the internet, cell phones, and costly long distance calls. I was heartbroken when my son was diagnosed with growth hormone deficiency in 1978. No way to communicate with others, no internet for information, no Facebook to network with others, just lost and alone. Ten years later, I was blessed with meeting two other mothers facing the same challenges I did. We talked about how difficult our journey was and how we could make a difference for new families entering the world of endocrine disorders. We decided to take on the challenge of a non-profit organisation and The MAGIC Foundation was established in 1989. MAGIC (**M**ajor **A**spects of **G**rowth **I**n **C**hildren) was initiated to help support families of children with "Growth" disorders but little did we know how many disorders were out there affecting a child's growth.

Since 1989 MAGIC has grown to 11 divisions, supporting specific disorders, so parents would have the opportunity to network with others facing similar situations affecting their child. Currently, our divisions include growth hormone deficiency, panhypopituitarism, septo optic dysplasia/optic nerve hypoplasia, Russell

(continued)

Box 2.3 (continued)

Silver syndrome, small for gestational age, congenital adrenal hyperplasia, precocious puberty, McCune-Albright syndrome/fibrous dysplasia, hypophosphatasia, Cushings, and adult growth hormone deficiency. Facebook groups for all these disorders, both children and adults, are available for networking.

In 2014, MAGIC received a Congressional Resolution for "Growth Awareness Week", the third week of September each year, to increase awareness of growth in children. MAGIC has actively participated in summits and roundtables with Endocrine Societies and Pharmaceutical Companies to provide input to the needs and support of affected families, including educational materials that would be beneficial to those families.

Areas of support have grown over the years to include:

- Quarterly Newsletters (children and adult).
- Annual Educational Convention (attendance approx. 1000+ annually) with over 30 medical professionals providing educational segments.
- 30+ Facebook Accounts
- Friday Email (updating families on research and educational articles).
- Division Consultants for each Division (parent of affected child or affected adult).
- Insurance Appeal Program (provide external appeals when denied therapy).
- International Division, "ICOSEP" (a coalition of support organisations to communicate and network worldwide).
- Web Site—www.magicfoundation.org (all educational brochures and personal stories).
- 30+ Educational Brochures (free to families, medical professionals, and health care professionals, written by medical professionals)
- Physician Referrals (both paediatric and adult endocrinologists).
- Challenge Legislative Issues/Laws affecting the health care of our families.

Annually, MAGIC continues to grow, implement new programs and support systems, continues to build awareness regarding children's growth and so much more. We continue to communicate with the medical community and all health care professionals and hope our services have provided the support and continued education families warrant. Referring families to MAGIC alleviates the feeling of being alone and connects them with others facing similar situations. We help them understand and support them from initial testing right through the years of treatment. You can help your families by simply telling them, "Contact MAGIC and you will not be alone".

Mary Andrews
CEO/Co-Founder
The MAGIC Foundation
mandrews@magicfoundation.org
cell 708-473-9596
contactus@magicfoundation.org

2.16 Useful Websites

https://apeg.org.au/patient-resources/hormones-me-booklet-series/

https://www.bsped.org.uk/clinical-resources/patient-information/patient-resources/

http://magicfoundation.org

http://pituitary.asn.au

www.childgrowthfoundation.org.uk

http://hgfound.org/

http://www.saynobullying.org/

www.noonansyndrome.org.uk

https://noonansyndrome.com.au

https://www.teamnoonan.org/#!

http://www.geneticalliance.org.au/...detail.php?Russell-Silver-Syndrome

https://magicfoundation.org/Growth-Disorders/Russell-Silver-Syndrome

https://dwarfismawarenessaustralia.com
www.lpaonline.org
www.skeletaldysplasiagroup.org.uk
www.bsped.org.uk

2.17 Conclusions

Short stature is a common presenting problem to a general practitioner, and is one of the most common reasons a child is seen in a paediatric endocrine clinic (Davies 2017). Any child presenting with a height outside of their expected potential for no known reason should be evaluated, and all girls being investigated should have a karyotype performed to assess for Turner syndrome.

Regular monitoring of growth using the same piece of equipment, the same technique, and where possible, the same observer, is essential to establish a child's growth pattern. If the growth pattern alters, or growth velocity remains low, further investigation should be undertaken by a paediatrician or endocrinologist to establish whether there is cause for concern or not. Early detection allows for maximal response if treatment is undertaken.

Treatment should always be discussed in consultation with the family as it has been shown that compliance is improved if families have some input into the decision-making. Commitment from the child / young person and family is imperative with regards to treatment compliance: treatment with GH is a once daily injection until final height is achieved, and a diagnosis of SPIGFD and treatment requires twice daily injections, both requiring long-term commitment.

Paediatric endocrine nurses occupy a unique position in the evaluation of short stature and the ongoing management of those receiving GH treatment or IGF-1 therapy. Regular review of the child's progress and ongoing support with treatment with the PENS are key to the child achieving the best possible outcomes. An important part of the PENS role is to understand both the clinical aspects of diagnosis and treatment and the effect this can have on the child and family and support them throughout this in order to achieve the best outcome.

Acknowledgments With special thanks to Mary Andrews, CEO/Co-Founder of the MAGIC Foundation, (MAGIC: **M**ajor **A**spects of **G**rowth **i**n **C**hildren) www.magicfoundation.org for her contribution to this chapter with a case study and information on the Patient Advocacy Group.

Appendix: GH Stimulation Test Information Sheet

GLUCAGON/ARGININE STIMULATION TEST INFORMATION SHEET

What is this test?

This test is carried out to assess hormones that the pituitary gland produces. **Glucagon** causes a number of temporary hormonal signals resulting in the release of growth hormone from the pituitary gland and stimulation of cortisol production. These levels are then measured in a series of blood tests. **Arginine** is an amino acid which also stimulates growth hormone secretion in the hypothalamus and pituitary gland. Some older children may need to take low doses of priming hormones before the test if they have delayed puberty so that the testing is accurate; your doctor will have advised if this is needed.

When is this test?

Your child is booked to attend for a glucagon/arginine stimulation test on.

How should I prepare my child?

- Your child will need to be admitted to the hospital for the day (approximately 5 h).
- **Your child should have nothing to eat or drink, except water, from 12 midnight the night before the test.** Babies less than 12 months or children under 10 kg need to fast for 4 h, so should have an early morning feed.
- **Please call to confirm with the endocrine testing nurse, the day before the test.**
- If your child is unwell, please contact us as the test may need to be rescheduled.
- Bring a favourite toy, activity, DVD, or book on the day to keep your child occupied.
- You will be admitted by the clerk and directed to the endocrine testing area.

What happens next?

- The nurse will record your child's height, weight, temperature, pulse and blood pressure, and oxygen saturations.
- Before we insert a cannula (a small needle with a plastic tube attached) into the vein, and so that we cause as little discomfort as possible, anaesthetic cream or an ice stick can be used to anesthetise the area. We will need to take multiple blood samples during the test, and the cannula allows all the samples to be taken from the same site.
- At the beginning of the test, a blood sample is taken and then an injection of glucagon is given into the thigh muscle.
- Another blood sample is collected **one hour later, and further samples are then taken at ½ hourly intervals for another 2 h.**
- The arginine solution is then given via an intravenous drip into the cannula over 30 min.
- **Four more blood samples are then taken every 15 min once the infusion is completed.**
- Some children may feel nauseated or complain of abdominal pain during the test, but this is usually temporary. Occasionally, a child may vomit. We can give medication to ease this.
- Your child's blood glucose level is checked during the test because low values sometimes occur and may need to be treated.

And finally…. after the test?

At the end of the test your child may eat, the cannula is removed and you will be discharged home.

Results are usually available after 2 weeks, so **before leaving make sure that you have details of the follow-up appointment.** If you have any questions following the test, contact your child's doctor or endocrine clinic.

References

Alatzoglou KS, Webb EA, Le Tissier P, Dattani MT. Isolated growth hormone deficiency (GHD) in childhood and adolescence: recent advances. Endocr Rev. 2014;35(3):376–432.

Albanese A, Hamill G, Jones J, Skuse D, Matthews DR, Stanhope R. Reversibility of physiological growth hormone secretion in children with psychosocial dwarfism. Clin Endocrinol. 1994;40(5):687–92.

Backeljauw PF, Underwood LE. Therapy for 6.5 - 7.5 years with recombinant Insulin-Like Growth Factor 1 in children with growth hormone insensitivity syndrome. J Clin Endocrinol Metab. 2001;86:1504–10.

Bartlett YK, Coulson NS. An investigation into the empowerment effects of using online support groups and how this affects health professional/patient communication. Patient Educ Couns. 2011;83(1):113–9.

Boyd A, Klug GM, Schonberger LB, McGlade A, Brandel JP, Masters CL, et al. Iatrogenic Creutzfeldt-Jakob disease in Australia: time to amend infection control measures for pituitary hormone recipients? Med J Aust. 2010;193(6):366–9.

Brook CGD, Clayton PE, Brown R. Brook's clinical paediatric endocrinology. 5th ed. Oxford: Wiley Blackwell; 2008.

Buchanan CR, Preece MA, Milner RDG. Mortality, neoplasia and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. BMJ. 1991;302(6780):824–8.

Butler G. Indications for growth hormone therapy. Paediatr Child Health. 2007;17(9):356–60.

Butler G, Kirk J. Paediatric endocrinology and diabetes. Oxford: OUP Press; 2011.

Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab. 2012;97(2):416–25.

Chesover AD, Dattani MT. Evaluation of growth hormone stimulation testing in children. Clin Endocrinol. 2016;84(5):708–14.

Clayton PE, Cowell CT. Safety issues in children and adolescents during growth hormone therapy--a review. Growth Hormon IGF Res. 2000;10(6):306–17.

Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152:165–70.

Cohen SS, Dwyer A. PENS position statement on bullying prevention. J Pediatr Nurs. 2018;39:91–3.

Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008;93(11):4210–7.

Cook DM, Yuen KC, Biller BM, Kemp SF, Vance ML, American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth

hormone use in growth hormone-deficient adults and transition patients - 2009 update: executive summary of recommendations. Endocr Pract. 2009;15(6):580–6.

Davies K. Assessment of growth failure in children: MIMS for Nurses Pocket Guide. London: Haymarket Publishing; 2004.

Davies K. Care of the child and young person with endocrine problems. In: Pryce J, McAlinden O, editors. Essentials of nursing children and young people. 1st ed. London: Sage; 2017.

Gau M, Takasawa K. Initial patient choice of a growth hormone device improves child and adolescent adherence to and therapeutic effects of growth hormone replacement therapy. J Pediatr Endocrinol Metab. 2017;30(9):989–93.

Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press; 1959.

Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–97.

Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990–3.

Laron Z. Genetic pituitary dwarfism with high serum concentration of growth hormone - a new inborn error of metabolism? Isr J Med Sci. 1966;2:152–5.

Lee PA, Chernausek SD, Hokken-Koelga ACS, Czernichow P. Management of short children born small for gestational age. Pediatrics. 2003;111:1253–61.

Maghnie M, Labarta JI, Koledova E, Rohrer TR. Short Stature Diagnosis and Referral. Front Endocrinol (Lausanne). 2017;8:374.

Maguire A, Ambler G, Craig ME. Short stature in children: when is further evaluation and referral requried? Endocrinology Today. 2013;2(1).

Mushtaq T. Recombinant IGF-1 therapy in children with severe prmary IGF-1 deficiency (SPIGFD). BSPED; 2015.

Pharmaceuticals I. Increlex. Ipsen Pharmaceuticals; 2007.

Quigley CA, Gill AM, Crowe BJ, Robling K, Chipman JJ, Rose SR, et al. Safety of growth hormone treatment in pediatric patients with idiopathic short stature. J Clin Endocrinol Metab. 2005;90(9):5188–96.

Quigley CA, Child CJ, Zimmermann AG, Rosenfeld RG, Robison LL, Blum WF. Mortality in children receiving growth hormone treatment of growth disorders: data from the genetics and neuroendocrinology of Short Stature International Study. J Clin Endocrinol Metab. 2017;102(9):3195–205.

Raine JE, Donaldson MDC, Gregory JW, van Vliet G, editors. Practical endocrinology and diabetes in children. 3rd ed. Chichester: Wiley - Blackwell; 2011.

Ranke MB, Price DA, Albertsson-Wikland K, Maes M, Lindberg A. Factors determining pubertal growth and final height in growth hormone treatment of idiopathic growth hormone deficiency. Analysis of 195 patients of the Kabi Pharmacia International Growth Study. Horm Res. 1997;48(2):62–71.

Rappaport EB, Fife D. Slipped capital femoral epiphysis in growth hormone deficient patients. Am J Dis Child. 1985;139(4):396–9.

Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010;126(4):746–59.

Rosenbloom AL. Sex hormone priming for growth hormone stimulation testing in pre- and early adolescent children is evidence based. Horm Res Paediatr. 2011;75(1):78–80.

Rosenfeld RG, Albertsson-Wikland K, Cassorla F, Frasier SD, Hasegawa Y, Hintz RL, et al. Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. J Clin Endocrinol Metab. 1995;80(5):1532–40.

Satoh M. Bone age: assessment methods and clinical applications. Clin Pediatr Endocrinol. 2015;24(4):143–52.

Savage MO, Backeljauw PF, Calzada R, Cianfarani S, Dunkel L, Koledova E, et al. Early detection, referral, investigation, and diagnosis of children with growth disorders. Horm Res Paediatr. 2016;85(5):325–32.

Skuse D, Albanese A, Stanhope R, Gilmour J, Voss L. A new stress-related syndrome of growth failure and hyperphagia in children, associated with reversibility of growth-hormone insufficiency. Lancet. 1996;348(9024):353–8.

Storr HL. Recombinant IGF-1 therapy in children with severe primary IGF-1 deficiency (SPIGFD). BSPED: UK IGF-1User's Group; 2015.

Tanner JM, Healy MJR, Goldstein H, Cameron N. Assessment of skeletal maturity and prediction of adult height (TW3 method): WB Saunders; 2001.

Urquhart T, Collin J. Understanding the endocrinopathies associated with the treatment of childhood cancer: part 2. Nurs Child Young People. 2016;28(9):36–43.

van Uden-Kraan CF, Drossaert CH, Taal E, Seydel ER, van de Laar MA. Participation in online patient support groups endorses patients' empowerment. Patient Educ Couns. 2009;74(1):61–9.

Wit JM, Kamp GA, Rikken B. Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. Pediatr Res. 1996;39(2):295–302.

3 Disorders of Sex Development (DSD)

Kate Davies

Contents

3.1 **What Is a DSD?** 41

3.2 **Nomenclature** 41
3.2.1 46, XX DSD 42
3.2.2 46, XY DSD 42
3.2.3 Sex Chromosome DSD 43

3.3 **Chromosomes and Embryology** 43

3.4 **Diagnostic Pathway** 44

3.5 **Infants** 45
3.5.1 Identification 45
3.5.2 Referral 46
3.5.3 Assessment 46
3.5.4 Diagnosis 47
3.5.5 Management 48

3.6 **Adolescents** 48
3.6.1 Primary Amenorrhea 48
3.6.2 Girls with Virilization 48
3.6.3 Boys with Delayed Puberty 48

3.7 **46, XX DSD** 49
3.7.1 Androgen Excess 49
3.7.2 Disorders of Ovarian Development 50
3.7.3 Other Causes 50

3.8 **46, XY DSD** 50
3.8.1 Clinical Presentation 50
3.8.2 Incidence 50
3.8.3 Tumour Risk 50
3.8.4 Disorders of Testicular Development 51
3.8.5 46, XY DSD Due to Defects in Androgen Synthesis or Action 51

K. Davies (✉)
Department of Advanced and Integrated Practice,
London South Bank University, London, UK
e-mail: kate.davies@lsbu.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_3

3.9 **Mixed Sex Chromosome DSD** 52
3.9.1 45, X/46, XY 53
3.9.2 46, XX/46, XY DSD 53
3.9.3 Klinefelter Syndrome: 47, XXY (See Chap. 10) 53
3.9.4 Turner Syndrome: Monosomy X or 45, X or 45, XO (See Chap. 40) 53

3.10 **Management** 54
3.10.1 Medical Management 54
3.10.2 Surgical Management 54
3.10.3 Psychosocial Management 54

3.11 **The Multidisciplinary Team (MDT)** 55
3.11.1 The Psychologist 55
3.11.2 The Paediatric Endocrinologist 55
3.11.3 The Paediatric Urologist/Surgeon 56
3.11.4 The Paediatric Endocrine Nurse Specialist (PENS) 56
3.11.5 Other MDT Members 56

3.12 **Nursing Considerations** 58
3.12.1 At Diagnosis 58
3.12.2 Ongoing Management 58
3.12.3 Transition and Beyond 59

3.13 **Conclusions** 59

3.14 **Useful Websites** 59

References 60

Abstract

The diagnosis of a DSD—a disorder of sex development—whether made in infancy or as a young person—involves a full multidisciplinary team. Progress has been made in recent years with the advances of nomenclature, treatment, and psychological approaches and the disorders have been categorized into more patient-friendly terminology, leaving behind confusing and upsetting labels and stigma. These predominant DSD will be discussed in accordance with the new categories, detailing clinical presentation, management and nursing considerations in order to implement best practice. Emphasis here is placed on a fully co-operative multidisciplinary team, but also the nurses' role, who can offer continued support and guidance to the child/young person and their families.

Keywords

Ambiguous genitalia · Chromosome · DSD
Gonads · Karyotype

Abbreviations

11-DOC	11-deoxycortisol
17-OHP	17 alpha-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
5αRD	5 alpha reductase deficiency
A4	Androstenedione
ACTH	Adrenocorticotropic hormone
AIS	Androgen insensitivity syndrome
AMH	Anti-Mullerian hormone
CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndrome
CNS	Clinical nurse specialist
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DSD	Disorder of sex development
FISH	Fluorescence in situ hybridization
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin releasing hormone
GP	General practitioner
HCG	Human chorionic Gonadotrophin
LH	Luteinizing hormone
MDT	Multidisciplinary team

MIS	Mullerian-inhibiting substance
MRKH	Mayer-Rokitansky-Küster-Hauser syndrome
MURCS	Mullerian, renal, cervicothoracic somite abnormalities
NICU	Neonatal intensive care unit
PAIS	Partial androgen insensitivity syndrome
PCOS	Polycystic ovarian syndrome
PENS	Paediatric endocrine nurse specialist
TS	Turner syndrome
UK	United Kingdom

Key Terms

- **Disorder of sex development:** An umbrella term used to describe a group of conditions that involve the internal reproductive system and/or external genitalia (previously known as *Intersex*).
- **Ambiguous genitalia:** Where the genitals do not appear to be clear either male or female.
- **Diagnostic pathway:** This is a kind of clinical tool, or map, to enable quality in the healthcare that is delivered, based on evidence-based practice.
- **Gonadal dysgenesis:** Where the gonads (ovaries or testes) are made of mainly fibrous tissue, are undeveloped, and do not function.
- **Multidisciplinary team:** A group of healthcare professionals from different professions, all providing their specific services for one patient.

Key Points

- Healthcare professionals involved in DSD care should follow the international consensus guidelines in order to offer optimum care.
- A diagnostic pathway should be followed, whether the child is presenting in infancy or in adolescence.
- A full multidisciplinary team should be in place in order to fully support and guide the family in the treatment needed.
- Paediatric endocrine nurses are in prime position to be the key advocate and liaison for the child/young person and their family.

3.1 What Is a DSD?

Disorders or differences of sex development (DSD) is a phrase used to describe a multitude of congenital conditions in which the physical development of either the chromosomes, the gonads, (i.e. the ovaries or the testes), or anatomy is unusual or atypical (Rothkopf and John 2014). It can also be described as where there is a difference between someone's 'genetic sex' to how their internal or external reproductive systems appear (Wisniewski et al. 2012). Many people use the term 'disorder', but that can lead some people to think of 'ill' children, so 'differences' is sometimes used instead. The incidence of actual ambiguous genitalia can occur in 1 in every 5000 live births (Rothkopf and John 2014), and is relatively rare. However, if all genital anomalies are to be considered, then a DSD can occur in approximately 1 in every 300 births (Rothkopf and John 2014). It is difficult to estimate exactly how many conditions come under the DSD umbrella: as the cause of a DSD is quite often a gene regulation breakdown (White and Sinclair 2012) which is responsible for gonadal development, there is the potential for more genetic variants yet to be identified, plus there are also a number of rare multiple malformation syndromes associated with DSD. However, a recent international consensus statement (Lee et al. 2006) has identified a useful classification tool for DSD.

3.2 Nomenclature

Previously to this consensus statement, various terms were used to describe different DSD conditions. Due to further developments in genetics, ethical considerations, patient advocacy voices,

as well as patients from affected families, plus also specialists working in the field (Pasterski et al. 2010) it was deemed necessary to replace these terms. Such terms that were used were intersex, hermaphroditism, and pseudohermaphroditism (Woodward and Patwardhan 2010) (See Table 3.1). 'Intersex' was used as a broad term to describe a clinical picture of a child with ambiguous genitalia, whereas hermaphroditism was used to describe an individual with both testicular and ovarian tissue (Raine et al. 2011) and pseudohermaphrodites were either male with testicular tissue or female, with ovarian tissue. Such terminology was confusing and often stigmatized patients and their families (Woodward and Patwardhan 2010). The new classification can be seen in Table 3.2.

Table 3.1 Proposed revised nomenclature

Previous	Proposed
Intersex	DSD
Male pseudohermaphrodite Undervirilization of an XY male Undermasculinization of an XY male	46, XY DSD
Female pseudohermaphrodite Overvirilization of an XX female Masculinization of an XX female	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XY female	46, testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

Taken from: Hughes, I. A. (2008) Disorders of Sex development: a new definition and classification *Best Prac Res Clin Endocrinol Metab* 22 (1) p.119–34

3.2.1 46, XX DSD

This category describes individuals who possess the usual number of chromosomes (Crissman et al. 2011) and two X chromosomes (female), but the external and/or internal sex ducts have not developed in the expected female way (Wisniewski et al. 2012). For example, the baby may be born with a womb and fallopian tubes, but their clitoris may look like a small penis. The most common form is congenital adrenal hyperplasia (CAH) and 21-hydroxylase deficiency (21-OHD) (***see Chap. 35***). However, other conditions also fall under this category, but can depend on disorders of ovarian development or androgen excess.

3.2.2 46, XY DSD

This is where the individual is born with a 46, XY (typically male) chromosomal make-up, but like the female 46, XX DSD, their internal or external structures have not developed in what should be

Table 3.2 DSD Classification table

46, XY DSD	46, XX DSD	Sex chromosome DSD
1. Disorders of gonadal (testicular) development: (a) Complete gonadal dysgenesis (Swyer syndrome) (b) Partial gonadal dysgenesis (c) Gonadal regression (d) Ovotesticular DSD 2. Disorders in androgen synthesis or action: (a) Androgen biosynthesis defect (e.g. 5αRD) (b) Defect in androgen action (e.g. CAIS, PAIS) (c) LH receptor defects (d) Disorders of AMH/AMH receptors	1. Disorders of gonadal (ovarian) development: (a) Ovotesticular DSD (b) Testicular DSD (c) Gonadal dysgenesis 2. Androgen excess (a) Foetal (e.g. 21-OHD) (b) Foetoplacental (e.g. aromatase deficiency) (c) Maternal (e.g. exogenous) 3. Other (e.g. cloacal exstrophy, vaginal atresia, MURCS, other syndromes	1. 45, X (Turner syndrome and variants) 2. 47, XXY (Klinefelter syndrome and variants) 3. 45, X/46, XY (MGD, ovotesticular DSD) 4. 46, XX/46, XY (chimeric, ovotesticular DSD)

Adapted from: Lee, P.A et al. (2006) *Consensus Statement on Management of Intersex Disorders* Pediatrics 118 (2) p. e489–e500

expected for a male. The reasons for a 46, XY DSD are more varied and complex in comparison to a 46, XX DSD, but are usually attributed to the foetus being unable to produce or respond to testicular hormones (Wisniewski et al. 2012)

3.2.3 Sex Chromosome DSD

The sex chromosome DSD is where there is sex chromosome aneuploidy—where there is an abnormal number of X or Y chromosomes (Hewitt and Warne 2012a)—with either an extra or missing chromosome. Here the gonad is affected, and therefore ambiguous genitalia may be present, with also puberty and perhaps fertility also affected.

3.3 Chromosomes and Embryology

It is important to comprehend the principles of sexual differentiation when discussing the foundations of any DSD, and there are three sequential stages: (See Box 3.1).

Specific genes around gestational age week 3 lead to the differentiation of the gonads (Biason-Lauber 2010), but it is now widely known that the SRY gene, which resides on the p arm of the Y chromosome, sends signals to 'sex neutral' tissue to develop into testes (Wisniewski et al. 2012). If this gene is missing, or does not work properly, then healthy testes will not develop. Gonads and internal (Wolffian and Mullerian ducts) and external genitalia will have similar appearance around this time (Raine et al. 2011).

However, around gestational ages week 6–7, these undifferentiated gonads begin to separate: if a Y chromosome is present, the gonad will develop into a testis, and gonadal cells will segregate into testicular cords and interstitial tissue (Rey and Grinspon 2011). The testicular cords are made up of somatic sertoli cells and germ cells, and it is these sertoli cells that produce anti-Mullerian hormone (AMH) or Mullerian-inhibiting substance (MIS). AMH is responsible for the regression of the Mullerian ducts. Testosterone is also made by the testes. In the *absence* of these two hormones, female anatomy is formed—as the Mullerian ducts have not regressed—EVEN if a Y chromosome is present.

As seen in Fig. 3.1 (Kobayashi and Behringer 2003), Mullerian ducts in an XX female that will develop into female reproductive structures (except ovaries), and they grow because there is no AMH to block their development. Therefore no exposure to AMH will enable the internal structures to develop into the upper end of the vagina, the cervix, the womb, and the fallopian tubes (Wisniewski et al. 2012). Conversely, the Wolffian ducts will develop into the epididymides, the two vas deferens, and the seminal vesicles, for the male reproductive system.

There are further hormonal influences that will have an impact on the development of the external genitalia. From around 8 weeks gestation, the male embryo will develop a penis from the genital tubercle, urethral folds will develop into the corpus spongiosum that surrounds the urethra, and the genital folds will also fuse to form the scrotum (Raine et al. 2011). This happens under the influence of a hormone called dihydrotestosterone (DHT), which is converted from testosterone. DHT is made when an enzyme called 5 alpha reductase is available (Wisniewski et al. 2012). If a baby does *not* make DHT, then a vulva will form, involving a clitoris, and the labia minora and majora. It is interesting to note, however, that there is no difference between the size of the clitoris and penis before the 14th week gestation: phalli growth usually peaks in the third

Box 3.1 The Stages of Embryological Differentiation (Rey and Grinspon 2011)

1. An 'undifferentiated' stage, where embryonic structures are identical and start to develop into XY (male) and XX (female) embryos
2. The gonadal stage, where testes or ovaries develop
3. The differentiated development of internal and external genitalia

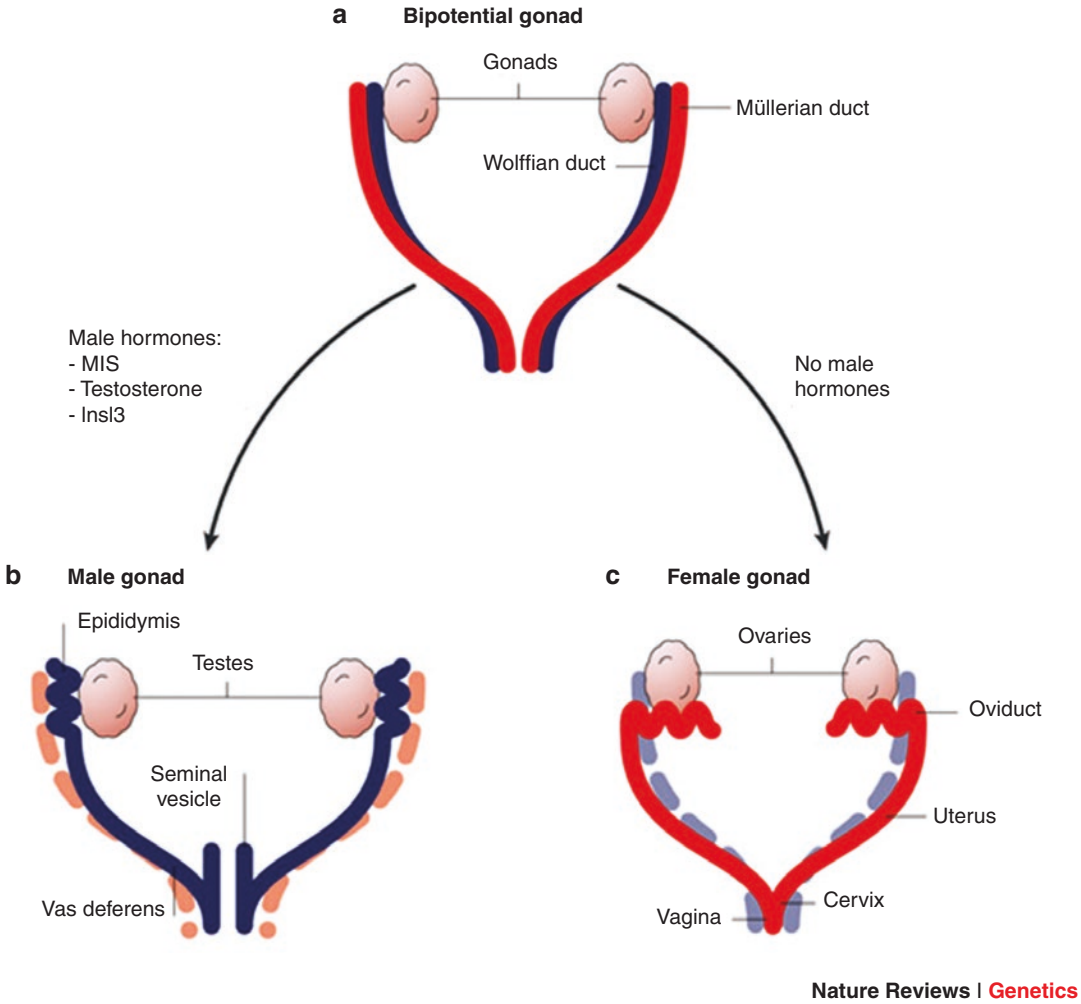


Fig. 3.1 Formation of internal reproductive structures. From: Akio Kobayashi & Richard R. Behringer. Developmental genetics of the female reproductive tract in mammals *Nature Reviews Genetics* 4, 969–980 (December 2003)

trimester, usually from around 28 weeks gestation (Rey and Grinspon 2011).

This is now apparent to see how ambiguous genitalia can occur: why some children who are XY may have female external genitalia, or why XX females may appear male (Wisniewski et al. 2012). It is, therefore, this presentation of a baby with ambiguous genitalia which will initiate a cascade of investigations and support for the child and family.

3.4 Diagnostic Pathway

New guidance (Ahmed et al. 2015) was formed by the United Kingdom (UK) Society of Endocrinology advising on the evaluation of infants and adolescents presenting with a suspected DSD. This guidance principally focuses on the diagnostic approach rather than lifelong management, and it is from this guidance that UK DSD centres follow.

3.5 Infants

Any baby where the appearance of their genitalia provokes questioning surrounding sex assignment needs to be investigated. Careful and sensitive management is needed, and a suggested diagnostic pathway (Kinsman et al. 2010) is seen in Fig. 3.2.

3.5.1 Identification

This is the first step where a suspected DSD in an infant is identified, usually by a midwife, or a paediatrician/obstetrician shortly after birth. It is essential that the baby is referred to a centre which has experience in DSD, and the referring personnel must contact the appropriate team with as much detail as possible, including:

3.5.1.1 Clinical Status

The referring team must describe if the baby is clinically well, for example, if they are ventilated, in an incubator, on antibiotics or intravenous fluids, or having problems with serum sodium or blood glucose levels.

3.5.1.2 Clinical History

A detailed description of the genitalia is needed, such as any hyperpigmentation, labial fusion, urethral meatus position, hypospadias, or chordee (where the head of the penis can curve upwards or downwards), and if the gonads are palpable. The Prader staging of external genitalia (Fig. 3.3) is used to classify the degree of virilization in external genitalia. Hypospadias can be classified by using the hypospadias diagram (Fig. 3.4), and the external masculinization score is used to describe states of labial

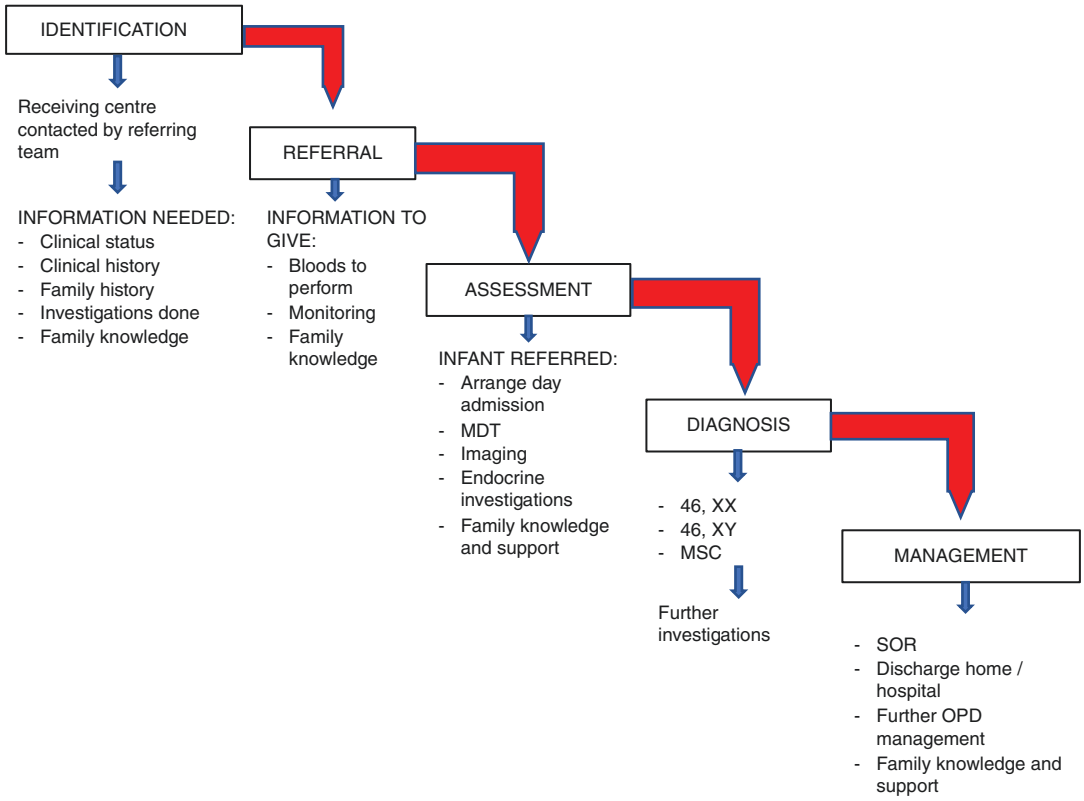


Fig. 3.2 Diagnostic pathway for an infant with a suspected DSD

Fig. 3.3 The Prader staging of external genitalia. From: Hewitt, J.K. & Warne, G. L. (2012) 46, XY DSD *in Disorders of Sex Development: An Integrated Approach to Management* p. 65 Springer, Wurzburg

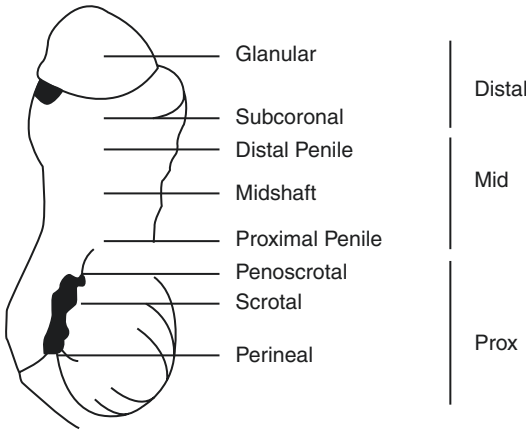


Fig. 3.4 Hypospadias descriptions. From: Hewitt, J.K. & Warne, G. L. (2012) 46, XY DSD *in Disorders of Sex Development: An Integrated Approach to Management* p. 65 Springer, Wurzburg

fusion and if and where the gonads are palpable (Fig. 3.5).

3.5.1.3 Family History

Details from the family are needed, such as antenatal scans and results of prenatal testing, and if there is any maternal history, such as exposure to any medications or other environmental factors (Hughes et al. 2012a), or whether any assisted techniques for conception were used (Ahmed and Rodie 2010). Sensitive questioning is also needed enquiring of ethnicity, any parental consanguinity, or any history of unexplained infant deaths in the family or any other noted cases of DSD.

3.5.1.4 Family Knowledge

Finally, this information needs to be treated with caution, and it is hoped that if the referral centre is unsure, then no definite sex or rearing has already been given.

3.5.2 Referral

Once it is determined that the infant needs to be referred, the receiving team can advise on the next steps to undertake before the baby can physically arrive at their hospital. An urgent karyotype needs to be performed (Rodie et al. 2011) marked urgent, but blood can also be sent for FISH analysis (fluorescence in situ hybridization); this is a test that can look for specific genetic material and, in this case, X- and Y-specific DNA (Hughes et al. 2007). The results of these can usually be received relatively quickly and can indicate if there is Y-specific material present. Daily monitoring of the baby is advised for serum urea and electrolytes and blood glucose. After the baby is 3 days old, then cortisol and ACTH levels can be recorded, plus also 17-hydroxyprogesterone (17-OHP). Samples taken before this can potentially be abnormal (Raine et al. 2011). 17-OHP is a steroid hormone which would be raised in cases of CAH (congenital adrenal hyperplasia) (***See Chap. 35***).

3.5.3 Assessment

Next, the baby should be admitted to the specialist centre, for a full-day admission. This would include meeting members of the multidisciplinary team (MDT) who could be involved.

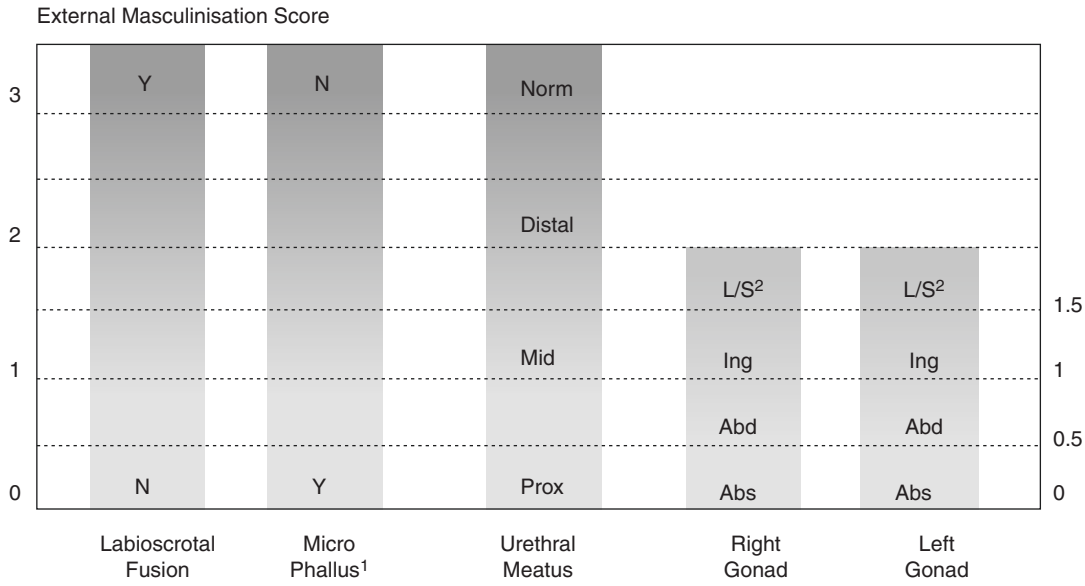


Fig. 3.5 The External Masculinization Score. From: Hewitt, J.K. & Warne, G. L. (2012) 46, XY DSD *in Disorders of Sex Development: An Integrated Approach to Management* p. 65 Springer, Wurzburg

Further clinical assessment would need to take place, including further endocrine investigations, possibly further and more detailed imaging, such as a pelvic and abdominal ultrasound to explore internal structures, and further blood tests looking at testosterone levels, anti-Mullerian hormone (AMH) (or Mullerian-inhibiting substance—MIS), inhibin B, gonadotrophins, and also urinalysis. AMH is detected in boys and is expressed in the sertoli cells in the embryological phases of testicular differentiation (Ahmed et al. 2015), and inhibin B also is produced in the testes.

Including the MDT is paramount, and the family should meet the paediatric endocrine nurse specialist (PENS), the paediatric endocrinologist, the paediatric urologist, and the psychologist, for optimum and sensitive management on this first day of meeting. The team need to work together to develop a plan for immediate clinical assessment and management, exploring differential diagnoses, sex of rearing/gender assignment, and treatment, ensuring that the family have a good understanding. Information leaflets should be available from support groups, and it is recommended to offer them with full explanations.

3.5.4 Diagnosis

Further investigations may need to be undertaken once the karyotype is confirmed to confirm the actual diagnosis. If 46, XX, a short synacthen test and a urine steroid profile are needed to be performed to confirm CAH (Butler and Kirk 2011). If 46, XY, an HCG (human chorionic gonadotropin) stimulation test should be performed, which is used to test the ability of any testes present to produce testosterone (Ishii et al. 2015) (see Box 3.2 below (Butler and Kirk 2011)) Good testicular function is indicated if testosterone rises above 5 nmol/L.

If the chromosomes are ‘mixed sex’, or 45, X/46, XY, then further investigations similar for Turner syndrome (***See Chap. 40***) need to be carried out, such as thyroid function, a cardiac echocardiograph, audiology, and Turner screening. In cases of 46, XX and 45, X/46, XY, early examinations under anaesthetic and/or laparoscopy for

Box 3.2 The HCG Test (Butler and Kirk 2011)

Dose

- 1000 units HCG IM daily for 3 days (infants)
- 1500 units HCG IM daily for 3 days (older children)

Procedure

- Day 1—Blood sample for testosterone, DHT, and other testosterone precursors (androstenedione (A4), dehydroepiandrosterone (DHEA), and 11-deoxycortisol (11-DOC). Give HCG
- Day 2—Give HCG
- Day 3—Give HCG
- Day 4—Specimen for testosterone, DHT, and other testosterone precursors

inspection of internal structures may be necessary, or genitograms to determine any merging between the vagina and urethra (Raine et al. 2011), although these investigations are only needed if the diagnosis is proving difficult (Ahmed et al. 2015).

3.5.5 Management

The decision of sex or rearing/gender assignment can, usually, be made at the end of the day of the admission, which is important for parents, as the need and desire to want to register the baby's birth with the 'correct' sex is important. The baby can be discharged either back to the referring hospital or home if appropriate. Full details have to be given for any immediate medical management, and education on any sick day and emergency management if the baby is 46, XX CAH, and the PENS' role here is paramount (***See Chaps. 37 and 62***). Further management and support is given, follow-up clinic appointments for the appropriate members of the MDT should be made and details of support groups given and explained (Ahmed et al. 2015).

3.6 Adolescents

A small group of DSD can present in adolescence and can present in one of three ways:

1. A girl presenting with primary amenorrhea (where menstruation has not yet commenced), with or without any breast development.
2. A girl who begins to virilize at puberty.
3. A boy with delayed puberty.

3.6.1 Primary Amenorrhea

A full history needs to be taken, including a family history, and full pubertal assessment (***See Chap. 4***). Further investigations are detailed in the UK guidance (Ahmed et al. 2015) but are also outlined in Fig. 3.6. A 46, XX disorder of Mullerian development would include Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, as this is where the vagina and womb may be underdeveloped or absent (***See Sect. 6***). Whichever cause, the management of girls presenting with primary amenorrhea should be referred to the gynaecology team.

3.6.2 Girls with Virilization

Girls presenting with hirsutism and cliteromegaly is usually indicative of two possible DSD: 5 alpha reductase deficiency (5αRD), and 17β hydroxysteroid dehydrogenase type 3 deficiency, which is a condition where testosterone is not synthesized properly.

3.6.3 Boys with Delayed Puberty

Most boys presenting with delayed puberty are classified as having 'constitutional delay' (Raine et al. 2011), but other avenues need to be explored and investigated. Testosterone and gonadotrophins need to be measured; if the gonadotrophins are raised, a karyotype should be taken to exclude Klinefelter syndrome (47,

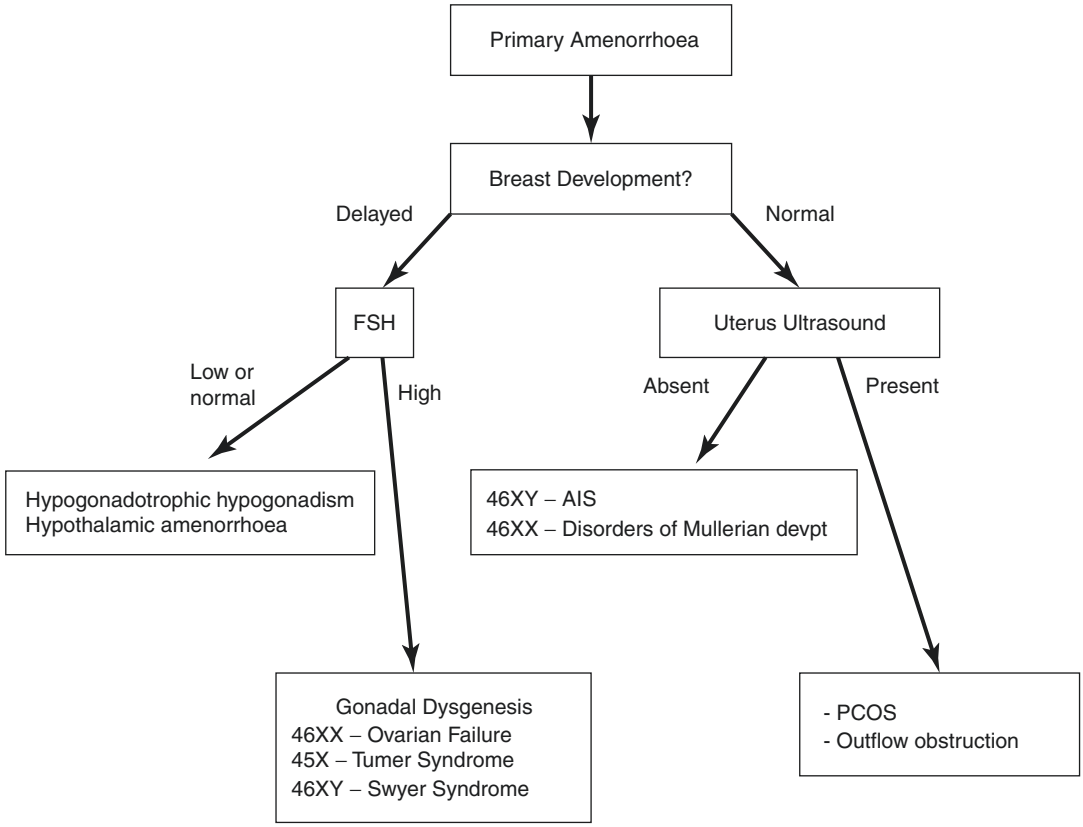


Fig. 3.6 Primary amenorrhoea investigations. From: Ahmed, S.F et al. (2015) Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015) *Clinical Endocrinology* 0, 1–18

XXY) (***See Chap. 10***) and 45,X/46, XY mosaicism (Ahmed et al. 2015).

3.7 46, XX DSD

As seen in the initial classification system (Lee et al. 2006), 46, XX DSD can encompass disorders of ovarian development, androgen excess, and other disorders.

3.7.1 Androgen Excess

More than 50% of all babies born with ambiguous genitalia are 46,XX (Warne and Hewitt 2012a), and this is due to the female foetus being exposed to too many male androgens (Davies 2016). The appearance of the external genitalia can vary in degrees of virilization, and this can be seen in the Prader virilization rating scale (Fig. 3.3). The source of the androgens can be testicular (Warne and Hewitt 2012a): 1 in every 20,000 men has a 46, XX karyotype, and this is due to a translocation of the SRY gene off the tip of the Y chromosome onto one of the X chromosomes. Phenotypically, these men may be similar to men with Klinefelter syndrome. However, the cause of the androgens is usually adrenal, and CAH is the most common cause for this (Woodward and Patwardhan 2010). The majority of these children are assigned as female when they present in the newborn era. (Rothkopf and John 2014) (***See Chap. 35***).

Aromatase deficiencies are also a less common type of enzyme defect, and sometimes the

cause may be due to something the mother has ingested, or maternal androgen-secreting tumours. (Warne and Hewitt 2012a)

3.7.2 Disorders of Ovarian Development

This can include 46, XX ovotesticular DSD, which used to be classified as 'true hermaphroditism' (Woodward and Patwardhan 2010). These individuals have both ovarian and testicular tissue present and will present in the neonatal period with ambiguous genitalia, and continue with virilization at puberty. If female sex was assigned, then they may need an orchidectomy, whilst a male may need an orchidopexy. (Woodward and Patwardhan 2010) The phenotype can vary, however, but often the testis is on one side (usually the right), and the ovotestis or ovary would tend to be on the left, and it is the ovary that is more likely to function (Hewitt and Warne 2012a).

3.7.3 Other Causes

Other causes for 46, XX DSD exist, such as disorders of Mullerian development; ovarian function is usually normal (Ahmed et al. 2015), but other physical presentations may manifest, including cloacal dystrophy, vaginal atresia, or MURCS (Mullerian duct aplasia renal agenesis cervicothoracic somite dysplasia) (Lee et al. 2006)

3.8 46, XY DSD

Conversely, 46, XY DSD is where the child has 46, XY chromosomes, but the internal and/or external reproductive system has not developed properly in what should be expected as male. (Wisniewski et al. 2012) It can be due to an interruption in any part of testicular development, abnormal androgen action, or other reasons.

3.8.1 Clinical Presentation

There is a varying amount of possible ways a child with 46, XY DSD can present. They may possess male internal organs (such as epididymides or vas deferens) but external genitalia may be under-masculinized, which can include a small penis resembling a clitoris, or unfused scrotum, which can look like labia. Testes may not have descended into the scrotum (See Fig. 3.5 on how to clinically assess), and the urinary opening may be at the base of the phallus instead of expected at the tip, which could indicate, for example, severe hypospadias (see Fig. 3.4) (Wisniewski et al. 2012). Children can therefore present with ambiguous genitalia at birth, no development of secondary sex characteristics in a boy, or primary amenorrhea in an adolescent girl (Hewitt and Warne 2012b). The reasons why the clinical presentation can vary so much is due to how much androgen production is affected, and also where this specifically occurs within the stages of testicular development.

3.8.2 Incidence

Due to the varying clinical presentations, the actual incidence is unknown, although it is estimated that hypospadias occurs in approximately 1 in every 125 male births (Hewitt and Warne 2012b), and complete androgen insensitivity syndrome (CAIS) is known to occur in 1 in every 20,000 births.

3.8.3 Tumour Risk

There is a risk of gonadal germ cell cancer in children with 46, XY DSD, and this needs to be explored sensitively. This can occur because there is a higher incidence of germ cell tumours in testes that have not developed properly, and Y chromosome material is present. (Hewitt and Warne 2012b) The risk varies in the specific 46, XY DSD condition, (Lee et al. 2006) and man-

agement can vary, whether it is close observation with regular endocrine clinic follow-up, biopsy, irradiation, or even a full gonadectomy (Lee et al. 2006). This remains controversial, and recent guidelines state that gonadectomy is not necessary before puberty for children with androgen insensitivity syndrome (Hughes et al. 2007). Gonadectomy, however, in partial androgen insensitivity syndrome (PAIS), is dependent on the sex of rearing.

3.8.4 Disorders of Testicular Development

In complete gonadal dysgenesis (or Swyer syndrome), children will look typically female, but have intra-abdominal 'streak' gonads, and will have some risk of potential tumour development. Streak gonads mean that the gonads (either testes or ovaries) are underdeveloped and do not function and are mainly made from fibrous tissue. In this instance, testes have not formed at all, or were 'lost' in early foetal development. Due to the lack of testes, there is therefore a lack of AMH, thereby resulting in external female looking genitalia, and also internal female reproductive structures (womb and fallopian tubes), but no ovaries (Wisniewski et al. 2012). The child with complex gonadal dysgenesis may be diagnosed if a girl presents with delayed puberty, and a routine karyotype has been performed. (Hewitt and Warne 2012b)

In contrast, in 46, XY partial or mixed gonadal dysgenesis, clinical presentation can vary, as there has been some degree of testicular development, so clitoromegaly may occur, ambiguous genitalia, or a very severe hypospadias (Ahmed et al. 2011). The internal Mullerian structures may or may not be present, and the testes can also vary in size and positioning. (Mendonca et al. 2009) Mixed gonadal dysgenesis signifies some degree of asymmetry in gonadal development, where there may be a 'dysgenetic' testis on one side, and a streak gonad on the other (Hewitt and Warne 2012b).

3.8.5 46, XY DSD Due to Defects in Androgen Synthesis or Action

There are four sub-categories that come under this specific classification: disorders of AMH and AMH receptors, luteinizing hormone (LH) receptor defects, androgen biosynthesis defects, and defects in androgen action.

3.8.5.1 Disorders of AMH and AMH Receptors

Gene mutations can occur which encode AMH or its receptor and can lead to persistent Mullerian duct syndrome (Hewitt and Warne 2012b), which means that Mullerian duct derivatives (i.e. a small womb and/or upper part of the vagina and fallopian tubes) are present because of the lack of action of AMH in foetal development. Phenotypically, the children will look male, but with cryptorchidism (absence of testes in the scrotum) and can present with herniation of the womb in the inguinal canal. A laparoscopic hysterectomy may need to be performed, as well as orchidopexy (surgery to bring the testes down into the scrotum.)

3.8.5.2 LH Receptor Defects

These conditions are more rare and consist of where LH receptor gene mutations have been identified that have an effect on LH receptor proteins, leading to Leydig cell hypoplasia (Ahmed et al. 2015), which means the Leydig cells in the testes (which make testosterone if LH is present), are underdeveloped. Children may present with micropenis, hypospadias, and a bifid scrotum (a deep cleft in the middle of the scrotum caused by incomplete labioscrotal fusion), leading to external genitalia to resemble a phenotypical female.

3.8.5.3 Androgen Biosynthesis Defects

Testosterone is metabolized by DHT, by an enzyme called 5 alpha reductase. If a child does not have enough of this enzyme, then DHT is not produced, therefore having an overall effect on

male development, resulting in a condition called 5 alpha reductase deficiency (5αRD). Phenotypically, children present with external female genitalia at birth, but will also have testes in the inguinal region, and internal male reproductive structures (Odame et al. 1992). Most children are reared as females and may undergo gonadectomy. However, if they have not had the surgery by the time they reach puberty, they will begin to virilize: their voices deepen, their phalluses enlarge, but they do not develop any facial or body hair, or acne. At puberty, these children may change their gender to male (Mendonca et al. 2010), and undergo testosterone replacement therapy, or use DHT cream (Odame et al. 1992). However, some may remain as females and subsequently undergo gonadectomy, vaginoplasty, and treatment with oestrogen therapy (Mendonca et al. 1996).

3.8.5.4 Defects in Androgen Action

If androgen receptors do not function properly, then the result may be varying degrees of androgen insensitivity, i.e. a lack of androgen response, and therefore incomplete virilization in a person with 46, XY make-up.

3.8.5.4.1 Complete Androgen Insensitivity Syndrome (CAIS)

CAIS is where a child is 46, XY, but is completely phenotypically female, and has intact testes. Clinical presentation may manifest in infancy, with inguinal hernia or labial swelling (containing the testes), which is rare (Hughes et al. 2012b), or in adolescence, when the adolescent presents to clinic with primary amenorrhea. She will have developed breasts, with a female body shape, which is due to increased oestrogen production by the aromatization of androgens. The testes in the inguinal area, if they have not been removed, may be uncomfortable (Hewitt and Warne 2009), but the risk of malignancy is significantly lower after puberty although lifelong surveillance is advised. To date, the topic of prophylactic gonadectomy in girls with CAIS is still very controversial (Mendonca et al. 2009)

Sex of rearing in CAIS is female, and the girls retain a female gender identity (Tadokoro-Cuccaro and Hughes 2014), with the girls tending to be satisfied with their sexual functioning in adult life, although this is dependent upon vaginal lengths and any previous surgeries (Wisniewski et al. 2000).

3.8.5.4.2 Partial Androgen Insensitivity Syndrome

Whereas gene mutations in androgen receptors are identified in more than 95% of women with CAIS, mutations are less common in PAIS (Mongan et al. 2015), and the phenotype depends on the severity of the androgen receptor dysfunction, and amount of androgen insensitivity. (Tadokoro-Cuccaro and Hughes 2014) However, there is usually some degree of genital ambiguity, and underdevelopment of the penis, severe hypospadias, and a bifid scrotum, which may contain gonads (Hughes et al. 2012b). Parental decisions on sex of rearing can be either as a boy or a girl, depending on the size of the phallus. If female, the testes may be removed to remove the possibility of changes due to testosterone, and again, the risk of germ cell tumours (Hewitt and Warne 2009), and the malignancy risk varies, depending on the location of the testes. If raised as male, then regular surveillance of the testes is essential, and recent data has shown that children with PAIS are raised as male (Tadokoro-Cuccaro and Hughes 2014) although breast development can occur at puberty. There may be a degree of gender dysphoria in adulthood, but again, this is dependent on phallus size and sex assignment at birth. (Mendonca et al. 2009)

3.9 Mixed Sex Chromosome DSD

Mixed sex chromosome DSD occurs when there is aneuploidy—i.e. an abnormal number of chromosomes and can be relatively common (47, XXX, 47, XXY, 45, X, or 47, XYY) or part of a mosaic karyotype (Hewitt and Warne 2012a). This is where one kind of karyotype is present in

some cells, and a different karyotype in other cells, for example, 45, X/46, XY.

3.9.1 45, X/46, XY

This is the most common karyotype which is linked with ambiguous genitalia, with CAH and AIS. The anatomy in affected children can result from gonadal dysgenesis, i.e. maldeveloped gonads. Where one gonad is *streak*, and the other is *dysgenetic*, the child is said to have *mixed gonadal dysgenesis*, so asymmetrical gonadal development (Biason-Lauber 2010; Hewitt and Warne 2009).

Children can present differently and have a varied phenotype, but those presenting with a male phenotype tend to be shorted and have dysgenetic testes (Hewitt and Warne 2012a). However, individuals with a female phenotype may have features similar to Turner syndrome, and most have short stature. They can present antenatally, at birth with ambiguous genitalia, or later in adolescence with short stature or delayed puberty, or even in the oncology setting with a germ cell tumour (Hewitt and Warne 2009). Due to this, it has been argued that gonadectomy should be performed in infancy if the child is to be reared as a female. If male, the testes need to be observed regularly with serum tumour markers, and potentially biopsy after puberty. Sex of rearing is dependent on the external genitalia phenotype.

3.9.2 46, XX/46, XY DSD

This is a chimeric genetic disorder, i.e. where a cell can be made up of different zygotes and can be referred to as chromosomal ovotesticular DSD. Because of this mixed sex chromosome, both ovarian and testicular tissues are found in either the same gonad, or the opposite gonad, just as in 46, XX ovotesticular DSD, or 46, XY ovotesticular DSD. The distribution amongst the gonads vary, but both ovarian follicles and seminiferous tubules are present.

Some women with ovotesticular DSD have become mothers, but no ovotesticular DSD males have become fathers (Hewitt and Warne 2012a), so it is clear that the ovary is dominant. If testicular tissue is not removed, then re-evaluation of endocrine status is essential at the time of puberty.

3.9.3 Klinefelter Syndrome: 47, XXY (See Chap. 10)

Klinefelter syndrome results from two or more X chromosomes in males. Symptoms can vary, and sometimes diagnosis is made when the adult male has investigations into infertility, due to high FSH and LH levels (Hewitt and Warne 2012a). There is decreased testicular function in most affected individuals, so smaller testes are present, and sometimes there may be some degree of learning difficulty (Biason-Lauber 2010).

3.9.4 Turner Syndrome: Monosomy X or 45, X or 45, XO (See Chap. 40)

Part or all of one of the X chromosomes is missing in Turner syndrome (TS). Girls with TS do not tend to come under the 'DSD' classification in clinical practice, but it sits within the consensus nomenclature, and many endocrine centres internationally will have their own TS clinics. There is a characteristic phenotype for girls with TS, including short stature and gonadal dysgenesis. Phenotypically, the girl with TS will also have female external genitalia. Diagnosis can be made antenatally, in infancy, in childhood where slow growth is noted, or adolescence, where the girl presents with delayed puberty and amenorrhea.

3.10 Management

3.10.1 Medical Management

It is common sense that the baby born with ambiguous genitalia needs urgent medical evaluation, including a thorough newborn physical examination (Devlin and Wilkinson 2008), specifically looking for any dysmorphic features (Warne and Hewitt 2012b). Urgent blood samples, as previously stated, need to be performed, as well as clinical monitoring in the immediate newborn period. If a diagnosis of salt wasting CAH is made, then commencing hydrocortisone and fludrocortisone is paramount, as well as salt replacement, (***See Chap. 35***) in order to prevent an adrenal crisis.

Hormone replacement therapy is needed in all females with mixed gonadal dysgenesis, or in genotypic males who have either had their testes removed, or where they experience testicular failure. (Warne and Hewitt 2012b)

3.10.2 Surgical Management

Surgical management of the child with a DSD remains controversial. Reconstructive surgery is performed for cosmetic reasons, to allow vaginal-penile intercourse, and to be able to achieve a 'sex-typical' manner for urination (i.e. for males to be able to stand whilst urinating) (Creighton et al. 2012). The controversy lies behind *if* to perform surgery, and *when.* Early infancy surgery is advocated by some as the procedure is easier, and that there is also less stigma for the family. However, some adults who have undergone surgery in this period are not happy with sexual function and satisfaction. (Creighton et al. 2012) Feminizing genitoplasty (clitoroplasty, vaginoplasty, and sometimes labiaplasty) is only performed in the most severe cases of virilization (Prader 3–5) (Lee et al. 2016), with an emphasis on preservation of erectile function and not cosmetic appearance being of utmost importance. The whole multidisciplinary team, alongside the parents, must be involved in decision-making for this aspect of care although guidelines do state to leave or delay as long as possible (Hughes et al. 2007).

Gonadectomies in under-virilized 46, XY DSD males also remain controversial as stated, and also in individuals with mixed sex chromosome DSD, where the gender identity may vary. (Vidal et al. 2010)

3.10.3 Psychosocial Management

Whilst it is important to focus on the physical aspects of a DSD, it cannot be underestimated that a vast input from psychological services is paramount. (Hughes et al. 2007) Support for the parents with a newborn with ambiguous genitalia is essential, as is support for the child and adolescent, irrespective of when a diagnosis is made. A psychologist can help the family with decisions regarding sex of rearing, timing of any surgery, and possible sex hormone replacement (Lee et al. 2012). Assistance can also be given in how best to tell friends and family on their child's diagnosis, and possible change of sex, especially if they were told something different antenatally (Loughlin 2012).

Support and guidance should be maintained as the child grows and develops, with caution given if there are any questions regarding gender identity. Gender role behaviour can be atypical in children with a DSD, but this is not necessarily an indicator for definitive gender re-assignment (Lee et al. 2016). Nevertheless, gender dysphoria can remain an issue (Hewitt and Warne 2009), especially in adults who may have had surgery as an infant/child, with an unsatisfactory outcome.

Psychological input is also necessary when contemplating diagnosis disclosure to the child or young person, regarding karyotype, gonadal status, and possible future fertility, and it is advised that acceptability and psychosocial adaptation is helped with honest disclosure (Hughes et al. 2007). The psychologist can work closely with the family on this, helping the child and family with counselling and guidance for an optimum quality of life.

3.11 The Multidisciplinary Team (MDT)

It is clear that the management of the child with a DSD, and their family, must take a full multidisciplinary approach (Hughes et al. 2007). Children with a DSD must be able to access centres of excellence which are fully equipped, manned, and experienced in dealing with DSD, and have a full team ready. An integrated team approach can be seen in Fig. 3.7. (Lee et al. 2016; Brain et al. 2010)

3.11.1 The Psychologist

This team member is so important and must be available to the child/young person and family from the very beginning (Moshiri et al. 2012). The diagnosis of a DSD can be unexpected and overwhelming, and, as discussed, advice and guidance can be given on how to verbalize concerns, how to deal with emerging emotions, and how to guide their child/young person in how to develop alongside their peers. Some families express the need to be in touch with other families experiencing the same, or similar, diagnosis (Boyse et al. 2014). Feelings of isolation or stigmatization can be reduced if the family feels they are not alone. Patient support groups can provide a valuable service to families, providing clear guidance and advice from other families (***See*** Sect. 3.12).

3.11.2 The Paediatric Endocrinologist

The paediatric endocrinologist will play a major role in the child's management and

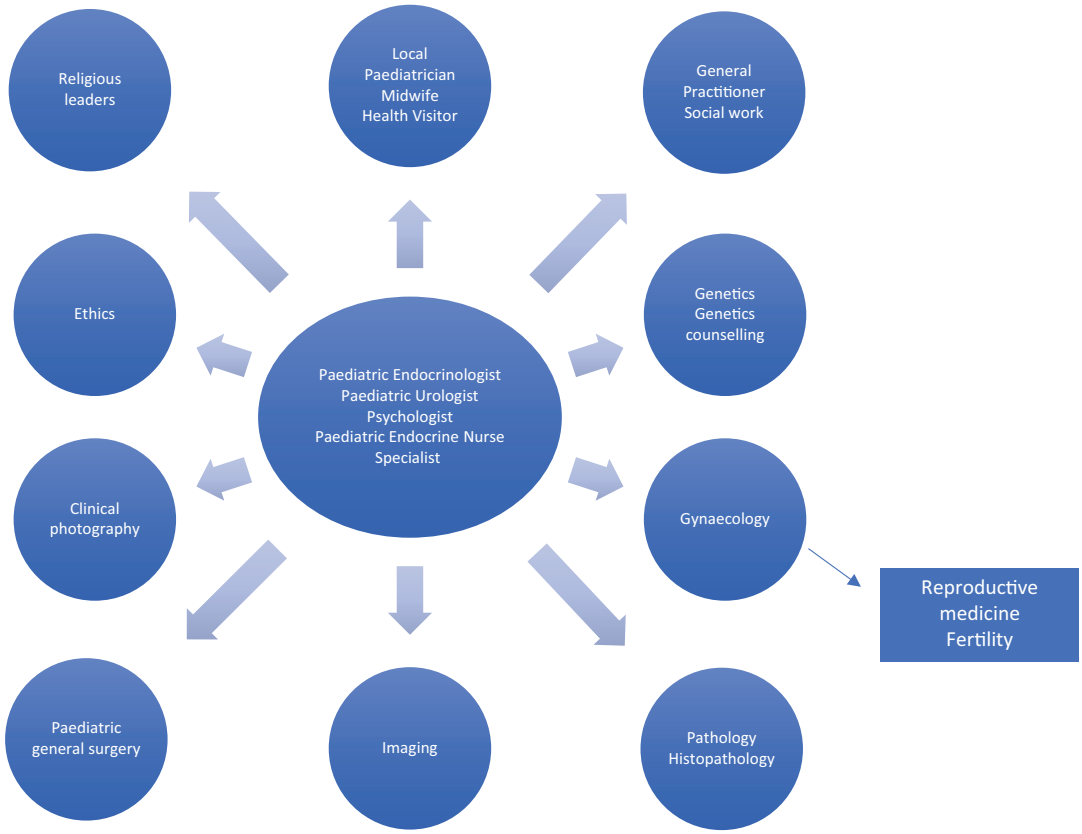


Fig. 3.7 An integrated approach

decision-making of any clinical investigations to be performed (Brain et al. 2010). They are often the first port of call when receiving a baby with ambiguous genitalia. As 46, XX CAH is the most common DSD (Hewitt and Warne 2009), management and education on adrenal crises, replacement, and other medication needs to be co-ordinated by a paediatric endocrine team. Further on, as the child grows, clinical monitoring may be necessary, with regard to hydrocortisone replacement and compliance, mineralocorticoid dosing and salt supplementation (Schaeffer et al. 2010), as well as growth monitoring and pubertal management, especially in individuals with non-functioning gonads (Lee et al. 2016). In addition, gonadotropin releasing hormone (GnRH) therapy may be required in young people where gender identity is uncertain, and also growth hormone therapy and oestrogen in girls with Turner syndrome.

3.11.3 The Paediatric Urologist/ Surgeon

The paediatric urologist also plays a key role. A joint meeting with the paediatric endocrinologist and family is ideal, so as to physically assess and clinically examine the baby with ambiguous genitalia together. As well as the external genitalia, the urologist should be able to palpate/locate the gonads. If any cosmetic surgery is to occur, it should be this experienced surgeon who deems it necessary and is confident in the eventual function and acceptable cosmetic appearance. Hypospadias repair also comes under their remit and also the need for gonadectomy if the risk of malignancy is high (Brain et al. 2010).

3.11.4 The Paediatric Endocrine Nurse Specialist (PENS)

The role of the nurse specialist has been advancing in specialist DSD services (Sanders et al. 2017). The PENS is key in just as a support for the child and family, but for liaising with the MDT, organizing investigations (Ahmed et al. 2015), and ensuring smooth running and organization of MDT clinical meetings. Much has been written on the role of the clinical nurse specialist ***(See Sect. 13)*** but the PENS multifaceted role can be seen in Fig. 3.8. It can be highlighted here that the role of the patient advocate is at the forefront of the multifaceted role. Families will often have the PENS' contact details and contact them directly with any queries or concerns, rather than waiting for their clinic appointment.

3.11.5 Other MDT Members

Although the healthcare professionals discussed are key (See Box 3.3), other team members play an important role in the care and management of a child with a DSD.

Gynaecologists can be available when the child is an infant to advise on potential outcome of any interventions and advise on pubertal management in girls (Brain et al. 2010). Biochemists can ensure swift management of expedited samples arriving in the laboratory and provide guidance on the investigation to be performed (Ahmed et al. 2015), likewise with genetics services. Ethicists, cultural and religious leaders can also not be discounted and conflicts may arise, and

Box 3.3 The MDT

"The Clinical Nurse Specialist (CNS) with specialist skills, knowledge and expertise, plays an essential role within the MDT in caring for children with a DSD condition, and their families. Providing psychological support is extremely important and requires the CNS to work in close liaison with the Clinical Psychologist to support these children from diagnosis throughout childhood into adolescence and adult life."

Nicky Nicoll, Clinical Nurse Specialist in Paediatric Endocrinology

Bristol Royal Hospital for Children, United Kingdom

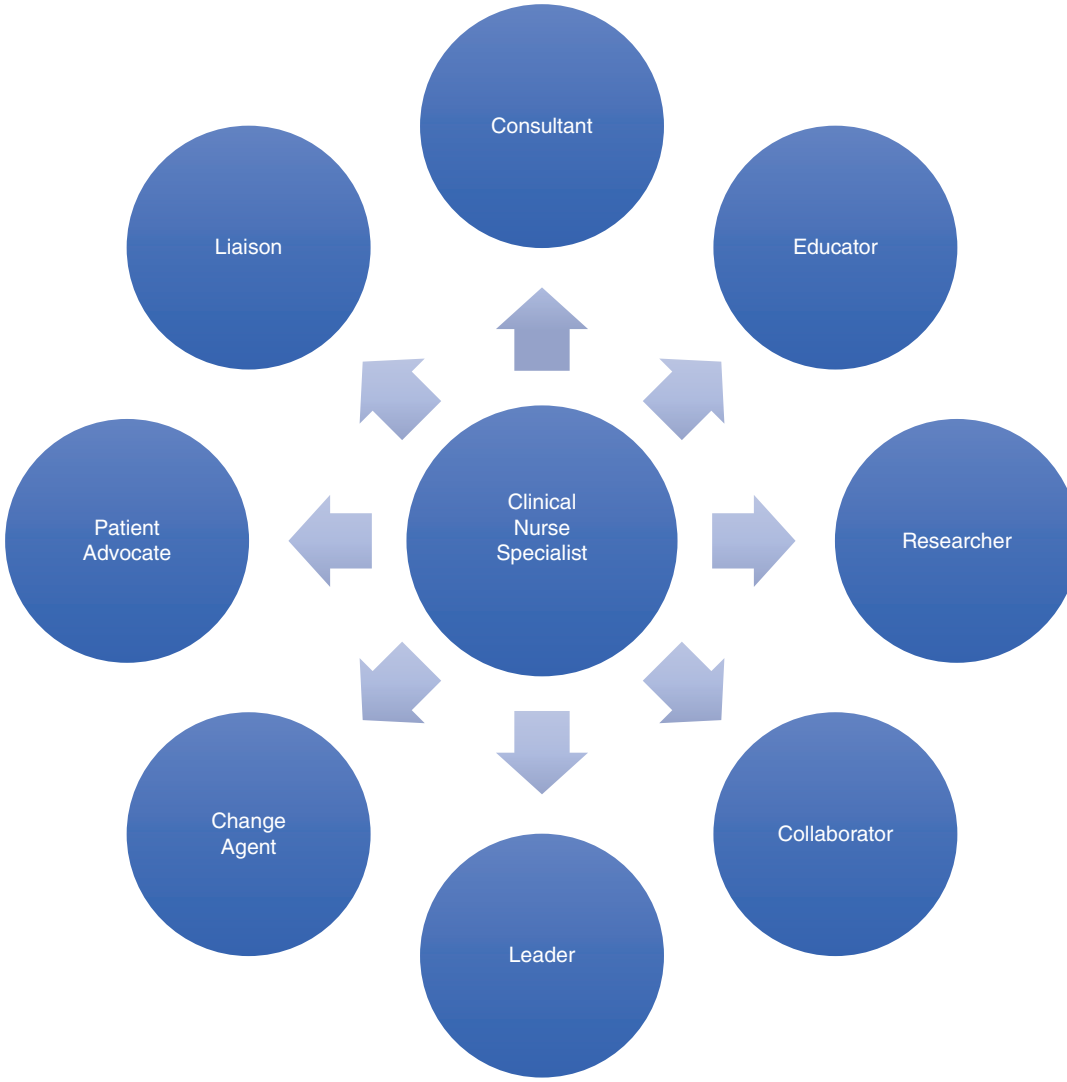


Fig. 3.8 The CNS role

ultimately clinical experts need to act in the best interests for the child (Brain et al. 2010). Ethical principles need to focus on the following: (Moshiri et al. 2012)

1. Minimizing physical risks
2. Minimizing psychological risks
3. Preserving potential fertility
4. Preserving the ability to have satisfactory sexual relationships
5. Respecting parental desires and beliefs

Respecting parental beliefs do need to be considered: for some, a DSD may still have a stigma, and social, religious, and cultural factors may play an important role when deciding on gender roles and gender assignment, especially in 5αRD. Religious leaders may also be able to offer the family continuing support.

Local teams need to be included, such as the local paediatrician, General practitioner (GP), or health visitors, who again can provide ongoing support to families. Links must be made with the GP who may be responsible for repeat medical

prescriptions and arrangements to be made with the local paediatrician for immediate paediatric ward access if the child suffers an adrenal crisis. Community nursing teams can also offer assistance in obtaining serum sodium samples in infancy if need be, plus GnRH analogue therapy or testosterone injections where necessary during adolescence. Multidisciplinary teamwork is essential all round to achieve the desired goals for the child and their family.

3.12 Nursing Considerations

3.12.1 At Diagnosis

PENS need to be aware from the beginning how to approach families who's child has been diagnosed with a DSD. Using 'medicalized' language can be daunting and confusing for parents (Sanders et al. 2011), so great care needs to be taken in using understanding terminology. Supporting literature is paramount, especially regarding how and when to administer hydrocortisone medication, or administering salt supplements, if the child has 46, XX CAH, plus also sick day and emergency management advice (***See Chap. 35***). Practicalities to consider for the initial meeting with the MDT during the first admission need to be considered and can be seen in Box 3.4.

The PENS can make contact with the family prior to the admission and explain the need for the practicalities outlined. Babies with ambiguous genitalia should begin their diagnostic pathway as soon as possible, usually within the first 5 days of life, so the PENS must be sensitive with the family who are going through an emotional upheaval regarding a potential diagnosis, notwithstanding having just given birth. The day of admission can be lengthy; as arrangements are usually made at short notice, the need for waiting times between visits from the MDT need to be explained, as they may be holding a clinic or in surgery, so their times need to be co-ordinated carefully. The PENS can act as an advocate and liaison for the family during the admission, enabling potential stressful situations to be eased, and being able to answer questions with non-medical jargon (Crissman et al. 2011).

Box 3.4 Admission Practicalities to Consider

For the ward:

- Is the baby ventilated/incubator dependent? (May need to go to NICU)
- Will the referring nurse stay? Does return transport need to be arranged?
- Is a private, comfortable area available for the baby and family?
- Ensure dynamic investigation medication is in stock on the ward (GnRH, synacthen, HCG).
- Arrange interpreter if needed
- Is there baby milk/bottles/teats/sterilizer/breast pump/fridge/freezer facilities available on the ward?
- Has the MDT been informed? Appointments may need to be made throughout the day.

For the parents:

- Bring maternal case notes/scans/reports
- Bring nappies, changes of baby clothes, milk, dummies, etc.
- Money for car parking
- Mobile phone charger/money for pay phone
- Advise that there may be long waits between MDT visits, so bring magazines/books, and also food and drink
- Bring a list of questions

3.12.2 Ongoing Management

Prior to discharge, the PENS needs to ensure that the family have a full understanding of the condition, and can offer further, less formal appointments with him/herself to continue with education and support. Again, the role of support groups and perhaps local families cannot be underestimated. Ongoing management in outpatient

clinics will be dependent on the specific DSD, but the PENS is the ideal healthcare professional to offer continuing support. Regular MDT meetings can be held monthly and provide updates to healthcare professionals on any emerging issues seen in the outpatient clinic.

3.12.3 Transition and Beyond

Management in adult services is very different to the paediatric world, and it is essential that a seamless transition, and not a simple transfer of care, is enabled (***See Chap. 6***) Long-term studies and data in young adults with DSD is still lacking (Crouch and Creighton 2014), but continued engagement with members of the MDT should be encouraged when meeting with adult services. Continued attendance can also provide healthcare professionals with valuable long-term data in order to be able to provide the best care in future generations of young people with a DSD.

For those young people with a DSD, if not diagnosed in infancy, the diagnosis may have been made recently, so their relationship with paediatric services may have been relatively short, if at all. Issues concerning genital examinations, gonadectomy, disclosure, and psychological issues need to be fully explored and appreciated (Crouch and Creighton 2014), with full realization that 'the patient' is now 'the adult', and all decisions to be made will now transfer to them (Schober et al. 2012). The MDT relationship, however, must not stop, and the journey should continue.

3.13 Conclusions

For children and young people with a DSD, and their families, diagnosis and further management can conjure up a great deal of uncertainty and confusion. Paediatric endocrine nurses need to have a good understanding regarding not just the aetiology and clinical aspects of the different DSD, but also the emotional and psychological impact that a diagnosis of a DSD can have. International consensus guidelines (Lee et al. 2006) have been formulated, and a new classification system has been formed, which has formed the framework of this chapter. Whilst the most common DSD have been discussed, the umbrella of DSD is vast, and not all conditions have been covered here. The emphasis, however, is on the full MDT working with and alongside the child and their family. The PENS needs to consider their multifaceted role and engage in the roles of not just 'clinical expert', but also as 'patient advocate' and 'liaison'. Parents want their child to live as 'normal' a life as possible (Crissman et al. 2011), and it is with the information and guidance from the PENS and the MDT that can hopefully enable seamless transition from diagnosis and beyond.

3.14 Useful Websites

www.dsdfamilies.org UK DSD support group

www.dsdteens.org UK DSD young persons support group

www.aissg.org UK Androgen Insensitivity Syndrome support group

www.aisdsd.org USA AIS support group for women and families

www.accordalliance.org International information page for healthcare professionals and families

www.heainfo.org USA Hypospadias and Epispadias Association

www.hypospadiasuk.co.uk UK Hypospadias support group

www.livingwithcah.com UK CAH support group

www.tss.org.uk UK Turner Syndrome support group

www.turnersyndrome.org USA Turner Syndrome support group

www.ksa-uk.co.uk. UK Klinefelter Syndrome support group

www.genetic.org USA Klinefelter Syndrome support group

www.livingmrkh.org.uk UK MRKH support group

www.MRKH.orgUSA MRKH support group

www.verity-pcos.org.uk UK PCOS support group

www.isna.org USA Intersex Society of North America

References

Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 2010;24(2):197–218.

Ahmed SF, Achermann JC, Arlt W, Balen AH, Conway G, Edwards ZL, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol. 2011;75(1):12–26.

Ahmed SF, Achermann JC, Arlt W, Balen AH, Conway G, Edwards ZL, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin Endocrinol. 2015;0:1–18.

Biason-Lauber A. Control of sex development. Best Pract Res Clin Endocrinol Metab. 2010;24(2):163–86.

Boyse KL, Gardner M, Marvicsin DJ, Sandberg DE. "It was an overwhelming thing": parents' needs after infant diagnosis of CAH. J Pediatr Nurs. 2014;29(5):436–41.

Brain CE, Creighton SM, Mushtaq I, Carmichael PA, Barnicoat A, Honour JW, et al. Holistic management of DSD. Best Pract Res Clin Endocrinol Metab. 2010;24(2):335–54.

Butler G, Kirk J. Paediatric endocrinology and diabetes. Oxford: OUP Press; 2011.

Creighton S, Chernausek SD, Romao R, Ransley P, Salle JP. Timing and nature of reconstructive surgery for disorders of sex development - introduction. J Pediatr Urol. 2012;8(6):602–10.

Crissman HP, Warner L, Gardner M, Carr M, Schast A, Quittner AL, et al. Children with disorders of sex development: a qualitative study of early parental experience. Int J Pediatr Endocrinol. 2011;2011(1):10.

Crouch NS, Creighton SM. Transition of care for adolescents with disorders of sex development. Nat Rev Endocrinol. 2014;10(7):436–42.

Davies K. Disorders of sex development–ambiguous genitalia. J Pediatr Nurs. 2016;31(4):463–6.

Devlin JK, Wilkinson A. Routine examination of the neonate. J Clin Examination. 2008;5:16–21.

Hewitt J, Warne GL. Management of disorders of sex development. Pediatr Health. 2009;3(1):1–65.

Hewitt JK, Warne GL. Mixed sex chromosome and ovotestiular DSD. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012a. p. 81–7.

Hewitt JK, Warne GL. 46, XY DSD. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012b. p. 63–80.

Hughes IA, Nihoul-Fekete C, Thomas B, Cohen-Kettenis PT. Consequences of the ESPE/LWPES guidelines for diagnosis and treatment of disorders of sex development. Best Pract Res Clin Endocrinol Metab. 2007;21(3):351–65.

Hughes IA, Morel Y, McElreavey K, Rogol A. Biological assessment of abnormal genitalia. J Pediatr Urol. 2012a;8(6):592–6.

Hughes IA, Davies JD, Bunch TI, Pasterski V, Mastroyannopoulou K, MacDougall J. Androgen insensitivity syndrome. Lancet. 2012b;380(9851):1419–28.

Ishii T, Matsuo N, Sato S, Ogata T, Tamai S, Anzo M, et al. Human chorionic gonadotropin stimulation test in prepubertal children with micropenis can accurately predict Leydig Cell function in pubertal or postpubertal adolescents. Horm Res Paediatr. 2015;84(5):305–10.

Kinsman L, Rotter T, James E, Snow P, Willis J. What is a clinical pathway? Development of a definition to inform the debate. BMC Med. 2010;8:31.

Kobayashi A, Behringer RR. Developmental genetics of the female reproductive tract in mammals. Nat Rev Genet. 2003;4(12):969–80.

Lee PA, Houk CP, Ahmed SF, Hughes IA. Society icwtpitICCoIobtLWPE, Endocrinology tESfP. Consensus statement on management of intersex disorders. Pediatrics. 2006;118(2):e488–500.

Lee P, Schober J, Nordenstrom A, Hoebeke P, Houk C, Looijenga L, et al. Review of recent outcome data of disorders of sex development (DSD): emphasis on surgical and sexual outcomes. J Pediatr Urol. 2012;8(6):611–5.

Lee PA, Nordenstrom A, Houk CP, Ahmed SF, Auchus R, Baratz A, et al. Global disorders of sex development update since 2006: perceptions, approach and care. Horm Res Paediatr. 2016;85(3):158–80.

Loughlin E. The family. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012. p. 193–201.

Mendonca BB, Inacio M, Costa EMF, Arnhold IJP, Silva FAQ, Nicolau W, et al. Male pseudohermaphroditism due to steroid 5 alpha reductase deficiency: diagnosis, psychological evaluation and management. Medicine. 1996;75(2):64–76.

Mendonca BB, Domenice S, Arnhold IJ, Costa EM. 46,XY disorders of sex development (DSD). Clin Endocrinol. 2009;70(2):173–87.

Mendonca BB, Costa EM, Belgorosky A, Rivarola MA, Domenice S. 46,XY DSD due to impaired androgen production. Best Pract Res Clin Endocrinol Metab. 2010;24(2):243–62.

Mongan NP, Tadokoro-Cuccaro R, Bunch T, Hughes IA. Androgen insensitivity syndrome. Best Pract Res Clin Endocrinol Metab. 2015;29(4):569–80.

Moshiri M, Chapman T, Fechner PY, Dubinsky TJ, Shnorhavorian M, Osman S, et al. Evaluation and management of disorders of sex development: multidisciplinary approach to a complex diagnosis. Radiographics. 2012;32(6):1599–618.

Odame I, Donaldson MD, Wallace AM, Cochran W, Smith PJ. Early diagnosis and management of 5a-reductase deficiency. Arch Dis Child. 1992;67:720–3.

Pasterski V, Prentice P, Hughes IA. Consequences of the Chicago consensus on disorders of sex development (DSD): current practices in Europe. Arch Dis Child. 2010;95(8):618–23.

Raine JE, Donaldson MDC, Gregory JW, van Vliet G, editors. Practical endocrinology and diabetes in children. 3rd ed. Chichester: Wiley - Blackwell; 2011.

Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab. 2011;25(2):221–38.

Rodie M, McGowan R, Mayo A, Midgley P, Driver CP, Kinney M, et al. Factors that influence the decision to perform a karyotype in suspected disorders of sex development: lessons from the Scottish genital anomaly network register. Sex Dev. 2011;5(3):103–8.

Rothkopf AC, John RM. Understanding Disorders of Sexual Development. J Pediatr Nurs. 2014;29(5):e23–34.

Sanders C, Carter B, Goodacre L. Searching for harmony: parents' narratives about their child's genital ambiguity and reconstructive genital surgeries in childhood. J Adv Nurs. 2011;67(10):2220–30.

Sanders C, Edwards Z, Keegan K. Exploring stakeholder experiences of interprofessional teamwork in sex development outpatient clinics. J Interprof Care. 2017;31(3):376–85.

Schaeffer TL, Tryggestad JB, Mallappa A, Hanna AE, Krishnan S, Chernausek SD, et al. An evidence-based model of multidisciplinary care for patients and families affected by classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Int J Pediatr Endocrinol. 2010;2010:692439.

Schober J, Nordenstrom A, Hoebeke P, Lee P, Houk C, Looijenga L, et al. Disorders of sex development: summaries of long-term outcome studies. J Pediatr Urol. 2012;8(6):616–23.

Tadokoro-Cuccaro R, Hughes IA. Androgen insensitivity syndrome. Curr Opin Endocrinol Diabetes Obes. 2014;21(6):499–503.

Vidal I, Gorduza DB, Haraux E, Gay CL, Chatelain P, Nicolino M, et al. Surgical options in disorders of sex development (dsd) with ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 2010;24(2):311–24.

Warne GL, Hewitt JK. 46,XX disorders of sex development. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012a. p. 53–61.

Warne GL, Hewitt JK. The medical management of disorders of sex development. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012b. p. 159–72.

White S, Sinclair A. The molecular basis of gonadal development and disorders of sex development. In: Hutson JM, Warne GL, Grover SR, editors. Disorders of sex development: an integrated approach to management. Wurzberg: Springer; 2012. p. 1–9.

Wisniewski AB, Migeon CJ, HFL M-B, Gearhart JP, Berkovitz GD, Brown TR, et al. Complete androgen insensitivity syndrome: long-term medical, surgical, and psychosexual outcome. J Clin Endocrinol Metab. 2000;85(8):2664–9.

Wisniewski AB, Chernausek SD, Kropp BP. Disorders of sex development: A guide for parents and physicians. Baltimore, MD: Johns Hopkins University Press; 2012.

Woodward M, Patwardhan N. Disorders of sex development. Surgery (Oxford). 2010;28(8):396–401.

Puberty: Normal, Delayed, and Precocious

4

Eileen Pyra and Wendy Schwarz

Contents

4.1 **Pubertal Development** 65
4.1.1 Introduction 65
4.1.2 Regulation of Puberty 65
4.1.3 Physical Changes During Puberty 66
4.1.4 Development of Secondary Sexual Characteristics 67
4.1.5 Nursing Considerations 68
4.1.6 Behavior Changes Associated with Puberty 69
4.1.7 Delayed Puberty 69
4.1.8 Precocious Puberty 76
4.1.9 Conclusions 83

References 83

Abstract

Puberty is an important developmental stage for transition from childhood to adulthood. The process of puberty involves hormonal, physical, and psychological changes. Puberty is influenced by genetic and environmental aspects. The timing of puberty varies greatly between ethnicity, geography, and healthy individuals. Within the scope of puberty, it is considered precocious if the female is less than 8 years of age, and the male less than 9 years of age. Puberty is considered delayed if the female is 13 years of age and the male is 14 years of age with no pubertal development. Nurses' understanding of normal puberty and its variants during this time is crucial for helping support children and their families. Whether that be support for when normal puberty occurs or if it's occurring too early or too late. The diagnosis, treatment, and nursing implications of either precocious or delayed puberty will be discussed in this chapter.

Keywords

Puberty · Delayed puberty · Precocious puberty · Adolescent

E. Pyra · W. Schwarz (✉)
Alberta Children's Hospital, Endocrine Clinic, Calgary, AB, Canada
e-mail: eileen.pyra@ahs.ca; wendy.schwarz@ahs.ca

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_4

Abbreviations

BA	Bone age
BMI	Body mass index
CA	Chronologic age
CAH	Congenital adrenal hyperplasia
CPP	Central precocious puberty
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulphate
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
HH	Hypogonadotropic hypogonadism
HPG	Hypothalamic pituitary gonad
HPO	Hypothalamic pituitary ovarian
IGF-1	Insulin-like growth factor 1
IM	Intramuscular
IPP	Incomplete precocious puberty
IU/L	International units/L
LH	Luteinizing hormone
MAS	McCune Albright syndrome
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
NHANES-III	National Health and Nutrition Examination Survey
OCP	Oral contraceptive pills
PA	Premature adrenarche
PDS	Pubertal Development Scale
PPP	Peripheral precocious puberty
PROS	Paediatric Research in Office Settings
PT	Premature thelarche
PWS	Prader-Willi syndrome
SC	Subcutaneous

Key Terms

- **Adrenarche:** increases in the secretion of adrenal androgen precursors, mainly dehydroepiandrosterone (DHEA) facilitate the appearance of pubic/axillary hair.
- **Androgen:** is responsible for sexual development in males and is produced by the testes. Women have smaller amounts of androgens that are produced in the ovaries. The most well-known androgen is testosterone, which is responsible for developing the secondary sex characteristics in men.
- **Estradiol:** is a steroid hormone made from cholesterol. The main function is to mature and maintain the female reproductive system. Estradiol also promotes development of breast tissue and increases bone and cartilage thickness.
- **Follicle Stimulating Hormone (FSH):** is released by the anterior pituitary, for pubertal development and function of the ovaries and testes. In females, this hormone stimulates the growth of ovarian follicles. In males, follicle stimulating hormone acts on the Sertoli cells of the testes to stimulate sperm production (spermatogenesis).
- **Gonadotropin Releasing Hormone (GnRH):** is produced and secreted by the hypothalamus to the anterior pituitary, where it stimulates the production of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH).
- **Hypothalamic-Pituitary-Gonadal Axis (HPG):** is the coordinated production of GnRH, LH, FSH, and sex steroids (testosterone and estrogen). The hypothalamus releases gonadotropin-releasing hormone (GnRH) in a pulsatile fashion. In response, the pituitary releases follicle stimulating hormone (FSH) and luteinizing hormone (LH), both of which ultimately control gonadal function.
- **Luteinizing Hormone (LH):** is a gonadotropic hormone produced in the anterior pituitary. In males, LH stimulates Leydig cells in the testes to produce testosterone. In females, LH binds to receptors in ovaries to regulate the production eggs.
- **Pubarche:** is the appearance of pubic hair as the results of rising levels of androgens secreted by the adrenal glands.
- **Spermarche:** is sperm development in boys, at puberty. Spermarche typically occurs between ages 11–15. It starts with the beginning of the development of secondary sexual characteristics, which in boys includes facial hair, voice deepening, and body growth.
- **Testosterone:** Testosterone also exerts effects all around the body to generate male

characteristics such as increased muscle mass, enlargement of the larynx to generate a deep voice, and the growth of facial and body hair.

- **Thelarche:** is the onset of female breast development. Isolated breast development in girls younger than 8 years of age is considered premature thelarche. It usually is benign but may signify a more complicated condition.

Key Points

- Puberty is an important developmental stage for transition from childhood to adulthood that involves hormonal, physical, and psychological changes.
- There is increasing evidence of the impact of genetic and environmental influences on puberty. Recent advances have helped to elucidate the genetic determinants of pubertal timing.
- Delayed puberty can be sorted into three main categories: hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, and functional (or transient) hypogonadotropic hypogonadism.
- The main goal for the management of precocious puberty is to prevent early fusion of the epiphyseal growth plate allowing for the attainment of adult height within the individual's genetic potential.
- Nurses have a key role in early identification of abnormalities in pubertal development and referral to pediatric endocrinologist for evaluation.

4.1 Pubertal Development

4.1.1 Introduction

Puberty is a developmental phase that is the result of a process of complex transformations involving both physical and psychological maturation. This process involves a period of rapid growth, development of secondary sexual characteristics, maturation of reproductive functions, bone mass accrual, as well as psychological and cognitive development. Genetics, hormones, health status, and environmental factors can influence this process (Lifshitz 2006). Although puberty usually occurs in a predictable pattern, it can be variable. Concerns about puberty and the changes that occur during puberty are some of the most common questions for nurses caring for children.

4.1.2 Regulation of Puberty

4.1.2.1 Neuroendocrine Regulation of Puberty

Activation of the hypothalamic-pituitary-gonadal (HPG) axis by gonadotropin releasing hormone (GnRH) results in the anterior pituitary releasing luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH primarily acts on the interstitial cells of the gonads stimulating the production of androgens, while FSH primarily stimulates the ovarian follicles to produce estradiol, inhibin, and gametes (egg and sperm), GnRH release is pulsatile in nature and occurs mostly at night in early puberty. As puberty progresses, the GnRH develops into an adult pattern throughout the day (Wolf and Long 2016).

4.1.2.2 Genetics

A large number of genes are involved in the complex process of initiating puberty. The discovery of Kisspeptins and G-protein has increased our understanding of the GnRH control mechanisms. Kisspeptins are series of peptides that are required for the activation of the hypothalamic-pituitary-gonadal (HPG) axis. During puberty, the *KISS1* is activated and generates the pulsatile GnRH to activate the HPG-axis (Kaur et al. 2012).

4.1.2.3 Timing of Puberty

The timing of puberty varies widely between individuals but tends to run closely within families. The first activation of the HPG system occurs in mid gestation. This is followed by a second activation in early postnatal life, sometimes referred to as "mini-puberty". The third activation occurs at the time of puberty. The onset of puberty

could either be the result of the disappearance of inhibitory factors, or the occurrence of stimulatory inputs, or both (Gajdos et al. 2010). Timing varies in the general population and is influenced by genetic and environmental factors Palmert and Hirschhorn (2003) suggest that 50–80% of the variations seen in pubertal timing is caused by genetic factors. Even taking into account the environmental factors, genetic factors are thought to play a more pivotal role.

Timing also varies within different population groups. From the National Health and Nutrition Examination Survey (NHANES III), the difference in Caucasian girls' age of puberty is 10.65–12.55 years, African American 9.7–12.6 years, and Mexican American 10.05–12.25 years. The timing of puberty in boys has not been as well documented. From the NHANES III study, it was found that Caucasian boys reached Tanner II pubic hair at median age of 12 years, African American at 11.2 years, and Hispanic at 12.3 years (Krieger et al. 2015). Despite ongoing discussion, data remains inconsistent on whether there is a trend toward earlier puberty. However, if there is a change in socioeconomic status, it may shift the age of puberty (Lahoti and Sills 2015).

4.1.2.4 Nutrition

Nutritional factors have been known to have an influence on pubertal timing. Nutrition during fetal life and early postnatal life has shown to have effects on physiologic development throughout life (Lifshitz 2006). Body mass index (BMI) is an important factor in the timing of puberty. A higher BMI is associated with early maturation; lower BMI is associated with delayed pubertal development.

4.1.2.5 Endocrine Disruptors

Endocrine disruptors are natural or synthetic environmental chemicals or pollutants that can alter or affect the normal physiologic endocrine process. Endocrine disruptors bind to hormone receptors and impede their function, by way of suppressing or activating the hormonal activity. These chemicals and pollutants are found in agriculture, cleaning products, cosmetics, plastic compounds, and are stored in fat tissue (Lahoti and Sills 2015).

4.1.3 Physical Changes During Puberty

4.1.3.1 Growth

The pubertal growth spurt accounts for 15–18% of final adult height. It is the fastest period of growth after the first 2 years of life (Lifshitz 2006). Estrogen, produced in the ovaries of girls and the aromatization of androgens in boys, accounts for the accelerated growth during puberty. The pubertal growth spurt is also the result of gonadal sex steroids, growth hormone, and insulin-like growth factor 1 (IGF-1). The growth spurt in girls coincides with the start of breast development (Tanner II). In boys, the growth spurt starts with a testicular volume of 10–12 mL (Tanner III). Thus, the growth spurt is a later pubertal development for boys, occurring an average of 2 years later than girls. Along with increase in linear growth, there is an increase in weight and percentage of body fat. Leptin regulates the amount of body fat. Leptin is considered the link between adipose tissue and growth (Wolf and Long 2016).

4.1.3.2 Bone Maturation

During puberty, bone maturation accelerates and epiphysis becomes fused. This maturation appears to parallel pubertal development (Lazar and Phillip 2012). Bone age is assessed based on the changes in the width of the epiphysis, the appearance of ossification centers, capping of the epiphysis and the fusion of the epiphysis (Weise et al. 2001). Bone age X-rays are universally accepted as a diagnostic tool, due to the minimal radiation to the bone and gonads. The most commonly used method for determining bone age is Greulich and Pyle Atlas (1959). This is a simple way of comparing the patient's X-ray of the left hand and wrist to that of the corresponding age and gender of the patient. It should be kept in mind that this is a subjective analysis. Greulich and Pyle are also based on Caucasian children in upper middle class in 1931–1942

and thus may be inaccurate assessment of other ethnicities.

4.1.3.3 Body Composition

In females during puberty, there is an overall increase in lean body mass; however, the percentage of lean body mass decreases due to the increase in adipose mass. The percentage of body fat is related to menstrual function. In males, lean body mass increases during puberty, which reflects increasing muscle mass and decreasing adiposity (Freedman et al. 2002).

4.1.4 Development of Secondary Sexual Characteristics

4.1.4.1 Female

Puberty onset for girls is generally within the range of age 8–13 years. Euling et al. have reported a decline in the age of onset of puberty since 1940. This has been linked to increasing rates of obesity (Krieger et al. 2015; Freedman et al. 2002).

Acceleration in growth is typically the first manifestation of puberty in girls. The second sign of puberty is breast budding, known as thelarche. Menarche typically occurs 2–2.5 years after thelarche. At the same time, pubic hair, known as pubarche, occurs as the result of increased adrenal androgen secretion. However, in as many as 20% of girls pubarche may precede thelarche (Lifshitz 2006).

The hormonal changes are initiated by the process of releasing gonadotropin-releasing hormone (GnRH) from the hypothalamus. LH, FSH, and estradiol levels will increase before any physical changes are seen. The levels of these hormones will further increase throughout puberty resulting in the physical changes that characterize puberty. These changes include breast maturity, genital growth (labia majora), maturation of the vaginal/uterus/endometrium, and change in body composition (female fat pattern). Growth of the uterus and elongation of the vagina occur at the same time that multiple follicles are developing in the ovaries. FSH promotes the growth of ovarian follicles and LH promotes the ovary to produce estradiol (Lifshitz 2006).

Menarche refers to the first menstrual bleed and typically occurs at Tanner stage IV breast and is rare before Tanner stage III (Lahoti and Sills 2015). The timing of menarche is influenced by genetic and environmental factors. With estradiol production, the vaginal mucosa is stimulated resulting in a thin white vaginal discharge. This process called leucorrhea is typically seen 6–12 months before menarche. The first menarche is often not associated with ovulation. In the first 1–2 years, the cycles are anovulatory and irregular. Cycles typically last 2–7 days and the average blood loss is 30 mL, ranging from 20 to 60 mL. There is international variation on the age of menarche related to socioeconomic conditions, nutrition, and access to health care (Gajdos et al. 2010). On average, girls may gain 4–6 cm of height after menarche (Fig. 4.1) (Lifshitz 2006).

Breast development is estrogen driven and may be asymmetrical and can be tender to palpation. The NHANES III study as well as the US Paediatric Research in Office Settings (PROS) have reported that breast development in girls occurs earlier than previously reported. Both studies reported earlier breast development; however, they did not find any decrease in the age of menarche. Other studies, from Denmark, China, and Europe have also shown a decrease in the age of breast development (Wolf and Long 2016; Lahoti and Sills 2015).

4.1.4.2 Male

Boys typically begin puberty between 9 and 14 years of age. Puberty is marked by testicular enlargement, penile length increase, and pubic hair growth (pubarche). There is a progressive rise in LH, FSH, and testosterone as a result of the upregulating of the hypothalamic-pituitary-testicular axis (Freedman et al. 2002). Boys typically identify pubic hair growth as the first identified sign of puberty. However, an increase in testicular size/volume, >3 mL, is the first physical sign of puberty. There can be an asymmetrical development of the testes. Axillary hair begins at mid-puberty due to the increase in androgen secretion. Other androgen-sensitive

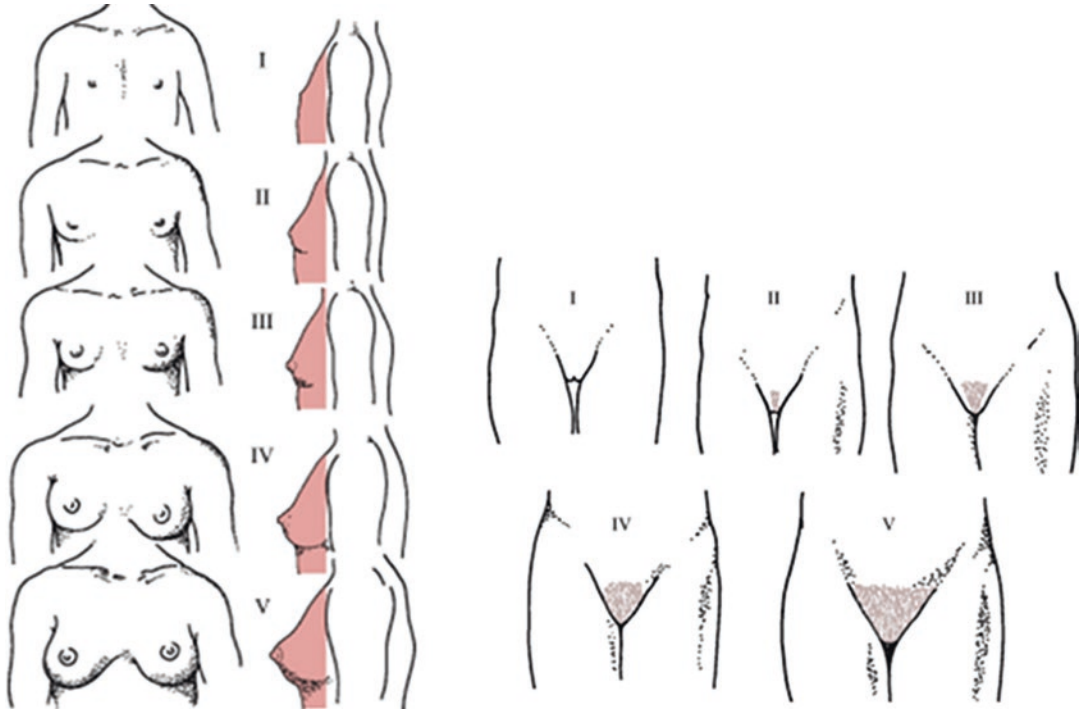


Fig. 4.1 Tanner stage of pubertal development

areas, including face, chest, back, arms, and legs, will then begin showing signs of hair development. Spermarche is the onset of sperm production. The average age of spermarche is 14 years and Tanner III for testes and pubic hair development (Lifshitz 2006; Wolf and Long 2016).

Normal variations in androgen and estrogen ratios can lead to pubertal gynecomastia. This can occur in approximately 50% of boys and typically resolves within 2 years (Lahoti and Sills 2015). It has also been speculated that it may occur in up to two-thirds of pubertal boys. It generally occurs in early or mid-puberty and will plateau at approximately 1 year with regression by 18 months. This is a common variant in normal pubertal development and does not usually indicate underlying abnormalities. However, pathologic causes should be considered (Lifshitz 2006).

4.1.5 Nursing Considerations

Assessment of sexual development or Tanner staging (or "sexual maturity rating" is becoming a more accepted term) provides a consistent tool to evaluate the progression of puberty (Marshall and Tanner 1969). Historically, puberty has been assessed by a physical exam, with the adolescent undressed. With the perceived intrusiveness of this examination, the Pubertal Development Scale (PDS) has been developed (Wolf and Long 2016). This tool focuses on the development of secondary sexual characteristics including: body hair, skin changes, growth spurt, facial hair, deepening of the voice in boys, and breast development and menarche in girls. The characteristics are rated on a 4-point scale. However, concerns have been raised with this form of assessment over the possibility of inaccurate reporting by the teen and the possible regression of the teen's self-reporting.

Teaching about testicular self-examination should be initiated during puberty. Testicular examination is helpful to identify testicular anomalies, as well as assessing pubertal progression.

It is important to properly examine breast tissue to distinguish actual breast tissue versus adipose tissue in the moderately to severely obese pubertal

female or male. For male gynecomastia, a thorough history should include whether there is drug use. Marijuana has been documented to cause gynecomastia in boys (Lahoti and Sills 2015).

Growth velocity is important to monitor in all children during puberty. Variation, or deviation, from the expected growth pattern may lead to detection of medical issues. Systemic illness may first present with poor growth before the onset of symptoms (i.e., inflammatory bowel disease, Celiac). The normal variation of growth between the sexes may cause concern for parents. These parents may be unaware of the different timing of the pubertal growth spurt between males and females (Lifshitz 2006).

Menses is often referred to as the fourth vital sign. What is a normal menstrual period? Talk to your patient to assess the frequency or regularity of their cycles, as well as the adolescent's understanding of their cycles. The World Health Organization international multicenter study found that the timing between first cycle was longer than 40 days in 38% of the girls, with the median being 34 days (Adams Hillard 2014; Bourguignon and Juul 2012). Cycles should increase in regularity with time. If they do not, then other pathology should be investigated, i.e., polycystic ovarian syndrome, eating disorders, thyroid disease or primary ovarian insufficiency. Chronic menstrual abnormalities may be associated with future health risks such as anemia, low bone density, and metabolic and cardiovascular risk (Fig. 4.2) (Wolf and Long 2016).

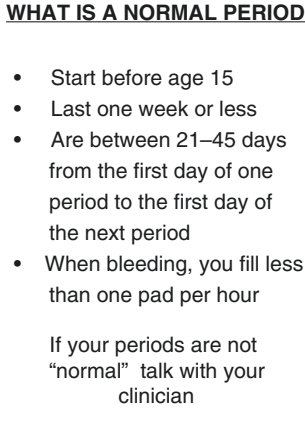


Fig. 4.2 Questions to assess menses

4.1.6 Behavior Changes Associated with Puberty

Biologic as well as social processes influence the behavior changes that occur during puberty. For the purpose of this chapter, we will focus on the biologic process. Hormonal changes affect anatomy and physiology as well as psychological changes through changes in the brain structure and function (Bourguignon and Juul 2012; Berenbaum et al. 2015; Giedd 2015). Adolescent psychological development is influenced by different aspects of puberty. Hormone-behavior links depend on context. As an example, a boy with high salivary testosterone levels may have genetic reasons or may have recently participated in an activity that increases testosterone (i.e., sexual activity or high intensity sports) (Duke et al. 2014). Studies suggest a relationship between testosterone and aggressive behavior, but results are not consistent across studies. Similarly, studies report a correlational relationship between estrogen and depression or aggressive tendencies in girls, but more research is also needed (Susman et al. 2003, 2010).

4.1.7 Delayed Puberty

Delayed puberty is defined as the lack of pubertal development by an age that is 2–2.5 standard deviations beyond the population mean (Abitbol et al. 2016). Delayed puberty affects approximately 2% of adolescents and can be a source of anxiety for the adolescent and their family. The accepted norms for delayed puberty are a chronological age of 13 for girls and 14 for boys. A delay in progression from onset of menarche of >4–5 years is considered prolonged. Delayed puberty may result from the dysfunction of the HPG or from secondary causes such as chronic illness or malnutrition (Palmert and Dunkel 2012).

4.1.7.1 Etiology of Pubertal Delay

Although the differential diagnosis for delayed puberty is varied, the most common cause is constitutional delay for both girls and boys.

Constitutional delay is seen when the HPG axis is delayed and the puberty starts at the far end of the normal spectrum. Constitutional delay should be a diagnosis of exclusion after other causes have been ruled out (Palmert and Dunkel 2012).

There is increasing evidence of the impact of genetic and environmental influences on puberty. Several genes have recently been identified as sources for hypothalamic dysfunction. These include, but are not limited to: leptin receptor deficiency mutations, kisspeptins, kisspeptin receptor *GPR54*, *GNRHR* gene mutations, X-linked Kallman syndrome, and transcription factor mutations (i.e., *PROP1*, *HESX1*) (Fenichel 2012).

Leptin receptor deficiency mutations are associated with delayed puberty. Leptin receptors are present in the hypothalamic region and act as a bridge between reproductive function and energy balance. Replacement of leptin can induce puberty if given at the correct timing in puberty (Farooqi et al. 1999).

Kisspeptins (*KISS1*) are series of peptides that are activated and generate pulsatile GnRH and enable the HPG-axis activation (recent advances in understanding and management). With the *KISS1* receptor mutation primary hypogonadotropic hypogonadism occurs (Kaur et al. 2012).

Environmental exposures such as chemicals (natural or synthetic) can alter normal physiologic endocrine processes. This alteration is often referred to as endocrine disruptors. The chemicals and pollutants accumulate in the environment and are introduced into the body through a variety of ways (e.g., through water, air, foods). These endocrine disruptors bind to hormone receptor and affect the signalling, resulting in suppression (or activation) of that hormone (Howell and Shalet 1998).

4.1.7.2 Categories of Pubertal Delay

Delayed puberty can be sorted into three main categories*: hypergonadotropic* hypogonadism, *hypogonadotropic* hypogonadism, and *functional* (or transient) hypogonadotropic hypogonadism.

Hypergonadotropic hypogonadism is characterized by elevated levels of LH and FSH due to lack of negative feedback from the gonads, while hypogonadotropic hypogonadism is characterized by low levels of LH and FSH due to pituitary or hypothalamic disorders. Functional hypogonadotropic hypogonadism is characterized by delayed maturation of the HPG axis due to an underlying medical condition (Palmert and Dunkel 2012).

Hypergonadotropic hypogonadism may be genetic or acquired. It is categorized by elevated FSH and LH, due to gonadal failure. This failure is caused by the HPG axis being activated and the feedback loop from the sex steroids to the hypothalamus is not present, resulting in elevated LH and FSH. Genetic causes include: Turner syndrome, gonadal dysgenesis, or androgen receptor mutations. Acquired causes include: exposure to chemotherapy or radiation, presence of antibodies (ovarian or gonadotropin), as well as infectious disease such as mumps, shigella, malaria, and varicella (Lifshitz 2006).

Hypogonadotropic hypogonadism (HH) is usually due to hypothalamic dysfunction. This dysfunction may be a delay in the HPG axis maturation resulting in the impaired secretion of GnRH and low levels of gonadotropins (LH and FSH). Causes of HH range from treatable underlying conditions such as a lack of GnRH synthesis (i.e., Kallman syndrome), a defect in the release of GnRH (i.e., leptin or *DAX-1* gene mutations), chronic illness, hypopituitarism (i.e., congenital or acquired from pituitary or hypothalamic lesions and tumors), syndromes (i.e., Prader-Willi, Noonan, cystic fibrosis), or under nutrition: intentional (anorexia, elite athlete) or unintentional. Some medications can also disrupt the HPG axis, such as antipsychotic drugs. Adverse events with stress can also interrupt pubertal development (Palmert and Dunkel 2012; Howell and Shalet 1998; Wei and Crowne 2016).

Kallman syndrome is the most common form of HH. The occurrence is 1:50000 in females and 1:10000 in males. It is usually characterized with anosmia (lack of sense of smell). Most cases are sporadic; however, 5% have a mutation of the *Kal1* gene. Midline defects, (i.e., cleft lip/palate)

are also associated with Kallman syndrome. Defect in the release of GnRH–DAX-1 plays a role in sexual differentiation and development of the adrenal gland, hypothalamus, hypophysis, and gonads. Leptin gene deficiency can lead to obesity which is known to cause delayed puberty due to hypogonadotropic hypogonadism.

Hypopituitarism (congenital), septo-optic dysplasia, absent septum pellucidum, or any midline defect can be a cause of hypogonadotropic hypogonadism. Craniopharyngioma is the most common childhood cranial lesion and surgery may lead to hypogonadotropic hypogonadism. Any cranial trauma such as head injury, or infections, infiltrative disease may also cause hypogonadotropic hypogonadism.

Prader-Willi Syndrome (PWS) is characterized by massive obesity which leads to hypothalamic dysfunction. Hypogonadism is a consistent feature of both males and females with PWS. Clinical presentation includes genital hypoplasia, delayed or incomplete puberty, and infertility in the clear majority.

Females with Noonan syndrome have normal pubertal development and ovarian function. Affected boys typically have undescended testes and abnormal Leydig cell function.

Functional hypogonadotropic hypogonadism is typically due to underlying chronic illness, such as inflammatory illness (i.e., celiac disease), thyroid disease, anorexia, bulimia, or excessive exercise that can cause poor growth and delay in puberty (Lifshitz 2006; Harrington and Palmert 2012).

4.1.7.3 Delayed Puberty in Girls

The current average age for a diagnosis of delayed puberty in girls in the United States is 13 years for breast development and 15 years for menarche (Lee 1980). Hypogonadotropic hypogonadism, also referred to as ovarian failure, is a common cause of delayed puberty in girls (i.e., Turner syndrome) (Refer to Chap. 40). Ovarian failure is also seen with autoimmune syndromes such as Addison's disease, type 1 diabetes, hyperparathyroidism, and others (Lifshitz 2006). Approximately 50% of girls who have pelvic radiation will develop primary ovarian failure (Howell and Shalet 1998).

HH as a cause of pubertal delay in girls is most commonly due to constitutional delay. In this population of girls, puberty will start spontaneously and will be maintained. There is often a family history of delayed puberty. Permanent hypogonadotropic hypogonadism is seen with defects in the GnRH secretion (i.e., Kallman syndrome) (Harrington and Palmert 2012).

Girls with normal development of secondary sexual characteristic who have a delay or absence of menarche should be worked up for an anatomical defect (e.g., Mayer-Rokitansky-Küster-Hauser), anovulatory state, or disorders of intersex (i.e., androgen insensitivity).

Primary amenorrhea is defined as no menses by age 16. However, any girl who has not had menses by age 15 should have an evaluation for causes. Primary amenorrhea implies a more permanent dysfunction of the hypothalamic pituitary ovarian (HPO) axis (Lifshitz 2006; Palmert and Dunkel 2012; Harrington and Palmert 2012).

It is well documented that chronic or severe illness will impede the HPG function. For example, the female athlete triad is a syndrome characterized by the coexisting diagnosis of an eating disorder, amenorrhoea, decreased bone density that is associated with morbidity and increased mortality. Figure 4.3 depicts the interaction between the eating disorders, HPG axis, and bone.

4.1.7.4 Delayed Puberty in Boys

Hypogonadotropic hypogonadism, also referred to as testicular failure, may cause pubertal delay in boys. The most common cause is Klinefelter syndrome. Other causes may be diminished testicular function (i.e., anorchia or vanishing testes syndrome), atrophic testes, Leydig cell aplasia, torsion, trauma, infection (mumps, coxsackie), chemotherapy, and radiation. Elevated gonadotropins are also seen in hepatic and renal disease (Lifshitz 2006; Palmert and Dunkel 2012).

Klinefelter syndrome occurs in about 1:500–1000 males. It is typically diagnosed in amniocentesis or during childhood. In some instances,

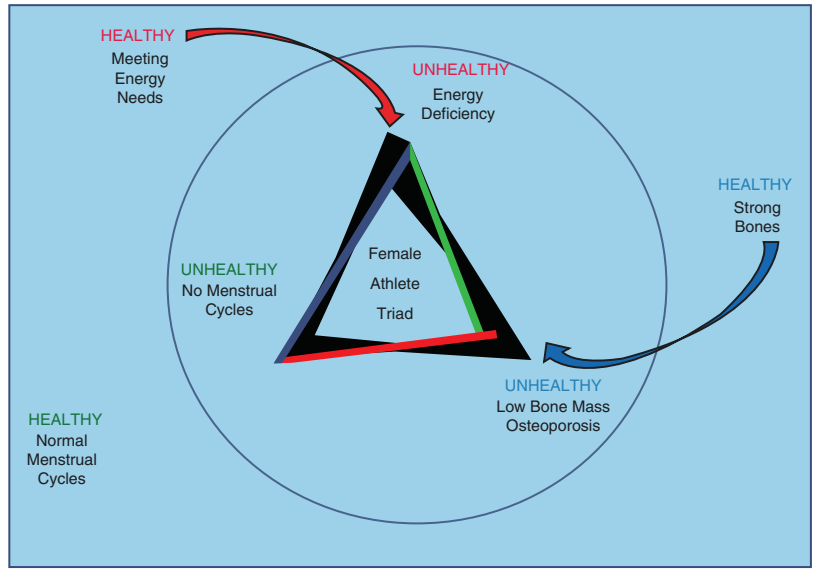


Fig. 4.3 Female athlete triad

delayed puberty and its subsequent work up may lead to the diagnosis. A delayed diagnosis may be made when infertility is an issue. Typical features are tall stature, disproportionate limb length, poor muscular development, micropenis, small firm testes, borderline IQ, poor social skills, and gynecomastia. The pubertal delay is caused by progressive hyalinization of testicular tissue and the seminiferous tubules (Lifshitz 2006; Palmert and Dunkel 2012). (Refer to Chap. 10).

In Leydig cell aplasia, the degree of masculinization is dependent on the mutation, ranging from micropenis to genital ambiguity. Testes may be small to normal size, FSH is typically normal, testosterone is low, and LH is elevated due to the inability to respond to LH or insensitivity (Lifshitz 2006; Palmert and Dunkel 2012).

Hypogonadotropic hypogonadism as a cause of pubertal delay in boys is most commonly due to constitutional delay. The cause however, could be transient or permanent. Transient causes include constitutional delay or chronic/systemic illness (i.e., inflammatory disease such as Crohn's). Permanent causes could be the result of genetic mutations, defects in the HPG—axis, hypopituitarism, or genetic syndromes (i.e., Kallman syndrome (see above) (Harrington and Palmert 2012).

Refer to Table 4.1 for a summary of common causes of delayed puberty.

4.1.7.5 Evaluation of Delayed Puberty

A detailed history and physical exam must be obtained with any child presenting with pubertal delay. The detailed history should include family history with timing of puberty (of parents, siblings, and extended family), parental heights (to calculate mid-parental height), birth and pregnancy details, childhood growth patterns, height velocity, consanguinity with the parents, previous illnesses, nutritional and exercise habits, psychological stressors, use of medications, exposure to chemotherapy or radiation, any syndromes diagnosed with the patient or relatives. A complete review of systems to assess for possible metabolic or hormonal causes, neurological symptoms (i.e., headaches, seizures, fundoscopic exam for papilledema), or developmental delay. Physical exam should include accurate height and weight (and plotting on growth chart), standing and sitting height, arm span, upper and lower segment ratio, Tanner staging, testing of smell, size and location of testes, and neurological assessment.

Table 4.1 Common causes for delayed puberty

Hypogonadotropic hypogonadism or HH		
Functional HH	Permanent HH	*Girls*
Hypothyroidism	*Genetic:*	Turner syndrome
Diabetes mellitus	Congenital or isolated/idiopathic HH	XX and XY gonadal dysgenesis
Growth hormone deficiency	Kallman syndrome	Primary ovarian failure
Cystic fibrosis	Septo-optic dysplasia	Oophoritis
Inflammatory bowel disease	Prader-Willi syndrome	*Boys*
Celiac disease	Laurence-Moon and Barder-Biedl syndromes	Gonadal dysgenesis
Systemic lupus	CHARGE syndrome	Vanishing testes syndrome
Juvenile rheumatoid arthritis	*Acquired:*	Testicular biosynthetic defects
Sickle cell disease	CNS tumors (astrocytoma, craniopharyngioma, germinoma, pituitary tumor	Orchitis
Thalassemia	Langerhans histocytosis	*Both sexes*
Chronic renal disease	Granulomatous or post-infection lesions of the CNS	Chemotherapy
Anorexia nervosa	CNS trauma, surgery, or radiation	Radiation
Malnutrition		Trauma
Intense exercise		Other syndromes (Noonan)

Baseline laboratory assessment of the child presenting with delayed puberty may include: complete blood count, thyroid function tests, electrolytes, albumin, creatinine, liver function tests, sedimentation rate, prolactin, morning serum cortisol, insulin-like growth factor 1 (IGF-1), FSH, LH, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex hormone-binding globulin, and karyotype. As a second line of testing, a GnRH stimulation test would be beneficial in evaluation of hypogonadotropic hypogonadism. Other testing may be indicated based on patient's symptoms and signs as well as family history (Palmert and Dunkel 2012).

Baseline radiologic assessment includes bone age (BA), which is helpful to distinguish between functional and permanent hypogonadism and is useful for adult height prediction. Although BA readings are qualitative rather than quantitative, it helps to round out the clinical picture that can lead to diagnosis and treatment options.

A pituitary or brain magnetic resonance imaging (MRI) is indicated only if there is a suspicion of intracranial lesion or defects, based on the physical exam and history. Ultrasound is useful in phenotypical males with cryptorchidism or phenotypical females suspected of androgen insensitivity; a pelvic ultrasound may be part of the initial assessment. However, in most cases of delayed puberty, this would be deferred or not done at all. Table 4.2 lists common tests utilized in the assessment of delayed puberty (Lifshitz 2006; Palmert and Dunkel 2012).

4.1.7.6 Treatment/Management of Delayed Puberty

Constitutional delay, in some cases, causes significant psychological stress, for the patient and the parents. If there is clinical or biochemical evidence that puberty has started, and the calculated adult height is appropriate, reassurance is often sufficient. However, induction of a pubertal growth spurt can be managed with a variety of medications. If the cause of delayed puberty that is due to a chronic illness, then the illness must be appropriately managed as much as possible to promote physiological puberty.

For girls, a low dose estrogen may be used to induce breast development. A starting dose of ethinylestradiol (a synthetic estrogen) at 2 micrograms/day, with a gradual increase to 20 μg/day, will allow for pubertal growth and gradual breast development. Natural estrogen (17β-estradiol) has much less metabolic effect and is prescribed in 0.2–2 mg/day either orally or by transdermal

Table 4.2 Assessment of delayed puberty

History	Examination	Investigations
Short stature	Serial accurate heights/weights	Baseline pituitary function TSH/FT4, prolactin, cortisol, IGF-1, electrolytes, karyotype
Parental history—age of puberty	Pubertal staging—Tanner	LH, FSH, DHEA-S, SHBG, testosterone/estradiaol
History of chronic illness or prolonged medication	Evidence of underlying chronic disease	CBC, ESR or sed rate, creatinine
Visual disturbances, headaches	Fundoscopy for signs of papilloedema	MRI
History of cranial or gonadal radiation or chemotherapy	Visual field	
Primary Amenorrhea		Pelvic ultrasound
Anosmia	Testing for sense of smell	
Learning difficulties	Inquire about problems with school or if an educational plan is implemented	
Behavior problems	Screen for behavioral concerns	Refer to psychologist for evaluation
Dietary history—evidence of malnutrition	Evidence of malnutrition	Albumin, calcium, magnesium
Exercise history	Inquire about amount and type of physical exercise	

Table 4.3 Treatment options for pubertal induction

Male		
Injection	Testosterone enantate	Start at 25–50 mg every 4 weeks for 3–6 months
IM or SC		Increase gradually every 6 months to 100–150 mg every 4 weeks
Transdermal	Metered dose 2%	Start at 10–20 mg (1–2 metered applications) daily
		Increase by 10 mg every 6 months to 60–80 mg
Female		
Oral	Ethinyl osstradiol Norethisterone 5 mg or medroxyprogesterone acetate 5 mg	Year 1–2 μg daily Year 2–4 μg daily Year 2.5–6 μg daily Year 3–8 μg daily Year 3.5–10 μg daily Year 4–20–30 μg daily—adult dose, with the addition of progesterone
	17β-estradiol	Initial dose 5 μg/kg daily Increase every 6–12 months to 10 μg/kg daily
Transdermal	17β-estradiol	Year 1—¼ patch twice a week Year 2—½ patch twice a week Year 2.5—alternate ½ and whole patch twice per week Year 3—whole patch twice per week

Adapted from Wei and Crowne (2016)

patch. Transdermal patches for girls are available in weekly patches. Once the full dose, of estrogen, is attained progesterone is added. Refer to Table 4.3 for dosing information. This can be done with as oral contraceptive pills (OCP). Some clinicians may prefer two separate compounds of; estrogen and progesterone. However, this may pose difficulties since the girl and her parent need to remember when to take the progesterone in combination with the estrogen. This increases the risk of issues with compliance and efficacy (Palmert and Dunkel 2012).

For boys, a low dose testosterone can be initiated to treat pubertal delay. See Table 4.3 for dosing information. Traditionally, testosterone has been given as an intramuscular (IM) injection. However, more recent data has shown that it can be given subcutaneously (SC) (Fraser et al. 2017). This can lead to patients and their families being taught self-administration. Transdermal patches of testosterone are also available and recommended areas of application are shoulders, upper arms, and abdomen. Testosterone is also available in a gel, supplied in a pump dispenser. Patients should be cautioned about contact with others and transference of the gel to other people. Side effects of androgen replacement therapy are associated with their physiologic effects (i.e., acne, oily skin, gynecomastia) consistent with puberty-related changes. Aromatase inhibitors that block the conversion of androgens to estrogens (and delay epiphyseal closure) are being investigated in clinical trials as a potential therapeutic approach for delayed puberty. Girls and boys with permanent hypogonadism are treated with initial sex-steroid therapy, like patients with constitutional delay, and doses are gradually increased to adult replacement levels. When fertility is desired, induction requires treatment with pulsatile GnRH or exogenous gonadotropins (Palmert and Dunkel 2012).

4.1.7.7 Psychological Issues Related to Delayed Puberty

Few studies have been done to look at the short- and long-term psychological impact of delayed puberty. In the limited studies that have been done, there are reports that delayed puberty in girls has more successful outcomes with regard to academic achievement and depressive symptoms, but late maturing boys had negative impact on school achievement. Among boys, delayed puberty has been linked to elevated depressive symptoms, externalizing behaviors (e.g., disruptive behavior, substance abuse) (Graber 2013). Boys may express concern about lagging in sports due to height and less muscular than peers. Girls may feel different from their peers due to lack of breast development and delayed menarche. It is important to remind adolescents and their parents that the hormonal and psychosocial experiences of puberty show significant individual differences, and one can expect the same with delayed puberty (Baams et al. 2015).

4.1.7.8 Nursing Considerations

Nurses have a key role in early identification of abnormalities in pubertal development and referral to pediatric endocrinologist for evaluation. Accurate anthropometric measurements and plotting on growth charts is critical for early recognition of abnormalities in development and growth.

The nurse has a key role as a member of the health care team to help improve the pediatric patient and family's experiences. Important aspects of the nurse's role include acknowledging the child or adolescent's vulnerability and lack of the experience with the health care system, their need for respect, privacy and confidentiality, communicating at an appropriate developmental level, and acknowledging their developing need for independence.

When the child/adolescent is diagnosed with an endocrine disorder, they may feel vulnerable. As with any new diagnosis, the patient and family should be made aware of any resources that may be available for them. These resources may include support groups, measures to help them attend appointments or access to treatments, and ways to deal with obstacles preventing them from obtaining the health care they need (e.g., school restrictions, travel, and other commitments).

The attitude of the health care staff should be respectful, supportive, and honest. Adolescents are particularly sensitive to the behavior of others and coping with a new medical diagnosis, such as delayed puberty, may heighten that sensitivity. The staff should be empathetic and non-judgmental.

During adolescence, privacy is a very important aspect of their interactions with the health care system. A routine genital examination may be a source of embarrassment and may be very stressful for the adolescent. The nurse should explain the need for the examination and offer privacy for undressing (behind a curtain, or alone in the examination room) and a gown to cover

themselves. Often adolescents do not want their parents present during the examination, however, this should still be discussed with the adolescent and parent. Alternatively, a chaperone may be offered (another nurse). This also safeguards the clinician against false accusations of impropriety.

The nurse should speak to the adolescent with respect, as well as with clarity and honesty. It is important to use active listening skills to see what is important to the adolescent. The nurse should avoid a "lecture-like" tone and avoid sounding confrontational, superior, or condescending. Make sure that the discussion is age appropriate which gives the adolescent the opportunity to ask questions. The individual adolescent should have the opportunity to be involved in the decision-making, regarding clinical investigations and treatment options. Explanations and information about hormonal replacement must be given to the patient and family. A discussion about future fertility and options available should also be discussed.

4.1.8 Precocious Puberty

This section will explore precocious puberty in terms of the clinical definition, the causes, how it presents, how it is diagnosed, the treatment options, as well as the expected outcomes and nursing implications related to the care of the child and family.

4.1.8.1 Definition

While there have been epidemiological studies published that document a trend toward an earlier initiation of puberty (Tena-Sempere 2013; Lee and Styne 2013), the classical and currently accepted definition of early or precocious puberty is the presence of secondary sexual characteristics of Tanner II breast development in girls before the age of 8 years and the presence of Tanner II genital development or testicular volume greater than or equal to 4 mL in boys prior to the age of 9 years. These clinical findings along with accelerated linear growth and advanced bone maturation constitutes the definition of precocious puberty (Lee 1980; Chirico et al. 2014; Radovick and Madhusmita 2018a).

4.1.8.2 Implications for Health and Development

The early production of sex steroids causes advanced bone maturation that decreases the linear growth potential and results in adult short stature due to early fusion of the growth plates (Thornton et al. 2014). As well, early age of menarche has been associated with increased risks of obesity, hypertension, type 2 diabetes, ischemic heart disease, stroke, estrogen-dependent cancer and cardiovascular mortality and development of breast cancer (Pienkowski and Tauber 2016). Some studies report that early puberty can be associated with an increase in adult sexual and delinquent behaviors and more psychological disturbances above general trends (Pienkowski and Tauber 2016).

4.1.8.3 Etiology and Presentation

Physical signs of early puberty can be a result of different causes that have been divided into three categories: central, peripheral, and incomplete precocious puberty (Latronico et al. 2016; Radovick and Madhusmita 2018b).

4.1.8.4 Central Precocious Puberty (CPP)

CPP or GnRH-dependent precocious puberty occurs when there is early activation and maturation of the hypothalamic-pituitary-gonadal axis leading to stimulation of the ovaries in girls and the testes in boys. The early production of GnRH by the pituitary stimulates the ovaries to produce estrogen and the testes to produce testosterone that results in the increase in breast tissue in girls and increased testicular volume in boys (Latronico et al. 2016; Chauhan and Grissom 2013; Macedo et al. 2016). CPP affects 1:5000–10,000 children (Lifshitz 2006; Chirico et al. 2014) and the prevalence is much higher in girls with at least 10:1 occurrence in females compared to males (Pienkowski and Tauber 2016; Macedo et al. 2016). CPP can result from organic, genetic, or idiopathic causes (Chirico et al. 2014; Macedo et al. 2016; Sultan et al. 2012).

Organic causes of CPP include lesions of the central nervous system such as benign hamartomas and malignant tumors usually found in the pineal region, or the optic pathway, such as hypothalamic gliomas (Wendt et al. 2014). Hydrocephalus, infection, trauma, and radiation can also impact the hypothalamus and pituitary and result in early production of GnRH with subsequent production of the relevant gonadal hormone (Bertelloni and Baroncelli 2013).

Genetics is the basis for a diagnosis of familial CPP. Inactivating mutations of the imprinted gene *MKRN3* is responsible for early onset of puberty that presents in certain families across generations (Sultan et al. 2012; Biro and Kiess 2016). This gene is found on chromosome 15q11.2. Inheritance occurs from fathers, so the phenotype can skip one or more generations and both sexes can be affected (Macedo et al. 2016). A very rare genetic cause of CPP involves activating mutations of the genes that encode the kisspeptin system, the major gatekeeper of pubertal onset through activation of the GnRH neurons (Tena-Sempere 2013; Macedo et al. 2016). Overexpression of kisspeptin leads to precocious puberty (Lee and Styne 2013).

Idiopathic CPP is when no lesion or genetic cause can be identified. This accounts for 70–90% of cases of CPP diagnosed in girls and rarely occurs in boys (Chirico et al. 2014; Pienkowski and Tauber 2016; Sultan et al. 2012). There is a slow progressive variant of CPP described in both sexes and is associated with adult height comparable to target height without intervention (Bertelloni and Baroncelli 2013). This form needs to be monitored closely, as the child may switch to rapid progression of puberty and acceleration of skeletal maturation and thus require intervention (Bertelloni and Baroncelli 2013).

The treatment options for CPP can involve close monitoring or intervention with a GnRH analog and will be discussed later in this section.

4.1.8.5 Peripheral Precocious Puberty (PPP)

PPP, or GnRH-independent precocious puberty, occurs when there is increase in the sex steroid, estrogen. or testosterone, and there is no evidence of activation of the hypothalamic-pituitary-gonadal axis, as GnRH is not stimulating the gonads to produce their respective hormones (Chirico et al. 2014). Causes include genetic, neoplasms, hypothyroidism and exposure to exogenous sex steroids (Macedo et al. 2016; Brown et al. 2013; Schoelwer and Eugster 2016). The treatments will be discussed along with the specific causes.

Genetic causes of PPP include congenital adrenal hyperplasia (CAH), McCune-Albright Syndrome (MAS), and familial male-limited precocious puberty (testotoxicosis).

- In CAH, if treatment is inadequate, there can be increased androgen levels secreted by the adrenal gland. This can lead to increased testosterone levels in boys and girls (Brown et al. 2013). (Refer to Chap. 34).
- MAS results from mutations in the *GNAS* gene that is located on chromosome 20q13.32 (Macedo et al. 2016; Brown et al. 2013). It is characterized by the presence of fibrous dysplasia, café-au-lait macules, and precocious puberty. Gonadotropin independent PP occurs in 15–20% of boys and 85% of girls affected with MAS. It is an uncommon condition & substitute: Gonadotropin independent PP occurs in 15–20% of boys and 85% of girls affected with MAS (Brown et al. 2013; Schoelwer and Eugster 2016). In girls, estrogen is secreted autonomously from functioning ovarian cysts and causes breast development, menstrual bleeding, increased linear growth, and advanced bone age (Schoelwer and Eugster 2016). Estrogen receptor modulators have been used to reduce the effects of elevated estrogen levels, such as ketoconazole that inhibits steroid biosynthesis and letrozole, an aromatase inhibitor, but there are concerns over long-term safety and efficacy. (Schoelwer and Eugster 2016). (Refer to Chap. 11).
- Familial male-limited precocious puberty or testotoxicosis is a rare disorder caused by activation of mutations in the gene, located on chromosome 2p21e, that encodes the luteinizing hormone and choriogonadotropin receptor (Latronico et al. 2016; Macedo et al. 2016; Schoelwer and Eugster 2016). It can

occur de novo or it can be inherited through autosomal dominance, and is limited to males. Females can be asymptomatic carriers (Latronico et al. 2016). It presents in boys, usually before the age of 4 years, with tall stature, rapid growth, enlarged penis but little testicular enlargement or pubic hair.

Neoplasms such as adrenocortical carcinoma, hepatoblastoma, or gonadal tumors lead to increased production of sex steroids independent of GnRH and cause PPP. These lesions need to be removed and treated as per oncology protocols (Wendt et al. 2014). Hypothyroidism may have associated sexual precocity in both boys and girls. The precise mechanism is unknown but may be related to increase levels of thyrotropin-releasing hormone in the hypothalamus and elevated levels of thyroid stimulating hormone in the pituitary that can act on the FSH receptor. The stimulation of FSH levels can result in production of gonadal sex steroids in the hypothyroid child (Wendt et al. 2014).

Exposure to exogenous sex steroid occurs when users of topical testosterone preparations fail to follow the recommended contact precautions. The increasing use of topical androgens in males with hypogonadism or for increased muscle accretion or enhanced libido has resulted in increased cases of PPP secondary to inadvertent exposure in prepubertal children. Case reports show a return to prepubertal testosterone levels for most children after 4–5 months from the exposure cessation (Martinez-Pajares et al. 2012).

4.1.8.6 Incomplete Precocious Puberty (IPP)

Conditions of incomplete precocious puberty are considered variants of normal puberty and include premature thelarche, premature adrenarche, and isolated metrorrhagia (Chauhan and Grissom 2013; Sultan et al. 2012).

Premature thelarche (PT) is the presence of breast tissue without other signs of secondary sexual characteristics. Breast development is bilateral 50% of the time while the rest are unilateral or asymmetrical. Most are breast Tanner stage II but breast volumes can be up to Tanner stage IV (Sultan et al. 2012). The breast enlargement usually regresses within months of appearing, but it can fluctuate over time and remain until other pubertal development occurs at an expected age. This usually occurs in children younger than 2 years old but can happen in children up to 7 years old as well (Lazar and Phillip 2012; Sultan et al. 2012; Brown et al. 2013). The cause is likely secondary to aromatization of adrenal androgens (Chauhan and Grissom 2013); however, the role of environmental impact in relation to endocrine disruptors is also considered relevant as the frequency of PT is increasing (Sultan et al. 2012). Many studies with girls report that higher adiposity is associated with thelarche prior to age 8 years, but there is no proven causal link to date (Lee and Styne 2013). Increased adiposity can decrease levels of sex hormone-binding globulin that leads to greater availability of circulating sex steroids (Chauhan and Grissom 2013; Biro and Kiess 2016). As well, the storage of estrogen and aromatization of estrogen precursors are increased with increased adiposity that can result in higher levels of estrogen independent of the HPG axis (Chauhan and Grissom 2013; Biro and Kiess 2016). Bone maturation is normal or may be slightly advanced (Lazar and Phillip 2012; Eksioglu et al. 2013). The enlarged breast tissue may be tender or painful, but there is no discharge and this self-limiting condition requires no treatment other than monitoring (Sultan et al. 2012; Brown et al. 2013).

Premature adrenarche (PA) is the presence of signs of androgen action before age of 8 years in girls and 9 years in boys (Lazar and Phillip 2012; Voutilainen and Jaaskelainen 2015). Pubic hair and/or axillary hair is present in about 50% of the cases. Adult body odor is a very common early sign of PA (Voutilainen and Jaaskelainen 2015) and oily hair or skin, comedones, acne, slightly increased linear growth, mood swings, and behavioral changes may occur (Voutilainen and Jaaskelainen 2015; Williams et al. 2012). It is more typically found in children older than 6 years and 8–9 times more frequently in girls compared to boys

(Sultan et al. 2012; Brown et al. 2013; Williams et al. 2012). There is an elevation of adrenal androgen precursors, dehydroepiandrosterone (DHEA), DHEA-S, and androstenedione; therefore, other causes of excess androgen levels must be excluded (Voutilainen and Jaaskelainen 2015). PA has been associated with preterm birth and SGA, as well as progression to overweight, obesity, and hyperinsulinism. These conditions may increase the risk of adrenal hyperandrogenism in some cohorts, but this is not conclusive in all populations (Sultan et al. 2012; Voutilainen and Jaaskelainen 2015). The BA can be advanced and linear growth increased before puberty, but individuals do reach their genetic potential for adult height (Lazar and Phillip 2012; Voutilainen and Jaaskelainen 2015). There is a wide variability in the presentation of PA but regardless of signs of androgen effect, once other causes of excess androgens are excluded this is considered a benign condition and there is no treatment (Williams et al. 2012).

Isolated metrorrhagia is bleeding from the uterus at irregular intervals. When this occurs in the prepubertal girl, it may be due to transient rises in estrogen from a functional ovarian cyst that is rarely treated but monitored closely. It may also be related to endocrine disruptors such as phthalates, phytoestrogens, and bisphenol A that may have the capacity to mimic estrogen and so result in activation of its hormonal activity (Chauhan and Grissom 2013; Sultan et al. 2012).

4.1.8.7 Diagnostic Evaluation

The gold standard in differentiating and diagnosing precocious puberty is the determination of a lab value of the LH and FSH response to purposeful stimulation of GnRH (Chirico et al. 2014). An LH response above 5–6 international units/L (IU/L) and/or a stimulated peak LH/FSH ratio above 0.66–1.0 is considered a centrally driven pubertal response and the child has CPP. If there is no stimulated LH or FSH response, then elevated levels of estrogen or testosterone are considered from a peripheral source and the child has PPP (Thornton et al. 2014).

A pelvic ultrasound for girls can detect ovarian masses and provide measurements of the uterus and ovaries. Measurements reported as significantly higher than normal in girls aged 0–8 years old supports the diagnosis of CPP. Ultrasound can also assess the progressive maturation of the uterus and ovaries and may assist in monitoring effectiveness of treatment (Sultan et al. 2012; Eksioglu et al. 2013).

BA X-ray of the left hand and wrist can provide information about the maturation stage of the bones as compared to the child's chronological age (CA). In a rapidly progressing CPP, the BA is greater than 2 SD above the CA and the concern is for loss of pubertal growth potential to occur at a usual time of development and a lessening of final adult height. The BA can be helpful in determining whether treatment is needed or if careful monitoring is adequate. A brain MRI is needed to identify or rule out the presence of CNS lesions (Lazar and Phillip 2012). Tumor markers (i.e. alpha fetoprotein, beta HCG) and adrenal DHEA and androstenedione are blood levels that help differentiate the etiology of PPP and IPP (Wendt et al. 2014).

4.1.8.8 Management

The main goals for the management of precocious puberty is to prevent early fusion of the epiphyseal growth plates (Chauhan and Grissom 2013), thus allowing for the attainment of adult height within the individual's genetic potential (Bertelloni and Baroncelli 2013). As well, it is desirable to stop premature sexual maturation at an age that is early with respect to other social development of the child in order to prevent potentially negative somatic and psychological outcomes (Bertelloni and Baroncelli 2013).

Onset of puberty in 6–8-year-old girls is controversial and when puberty starts at 8–9 years old in girls there is no benefit achieved by treating (Chauhan and Grissom 2013; Bertelloni and Baroncelli 2013). Another study reported that boys and girls older than 6 years at onset of puberty and treated with GnRH had a less than expected actual improvement in height prognosis (Lazar and Phillip 2012).

The decision to intervene depends on the etiology, the child's age at presentation, the rapid rate of pubertal progression, the accelerated height velocity, and a BA advancement greater than 2 SD for girls. As boys have acceleration of bone maturation and growth rate later in puberty, rather than using the BA, an increase in testicular volume and secondary sexual characteristics associated with increased testosterone levels are better indicators (Lazar and Phillip 2012).

Surgery and radiation therapy of the CNS lesion are used for a minority of patients with organic causes of CPP (Bertelloni and Baroncelli 2013) and hypothalamic hamartomas should not be treated by surgery (Latronico et al. 2016).

4.1.8.9 Medical Treatment

The treatment of choice for idiopathic and non-treatable organic causes of CPP are synthetic analogs of GnRH (Bertelloni and Baroncelli 2013). The analog has a highly specific binding to the GnRH receptor (Bertelloni and Baroncelli 2013) and after an initial brief stimulation of gonadotropin release there is a desensitization of the gonadotropin-secreting cells to native GnRH that results in suppression of LH and FSH production and subsequent return of the sex steroid to prepubertal levels (Bertelloni and Baroncelli 2013; Brown et al. 2013).

The optimal dose needed to achieve pituitary desensitization continues to be debated. It is important to note that if suppression is incomplete during treatment, GnRH analog may actually stimulate pubertal progression and bone age advancement, thus impairing desired outcome of treatment (Bertelloni and Baroncelli 2013).

The forms of GnRH analog available are daily SC, monthly depots given by IM injection, depots lasting up to 12 weeks given by IM injections, and implants that last up to 24 months (Bertelloni and Baroncelli 2013). Another medication that comes as a nasal spray is currently not commonly used and will not be discussed.

Leuprolide and triptorelin provide GnRH analog most commonly as formulations of 3.75 mg or 7.5 mg strength given every 4 weeks or 11.25 mg or 22.5 mg strength given every 12 weeks, while Goserelin has a 3.6 mg every 4 weeks and a 10.8 mg every 12 weeks formulation (Bertelloni and Baroncelli 2013). If hormonal or clinical criteria warrant, these products may require shorter intervals between injections to achieve adequate gonadotropin suppression (Bertelloni and Baroncelli 2013). From personal practice when a dose of 7.5 mg given every 3 weeks was not sufficient for suppression, a combination of 7.5 mg and 3.75 mg monthly formulation were combined in one syringe to provide 11.25 mg every 3 weeks, as there is no 11.25 mg monthly formulation. The option of using a product that has a longer interval, so that injections are given every 12 weeks instead of every 4 weeks, can improve compliance and quality of life for the child and family (Bertelloni and Baroncelli 2013). The every 12-week formulation has a larger volume per injection, 1.8 mL versus 1.0 mL for the 4-week formulation, so for smaller children this would need to be a consideration. As well, the longer interval product is thicker, and children find that it is more painful albeit it requires less injections.

Yearly histrelin implants seem to provide adequate suppression; however, the clinical experience is limited (Bertelloni and Baroncelli 2013). This involves a surgical subcutaneous implant that suppresses gonadotropins for 12–24 months (Latronico et al. 2016).

Adverse effects such as headaches, rash, gastrointestinal complaints, or hot flashes have been reported in 3–13% of children receiving GnRH analog but are usually transient and resolve spontaneously or with treatment of the symptoms (Latronico et al. 2016). Local complications, such as sterile abscess, has been reported in 1.5–5% of children and are thought to be due to reactions to a variety of polymers used in slowing down the release of the medication in the depot and implant formulations (Chirico et al. 2014; Thornton et al. 2014; Bertelloni and Baroncelli 2013). If these forms of GnRH are not tolerated, the daily subcutaneous formulation can be used.

Efficacy of GnRH analog treatment can be done with a single LH sample taken 30–120 min after the injection of every 4 week or 12-week

GnRH analog formulation. Suppression of the LH level to less than 4.5 IU/L indicates adequate suppression (Latronico et al. 2016). BA can also determine effectiveness of treatment and can be measured every 6–12 months. Initially, skeletal advancement slows to 6–12 months per year and later may show no advancement in both girls and boys receiving GnRH analog (Lazar and Phillip 2012).

In some children, there is an excessive growth velocity deceleration that occurs during treatment and for which there is no known mechanism (Bertelloni and Baroncelli 2013). These children may benefit from adjunctive treatment with GH or very low doses of 17B-estradiol (Bertelloni and Baroncelli 2013) or oxandrolone to optimize growth velocity and adult height; however, very few studies have been reported on this (Latronico et al. 2016).

4.1.8.10 Discontinuation of Medical Treatment

Factors to consider when deciding to discontinue GnRH analog treatment include the family's perspective, psychological, and social issues, as well as the child's response to treatment and the current bone age (Bertelloni and Baroncelli 2013) (G). In most instances, stopping treatment when the BA is close to the physiological age for pubertal onset for girls, which would be 11.5–12.5 years and a similar corresponding BA; for boys a BA of 13.5–14 years, which is close to male peak height velocity (Lazar and Phillip 2012; Latronico et al. 2016; Bertelloni and Baroncelli 2013; Brown et al. 2013).

Following discontinuation of GnRH analog, female menstrual cycle resumes 12–16 months later; however, a wide range of 2–61 months has been reported (Chirico et al. 2014; Latronico et al. 2016; Chauhan and Grissom 2013). Typically, the HPG axis returns to normal within 12 months after stopping treatment (Williams et al. 2012).

Following removal of the final implant of histrelin, recovery of the hypothalamic-pituitary axis has been reported at 6 months (Latronico et al. 2016).

Long-term implications from receiving GnRH analog treatment have been studied. Data suggests that this treatment does not cause or aggravate obesity and does not affect body composition (Thornton et al. 2014; Latronico et al. 2016; Bertelloni and Baroncelli 2013). As well, bone mineral density may decrease during GnRH analog treatment, but subsequent bone mass accrual is usually preserved, and peak bone mass is not negatively affected in either sex (Latronico et al. 2016; Bertelloni and Baroncelli 2013). Long-term data indicates that there is no adverse effects related to normal reproduction function and reproductive potential in both sexes and gonadal function is reactivated once treatment is stopped (Chirico et al. 2014; Latronico et al. 2016). There is no evidence that GnRH analog treatment predisposes females to PCOS or menstrual irregularities (Bertelloni and Baroncelli 2013).

4.1.8.11 Psychosocial Implications

Boys with early pubertal development can be perceived as more mature and smart, while girls have been found to have more difficulty in academic and social environments. As well, girls with early signs of puberty may attract the attention of older boys, thus putting them at risk for exploitation or abuse, as they are not mentally mature enough to handle these situations. Studies have shown that both sexes who mature earlier are at increased risk of participating in risk-taking behaviors at an earlier age (Brown et al. 2013).

4.1.8.12 Nursing Implications

1. Respecting patient and parent needs.
   - The time of diagnosis can be overwhelming for families and nurses can offer vital support in helping the families to understand the medical diagnosis and what is involved with treatment. Written material is valued as many parents are not able to take in all the information that is frequently given at the time of diagnosis. Parents may feel that their child is socially vulnerable when going through puberty too early. They may feel overprotective and fearful that their child may be teased or exploited

by others as they have sexually developed too soon compared to their peers.

2. Coordinating and integrating care that considers the needs and perceptions of patients and their families.
   - Treatment for CPP usually involves scheduled injections, ongoing monitoring with blood tests and medical examinations, which takes time away from parent's work and children's school. Parents may feel unsure of how to explain the need for these absences to school personnel and may need support such as letters of confirmation of appointments. Children may feel embarrassed at having to leave school to attend medical appointments. Costs related to missed work, travel expenses, and parking may be too much for families. The nurse can endeavor to schedule injections and physician assessments at the same time to reduce visits to the medical center.
3. Providing information, communication, and education throughout the care continuum.
   - Families may not know how to discuss their child's early body development with the child. Most young children will ask questions if they want to know something so parents need to be prepared to give them answers tailored to their child's developmental level, so they can understand. As these children are often tall for their actual age, others may expect more from them or treat them as if they were older. Parents may need help to know how to handle these situations. A "buddy" family may be helpful to the parent and child, so they can talk with someone who has had a similar experience.
4. Providing for timely and effective means of pain management.
   - Offer a child friendly space that is inviting and not scary.
   - Have a discussion with parents to help them understand their role in supporting their child during a painful or fear inducing procedure. Allow the child and parent to express their feelings so that they feel heard and understood and be honest about what to expect. If the child or parent has a fear of needles, more specialized help from child life specialists or child psychologists may be helpful.
   - Use principles of lessening pain of injections and blood tests such as topical numbing medication, skin vibration placed between the injection site and the nerve pathway to the brain, distraction technics, and deep breathing are a few examples of the guidelines suggested by Taddio et al. (2010) (Also see Chap. 5).
5. Include parents and families as partners in the health care team.
   - Extended family members may have questions or concerns that the parents are not able to answer. The parents may feel precocious puberty is an awkward social situation and may need help discussing with family, friends, or those providing child care when parents feel this information needs to be shared.
   - The discussion about stopping treatment for CPP is a time that families need to have information and support about what to expect in terms of progressing through puberty and future implications for normal progression and fertility aspects.

Case Study

4-year-old girl, MG, with Tanner stage 3 breasts and increased height velocity.

GnRH stimulation test shows LH = 60 IU/L, FSH = 20 IU/L, estradiol = 277 pmol/L.

Bone age = 7 years.

MRI of head is normal.

No history of other medical conditions or head trauma.

Mom is fearful that her little girl has lost her childhood and is vulnerable to other children's teasing and even exploitation. MG is terrified of needles and doesn't know why she has to be poked and have the private parts of her body examined.

The pediatric endocrinologist and pediatric endocrine nurse meet with the family to discuss the diagnosis of CPP and prescribes Lupron

Depot (leuprolide) 7.5 mg IM monthly with follow-up labs 40 min post third injection to check for suppression of LH, FSH, and estradiol.

What do you think is important to discuss with the parents?

How could you support MG with the treatment regime in the coming months?

4.1.9 Conclusions

Puberty is not a single process that follows a definitive road map. Time of onset, tempo, and completion of puberty are all variable. It is imperative that a thorough history and physical examination are done to assess the status of puberty. An understanding of pubertal development, including typical or abnormal variations is essential for nurses to provide patient or parent education and guidance.

The timing of puberty varies greatly between individuals, ethnicities, geographical area, environmental, socioeconomic, and nutritional states. The approach to delayed puberty is dependent on the cause of the delay. There is ongoing research into the causes and treatment options for delayed or precocious puberty. It is important for the nurse to be cognizant that the child who presents with delayed or precocious puberty is dealing with physiological as well as psychological issues, both of which need to be addressed. The goal of treatment is to preserve final adult height potential and to support children and their families throughout the process.

References

Abitbol L, Zborovski S, Palmert MR. Evaluation of delayed puberty: what diagnostic tests should be performed in the seemingly otherwise well adolescent? Arch Dis Child. 2016;101(8):767–71.

Adams Hillard PJ. Menstruation in adolescents: what do we know? And what do we do with the information? J Pediatr Adolesc Gynecol. 2014;27(6):309–19.

Baams L, Dubas JS, Overbeek G, van Aken MA. Transitions in body and behavior: a meta-analytic study on the relationship between pubertal development and adolescent sexual behavior. J Adolesc Health. 2015;56(6):586–98.

Berenbaum SA, Beltz AM, Corley R. The importance of puberty for adolescent development: conceptualization and measurement. Adv Child Dev Behav. 2015;48:53–92.

Bertelloni S, Baroncelli GI. Current pharmacotherapy of central precocious puberty by GnRH analogs: certainties and uncertainties. Expert Opin Pharmacother. 2013;14(12):1627–39.

Biro FM, Kiess W. Contemporary trends in onset and completion of puberty, gain in height and adiposity. Endocr Dev. 2016;29:122–33.

Bourguignon JP, Juul A. Normal female puberty in a developmental perspective. Endocr Dev. 2012;22:11–23.

Brown DB, Loomba-Albrecht LA, Bremer AA. Sexual precocity and its treatment. World J Pediatr. 2013;9(2):103–11.

Chauhan A, Grissom M. Disorders of childhood growth and development: precocious puberty. FP Essent. 2013;410:25–31.

Chirico V, Lacquaniti A, Salpietro V, Buemi M, Salpietro C, Arrigo T. Central precocious puberty: from physiopathological mechanisms to treatment. J Biol Regul Homeost Agents. 2014;28(3):367–75.

Duke SA, Balzer BW, Steinbeck KS. Testosterone and its effects on human male adolescent mood and behavior: a systematic review. J Adolesc Health. 2014;55(3):315–22.

Eksioglu AS, Yilmaz S, Cetinkaya S, Cinar G, Yildiz YT, Aycan Z. Value of pelvic sonography in the diagnosis of various forms of precocious puberty in girls. J Clin Ultrasound. 2013;41(2):84–93.

Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341(12):879–84.

Fenichel P. Delayed puberty. Endocr Dev. 2012;22:138–59.

Fraser B, Jacob J, Kirouac N, editors. SubQ T…is it for me? Reviewing the increasing use of subcutaneous testosterone injections. International Pediatric Endocrine Nurses Summit; 2015; Washington DC. J Pediatr Nurs. 2017.

Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics. 2002;110(4):e43.

Gajdos ZK, Henderson KD, Hirschhorn JN, Palmert MR. Genetic determinants of pubertal timing in the general population. Mol Cell Endocrinol. 2010;324(1–2):21–9.

Giedd JN. The amazing teen brain. Sci Am. 2015;312(6):32–7.

Graber JA. Pubertal timing and the development of psychopathology in adolescence and beyond. Horm Behav. 2013;64(2):262–9.

Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, CA: Stanford University Press; 1959.

Harrington J, Palmert MR. Clinical review: Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. J Clin Endocrinol Metab. 2012;97(9):3056–67.

Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin N Am. 1998;27(4):927–43.

Kaur KK, Allahbadia G, Singh M. Kisspeptins in human reproduction—future therapeutic potential. J Assist Reprod Genet. 2012;29(10):999–1011.

Krieger N, Kiang MV, Kosheleva A, Waterman PD, Chen JT, Beckfield J. Age at menarche: 50-year socioeconomic trends among US-born black and white women. Am J Public Health. 2015;105(2):388–97.

Lahoti A, Sills I. Update on puberty and its disorders in adolescents. Adolesc Med State Art Rev. 2015;26(2):269–90.

Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol. 2016;4(3):265–74.

Lazar L, Phillip M. Pubertal disorders and bone maturation. Endocrinol Metab Clin N Am. 2012;41(4):805–25.

Lee PA. Normal ages of pubertal events among American males and females. J Adolesc Health Care. 1980;1(1):26–9.

Lee Y, Styne D. Influences on the onset and tempo of puberty in human beings and implications for adolescent psychological development. Horm Behav. 2013;64(2):250–61.

Lifshitz FE. In: Lifshitz F, editor. Pediatric endocrinology. 5th ed. New York: Marcel Dekker; 2006.

Macedo DB, Silveira LF, Bessa DS, Brito VN, Latronico AC. Sexual precocity—genetic bases of central precocious puberty and autonomous gonadal activation. Endocr Dev. 2016;29:50–71.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303.

Martinez-Pajares JD, Diaz-Morales O, Ramos-Diaz JC, Gomez-Fernandez E. Peripheral precocious puberty due to inadvertent exposure to testosterone: case report and review of the literature. J Pediatr Endocrinol Metab. 2012;25(9–10):1007–12.

Palmert MR, Dunkel L. Clinical practice. Delayed puberty. N Engl J Med. 2012;366(5):443–53.

Palmert MR, Hirschhorn JN. Genetic approaches to stature, pubertal timing, and other complex traits. Mol Genet Metab. 2003;80(1–2):1–10.

Pienkowski C, Tauber M. Gonadotropin-releasing hormone agonist treatment in sexual precocity. Endocr Dev. 2016;29:214–29.

Radovick SM, Madhusmita M, editors. Pediatric endocrinology. Cham: Springer International; 2018a.

Radovick SM, Madhusmita M, editors. Pediatric endocrinology: a practical clinical guide. Cham: Springer International; 2018b.

Schoelwer M, Eugster EA. Treatment of peripheral precocious puberty. Endocr Dev. 2016;29:230–9.

Sultan C, Gaspari L, Kalfa N, Paris F. Clinical expression of precocious puberty in girls. Endocr Dev. 2012;22:84–100.

Susman EJ, Dorn LD, Schiefelbein VL. In: Weiner IB, editor. Puberty, sexuality, and health. New York: Wiley; 2003.

Susman EJ, Dockray S, Granger DA, Blades KT, Randazzo W, Heaton JA, et al. Cortisol and alpha amylase reactivity and timing of puberty: vulnerabilities for antisocial behaviour in young adolescents. Psychoneuroendocrinology. 2010;35(4):557–69.

Taddio A, Appleton M, Bortolussi R, Chambers C, Dubey V, Halperin S, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline (summary). CMAJ. 2010;182(18):1989–95.

Tena-Sempere M. Keeping puberty on time: novel signals and mechanisms involved. Curr Top Dev Biol. 2013;105:299–329.

Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. Pediatr Endocrinol Rev. 2014;11(3):306–17.

Voutilainen R, Jaaskelainen J. Premature adrenarche: etiology, clinical findings, and consequences. J Steroid Biochem Mol Biol. 2015;145:226–36.

Wei C, Crowne EC. Recent advances in the understanding and management of delayed puberty. Arch Dis Child. 2016;101(5):481–8.

Weise M, De-Levi S, Barnes KM, Gafni RI, Abad V, Baron J. Effects of estrogen on growth plate senescence and epiphyseal fusion. Proc Natl Acad Sci U S A. 2001;98(12):6871–6.

Wendt S, Shelso J, Wright K, Furman W. Neoplastic causes of abnormal puberty. Pediatr Blood Cancer. 2014;61(4):664–71.

Williams RM, Ward CE, Hughes IA. Premature adrenarche. Arch Dis Child. 2012;97(3):250–4.

Wolf RM, Long D. Pubertal development. Pediatr Rev. 2016;37(7):292–300.

5 Treatment Issues in the Care of Pediatric Patients with Endocrine Conditions

Peggy Kalancha, Nicole Kirouac, and Eileen Pyra

Contents

5.1 **Injections and Pain Reduction Strategies** 87
5.1.1 Defining Subcutaneous vs. Intramuscular Injections and Best Practice 87
5.1.2 Pain Reduction and Distraction Techniques Based on Evidence and Best Practice 88

5.2 **Gender Creative and Transgender Youth (Gender Dysphoria)** 90
5.2.1 Definitions 91
5.2.2 Diagnostic Criteria 91
5.2.3 Treatment Guidelines 91
5.2.4 Public Education and Support 91
5.2.5 Conclusions 94

5.3 **Girls with Developmental Disability and Puberty** 94
5.3.1 Pubertal Benefits 95
5.3.2 Pubertal Onset Differences 95
5.3.3 Assessment of Patients 95
5.3.4 Medical Treatment Options 97
5.3.5 Permanent Surgical Treatment 98
5.3.6 Nursing Strategies 98

5.4 **Conclusions** 99

References 99

P. Kalancha
Clinical Resource, Pediatric Endocrine and Gynecology Clinics, Alberta Children's Hospital, Calgary, AB, Canada
e-mail: peggy.kalancha@ahs.ca

N. Kirouac
St. Amant Inc., Winnipeg, MB, Canada
e-mail: nkirouac@stamant.ca

E. Pyra (✉)
Pediatric Endocrine Clinic, Alberta Children's Hospital, Calgary, AB, Canada
e-mail: eileen.pyra@ahs.ca

Abstract

Treatment issues commonly encountered in pediatric endocrine practice include: preparing children for painful procedures, care of transgender youth, and pubertal issues of girls with developmental disabilities. This chapter provides an overview of these topics.

Pediatric endocrine nurses frequently request blood testing of their patients. Also, nurses teach parents to provide blood sugar

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_5

testing or injections to their children. Selection of the correct needle length is important to ensure correct distribution of medication. Injections and finger sticks are painful or anxiety producing for infants, children, adolescents, and their parents. Many people develop long-term fear or avoidance of needles because of negative childhood experiences. As patient advocates, nurses can ensure that parents and children are prepared for potentially painful experiences by utilizing evidence-based strategies to decrease pain and anxiety. Recognizing that memories of painful experiences can impact current treatment or future experiences allows nurses to intervene to improve upon these. Knowing the guidelines for reducing pain from procedures and practicing these can significantly impact a child's life.

Children who present as gender creative or transgender may be diagnosed with gender dysphoria and require treatment in a pediatric endocrine environment. Following a diagnosis of gender dysphoria by a qualified mental health practitioner, pediatric endocrine nurses can assist with education and support as well as treatment for the youth. Endocrine treatments should be provided following guidelines and standards of care and may include the use of puberty blocking pharmacologic agents or prescribing cross hormone therapy to support transition. Pediatric endocrine nurses can advocate for the best possible hormone treatment for transgender youth to encourage optimal outcomes.

Providing gynecologic care for young women affected with physical or developmental disability during puberty can be complex. Parents of these youth are very concerned as their young person starts to grow and change. This chapter reviews the complex needs of this group of children/adolescents and reviews available medical treatment options. We will also review a number of strategies that nurses can implement to help families to improve quality of life and patient reported outcomes.

Keywords

Cerebral palsy · Contraception · Developmental disabilities · Gender dysphoria · Menstruation Needle fear · Pediatric · Pain reduction Procedural pain · Transgender youth

Abbreviations

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
cm	Centimeter
CP	Cerebral palsy
DD	Developmental disabilities
DSM-5	American Psychiatric Association Diagnostic and Statistical Manual Version 5
FSH	Follicle stimulating hormone
GAT	Growth attenuation therapy
GD	Gender dysphoria
GnRH	Gonadotropin releasing hormone
HELP-in KIDS	Help Eliminate Pain in KIDS Team
IM	Intramuscular
IUD	Intrauterine device
kg	Kilogram
LARC	Levonorgestrel IUD implants
LGBTQ	Lesbian, gay, bisexual, transgender, queer
LH	Luteinizing hormone
mm	Millimeter
NSAIDS	Non-steroidal anti-inflammatory drugs
OCP	Oral contraceptive pills
PENS	Pediatric Endocrinology Nursing Society
SC	Subcutaneous
SOC	Standards of care
TG	Transgender
WPATH	World Professional Association for Transgender Health

Key Terms

- **Needle phobia:** Extreme fear of medical procedures involving injections or blood draw.
- **Gender dysphoria:** Conflict between a person's physical or assigned gender and a person's emotional or psychological identity.
- **Developmental disabilities:** Diverse group of conditions due to impairment in physical, psychological, language, or behavior that arise before adulthood.

Key Points

- Understand best practices for subcutaneous and intramuscular injections in children. Know the recommendations for injection depth for infants, children, and teens.
- Recognize the benefit of knowing and using pain reduction guidelines for all procedures that break the skin in infants, children, and teens.
- Know the diagnostic criteria and treatment guidelines for transgender children and teens as it relates to endocrinology.
- Puberty is a normal developmental process for all children with many physical, psychological, and cognitive changes. Teens with developmental disabilities gain these benefits as well.
- Teens with developmental disabilities often process through puberty smoothly, and it can be less traumatic than families expect.

5.1 Injections and Pain Reduction Strategies

Children and adolescents who are being evaluated for potential endocrine conditions typically require venipuncture and treatments may often involve years of injections. Carefully choosing the size and length of needles used for injections helps to reduce pain and ensure that medications are administered either subcutaneous (SC) or intramuscular (IM) as prescribed. Ensuring age-appropriate pain-free strategies are used for such procedures from the start should be a priority for all health care providers. Finally, it is now known that memories of negative painful procedures in children lead to decreased compliance of treatment regimens and long-term avoidance of medical care as adults as well as a higher risk of chronic pain development (Noel et al. 2017; McMurtry et al. 2015; Thrane et al. 2017).

5.1.1 Defining Subcutaneous vs. Intramuscular Injections and Best Practice

Needle injection depth recommendations and availability have changed over time. Choosing the right needle length for the prescribed type of injection can help decrease anxiety and pain in the child or adolescent. Ultrasound studies now demonstrate that in order to achieve a subcutaneous injection depth on anyone the needle should be of a 6-mm length or shorter (Hofman et al. 2007; Koster et al. 2009). Most insulin and growth hormone delivery devices are compatible with needle lengths of 4–6 mm to ensure SC injection depth is maintained. A 6-mm needle is recommended to be given at an angled insertion with a pinched skin fold technique to ensure SC depth. Intramuscular injections are reached with a needle length of 8 mm or longer for children up to 60 kg. For those over 60 kg a 1 in (2.5 cm). length needle is recommended to achieve intramuscular depth. This is helpful when considering the change of medication administration routes for testosterone, for example, to change from biweekly or monthly intramuscular to weekly subcutaneous. Recent studies provide support that SC testosterone injections may allow for increased independence and much improved comfort and compliance of this necessary medication.

5.1.2 Pain Reduction and Distraction Techniques Based on Evidence and Best Practice

In 2010, a cross-Canada-independent national multidisciplinary group titled the Help Eliminate Pain in KIDS Team (HELP-in KIDS) developed clinical practice guidelines for vaccination injections in children. Dozens of studies involving thousands of children were reviewed in the development of these guidelines. This helps health care providers and parents identify strategies for injection pain prevention and reduction in infants and children. In 2015, those guidelines were updated to include adults and renamed the Help in Kids & Adults Team (Taddio et al. 2015). The development of the guidelines included examinations of over 130 studies looking at the management of pain across the lifespan. Key components of the guidelines include the following five domains of pain management interventions: (1) Procedural (2) Physical (3) Pharmacologic (4) Psychological (5) Process. The important highlights of these domains for endocrine nurses are summarized in Table 5.1.

High levels of needle fear can be described as a persistent, intense apprehension of or fear in response to a needle procedure and that a person may endure needles with intense distress or avoidance (Taddio et al. 2015). Should you suspect an individual has high levels of needle fear, the person should be referred to a mental health professional with knowledge and skills in needle fear as soon as possible.

One needs to consider a child or adolescents' past experiences of painful procedures before planning new procedures. It is well known that negative experiences with needles or blood draws (venipuncture) can lead to avoidance of medical care as adults (Noel et al. 2012). These negative experiences can start as early as infancy. Reframing memories of pain has been well described by child psychologist, Melanie Noel, from Calgary, Alberta, Canada (Noel et al. 2012). She describes how a child's memory of pain intensity is a better predictor of future pain perceptions than their actual reported pain intensity. Fear contributes to the memory of the event as fear is better remembered than the actual pain sensation. Through reframing memories of pain, one can lessen anticipatory fear and help the child manage the painful experience (Noel et al. 2012).

Table 5.1 HELP in Kids and Adults Guideline summary for Endocrine Nurses

Procedural interventions (injection techniques)	*Age group*
Rapid injection with no aspiration for all intramuscular injections	ALL
Inject the most painful medication last for multiple injections	ALL
Use the Vastus Lateralis injection site for intramuscular injections	<1 year especially
Physical interventions (body position and activity)	*Age group*
Breastfeeding during injections (if unable, use non-nutritive sucking)	<2 years
Skin to skin contact during injections	<1 month
Holding child during injections (upright in a bear hug or on the lap)	<3 years
Child/youth sitting up (not lying down)	>3 years
Vibrating device with cold (apply on and then just above injection site)	>3 years
Rub/stroke proximal to the injection site vigorously prior to and during injections (helpful to do in the palm of the hand for finger pokes)	>4 years
Pharmacologic interventions	*Age group*
Topical anesthetics (apply up to 1 h before the procedure)	ALL
Breastfeeding or sucrose +/or glucose solution (2 mL of 24–50% strength solution given 1–2 min prior to injection) with non-nutritive sucking	< 2 years
Oral analgesics prior to injections are not proven to be helpful	ALL
Psychological interventions	*Age group*
Distraction techniques (toys, bubbles, electronic devices)	ALL
DO NOT TELL them "it won't hurt"	ALL
Encourage them to take slow deep breaths (use bubbles or pinwheels)	>3 years
Praise the child/youth for engaging in distraction methods	ALL
Process interventions	*Age group*
Education of clinicians in pain management for injections	ALL
Education of parents before (preferred) or on the day of the injection	0–17 years
Education of the individual having the injection	>3 years
Parent presence for injections	<10 years

Adapted for finger pokes, subcutaneous and intramuscular injections, venipuncture
Adapted from Taddio et al. (2015)

Table 5.2 Resources for nurses to help make procedures pain free

Help **EL**iminate **P**ain in Kids & Adults Guidelines http://phm.utoronto.ca/helpinkids/
Children's Comfort Promise from Children's Minnesota www.childrensmn.org/services/care-specialties www.noneedlesspain.org
"It doesn't have to hurt" is an initiative led by the Centre for Pediatric Pain Research to get research evidence about children's pain directly into the hands of parents who can use it www.itdoesnthavetohurt.ca
International Forum for Injection Technique (FIT) www.fit4diabetes.com
Procedural pain management: A position statement with clinical practice recommendations by the American Society for Pain Management Nursing www.aspmn.org http://www.aspmn.org/documents/Czarnecki_ProcPainPositionStatement_2011.pdf
Distraction in Action Tool: predictive model and individualized coaching information https://webapps1.healthcare.uiowa.edu/CPadApp

Adults, in particular parents, can have a powerful influence before, during, and after the painful procedure by talking to children to help them reframe their memories in a more positive light. Talk about what the child thought went well and focus on what they did that was helpful such as taking deep breaths, blowing bubbles, being brave, and holding still. Praise them for what they did well even if it was the smallest thing so that the focus is positive. You can use "pain denying" talk such as "You were really brave. You didn't even cry, it was like it didn't hurt" (Noel et al. 2012). Tell children that their memory matters and suggest to the child that they focus on the helpful things the next time they have a painful experience, so they learn that they can control how they feel about the situation. Pain-relieving strategies and reframing memories of pain need to involve the nurse, the parent, and the child. Recent research highlights the efficacy of the use of distraction as a cognitive-behavioral intervention to assist children with painful procedures. Nurse researchers at the University of Iowa developed a web-based tool, "Distraction in Action," which is a predictive model that identifies a child's risk for distress with painful procedures and provides instructions for coaching and the use of distraction techniques based on the individual child's characteristics (McCarthy et al. 2010). A list of resources for nurses to help make procedures less painful can be found in Table 5.2.

Case Scenario 1

Finger poke fear

A 6-year-old boy presents to the endocrine clinic with a history of query hypoglycemia. It is decided that he should have a random blood sugar today with a personal blood glucose monitor and take this home to monitor during times of symptoms. He immediately retreats to the corner of the room at the mention of a finger poke. He hides his hands behind his back and says, "no way." The pediatric endocrine nurse gathers supplies for blood sugar testing including a battery operated "vibrating massage tool" that fits in the palm of the hand. She proceeds to show the family the blood glucose testing procedure and asks the father if the boy can help to assess his blood sugar first to test it out. The father agrees. The nurse shows the child how to have the father hold the vibrating massage tool in the palm of his hand and explains how this tool will tell his brain to focus on the vibration so that the finger poke won't hurt so much. After further direction from the nurse the child proceeds to test his father's blood sugar—with great success! Minutes later with a new lancet in the lancing device and new strip in the machine the 6-year-old boy holds the massage tool in the palm of his own hand. As the nurse speaks with parents to not draw too much attention, the boy pokes his own finger and smiles saying, "I hardly felt anything" as he reaches for the glucometer to bring it to the drop of blood. His parents were amazed that he actually did this

on his own, considering how afraid he was just 10 min. earlier. The time taken by the nurse to acknowledge the child's anxiety about the finger poke and find strategies to help decrease pain allowed for this first encounter to have a positive outcome for this child and his parents. Praising the child and talking about how he was able to do his own finger poke will help reframe the memory of this experience so that he remembers the positive parts. This will allow him to feel more in control the next time he has to face a painful experience.

Case Scenario 2

Infant and venipuncture

A 1-year-old girl with a diagnosis of congenital adrenal hyperplasia is being seen at the endocrine clinic for a follow-up appointment. Upon checking in, her mother is looking anxious and asks if her daughter really needs to have a blood test today. The nurse answers "*yes*" and explains how the test results are needed to make adjustments in medications in order to ensure adequate treatment. The mother proceeds to say that this is too distressing for her and her daughter; she had to hold her down last time and they were both crying. The nurse recognizes that the past experiences with venipuncture have not been positive for this child or her mother and aims to improve this. The nurse offers an analgesic cream for the venipuncture site. Options of breast or bottle-feeding during the procedure are reviewed, explaining how this helps to decrease the painful sensation for the infant. Further time is taken to explain the importance of making the venipuncture as pain and stress free for both the girl and her family. The mother agrees to the analgesic cream and this is applied by the nurse to two sites on the infant, in case one venipuncture attempt is unsuccessful. The infant's mother explains that she is breastfeeding; therefore, she would like to choose this option when it is time for the venipuncture. With the support of the nurse, the mother holds her child in a comfortable breastfeeding position allowing for her infant's arm to be accessible. The infant fusses with the tourniquet application but continues to breastfeed. The venipuncture proceeds with success. She does not react at all when the needle is inserted. Her mother is able to comfort her quickly after the blood is taken. The nurse supports both the baby and her mother during and after the venipuncture with positive words. The mother comments that she wished she had known these tips months ago and plans on using them moving forward. The nurse explains to the mother that in the future she can ask for help to make needles less painful for her child, especially if options are not offered ahead of time. The nurse follows with explaining that as the child grows new options would be made available to ensure less painful procedures and create positive experiences, including reshaping memories of pain as needed.

5.2 Gender Creative and Transgender Youth (Gender Dysphoria)

Endocrine nurses in a pediatric or adult setting one day will very likely encounter an individual who presents themselves somewhere on a non-typical gender spectrum. Gaining knowledge and developing an understanding and respect for each person's gender expression or presentation is every health care provider's duty in order to provide appropriate support and health care. Not all nursing education programs provide thorough training for students in gender diversity. There are thousands of nurses in the workforce currently who trained over 10, 20, and 30 years ago prior to any cultural or gender awareness programs. Personal beliefs and bias of nurses can significantly impact the health and access to timely care for transgender (TG) individuals (Dorsen 2012; Strong and Folse 2015; Zunner and Grace 2012). Knowing the diagnostic criteria, standards of care, clinical practice guidelines, and supports for TG people can help endocrine nurses make a very important impact in their lives.

The Pediatric Endocrinology Nursing Society (PENS) has a position statement on transgender youth. This document is an excellent resource for all nurses involved with transgender individuals. PENS recommends that all health care professionals receive "gender inclusive and awareness

training during both their professional education programs and their workplace orientation for the protection and inclusivity of children, youth and adults who fall under the transgender umbrella" (Kirouac 2015).

5.2.1 Definitions

Gender can be described as how one "feels" as either masculine, feminine, somewhere in between or neither (Veale et al. 2017; Bonifacio and Rosenthal 2015). This gender feeling is sometimes different than one's assigned sex at birth that is typically based on external genitalia. Gender dysphoria (GD) has been described as "Discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary characteristics)" (World Professional Association for Transgender Health 2017). Children of all ages may present with gender dysphoria. Most very young prepubertal children who may show some signs of cross gender curiosity, expression, and potential dysphoria over time are more likely to identify as gay or lesbian and not persist to be transgender. Young children who very strongly persist with their gender dysphoria into puberty are more likely to continue through to adulthood identifying as transgender (Bonifacio and Rosenthal 2015).

5.2.2 Diagnostic Criteria

For years, those identifying as transgender had been labelled as having gender identity disorder. The last edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) published in 2013 renamed the clinical description as gender dysphoria—removing "disorder" (American Psychiatric Association 2013). A qualified mental health practitioner should assess and diagnose all children and adolescents prior to any initiation of feminizing or masculinizing cross hormone therapy.

The increasing body of literature supporting gender expression and acceptance over the past 10 years exceeds the archaic methods of some recommendations that transgender individuals be "repaired" as if they were broken. Reparative or conversion therapy is now banned in some countries and goes against one's human right of gender expression (Bonifacio and Rosenthal 2015).

5.2.3 Treatment Guidelines

The inter-professional World Professional Association for Transgender Health (WPATH), formerly known as the Harry Benjamin International Gender Dysphoria Association, which originated in 1979, developed and updated the "Standards of Care" (SOC) for the treatment of transgender individuals. These standards are supported worldwide and can help to ensure transgender individuals have access to equitable care no matter where they live. This 120-page standards of care was last updated in 2011 making it the 7th version (World Professional Association for Transgender Health 2017).

The Endocrine Society has released a 2017 update to their previous 2009 Clinical Practice Guidelines for the Treatment of Transsexual Individuals, now titled "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline" (Hembree et al. 2017). Following the WPATH and Endocrine Society Clinical Practice Guidelines will help inter-professional clinics provide competent, sensitive, and timely care for gender creative and transgender youth (Hembree et al. 2017). A summary of current clinical guidelines in the care of Transgender Youth for Endocrine Nurses is summarized by Kirouac and Tan (2017), with permission this can be found in Table 5.3.

5.2.4 Public Education and Support

Health care, school, and social experiences of self-identified transgender youth and young adults have not been very positive. A Canadian Trans Youth Health Survey was performed by an inter-professional team across Canada for 14–25 year olds. Responses from over 900 peo-

Table 5.3 Assessments, hormone therapy, and monitoring for transgender youth

Tanner staging examination for puberty status		
Puberty blocking <u>if</u> Tanner stage 2 or higher <u>and</u> desired by the youth Ensure there is no interfering untreated psychiatric comorbidity, youth has the ability to consent, parents/guardian offering support *Use an injectable gonadotropin releasing hormone (GnRH) agonist** 3.75–7.5 mg intramuscularly q 4 weeks OR 11.25–20 mg intramuscularly q 12 weeks *Every 3 months monitor**: height, weight, sitting height, tanner stage, LH, FSH, estradiol, and/or testosterone as appropriate. *Every year**: renal and liver functions, lipids, glucose, insulin, HgA1C. Bone density if warranted (deemed high risk) and bone age of left hand		
Male to female (MTF)[a] *Antiandrogens**:		Female to male (FTM) *Menses cessation if not using GnRH*
Spironolactone (monitor Se. Na + q 2–3 months in year 1) Cyproterone acetate[b]	50 mg/day, increase q 2–4 weeks by 50 mg (max 200 mg/day) 50–100 mg/day	Consider using oral or injectable contraceptive methods that could stop menses or Intrauterine device (e.g., Mirena, by Adol. Gynecology)
Discuss desire for and potential availability of fertility preservation options Refer to fertility specialist prior to cross hormone therapy treatment if desired		
Once there is a gender dysphoria diagnosis per DSM-5 by a qualified mental health practitioner and desire for cross hormone therapy		
Age 16 years and after baseline bloodwork (below*): Informed consent for induction of female puberty Using oral 17-Beta estradiol, Increasing the dose every 6 months: 5 µg/kg/day, 10 µg/kg/day, 15 µg/kg/day, 20 µg/kg/day Adult dose = 2 mg/day		Age 16 years and after baseline bloodwork (below*): Informed consent for induction of male puberty Using intramuscular testosterone esters: Enanthate (200 mg/mL) or, cypionate (100 mg/mL) Increasing the dose every 6 months: 25 mg/m^2 per 2 weeks IM, 50 mg/m^2 per 2 weeks IM 75 mg/m^2 per 2 weeks IM, 100 mg/m^2 per 2 weeks IM Can be divided into weekly subcutaneous (SC) doses for increased independence, <pain[c]
See every 2–3 months in first year on cross hormone tx., then 1–2 times per year, monitor blood pressure *Baseline and q 3 months fasting labs: CBC, liver Fcn, lipids, Gluc, BHCG (FTM), Prl, Testo, estrogen		
		Discuss desire for top surgery and send referral if needed (age of consent is center dependent)

Reproduced with permission from Kirouac and Tan (2017)
*Adapted from the Endocrine Society Clinical Practice Guidelines (Hembree et al. 2017)
[a]Estrogens used with or without antiandrogens or GnRH agonist
[b]Not available in the United States
[c]Personal communication, Canadian Pediatric Endocrine Nurses Group, Toronto, November 2016

ple showed prominent themes such as the lack of awareness, understanding, and practical knowledge of health care practitioners (Veale et al. 2017). Many individuals do not feel safe talking about gender preference especially with health care providers that have cared for them since birth.

A joint United States and Canada Qualitative Study of Community Resources and Supports for LGBTQ Adolescents found that critical support is found from inclusive education, gay-straight alliances (GSAs), and anti-bullying policies in schools (Eisenberg et al. 2018). Nurses are in a very good position to ask students and parents about access to such resources and encourage participation. There continues to be publications set out by this prominent research group through www.saravyc.ubc.ca.

Nurses are in a unique position to advocate for individuals who present somewhere on the gender spectrum, especially transgender and gender creative youth. A summary of ways to create gender inclusive clinical spaces are outlined in Table 5.4 (Kirouac and Tan 2017). The opportunity to make a positive impact in the life of a gender creative or transgender youth is always there—stay well informed and always listen carefully.

Table 5.4 Creating clinical spaces that are gender inclusive

Know the resources for nurses and families: These are always current from www.bcchildrens.ca/health-info/coping-support/transgender-resources
Have "rainbow" (LGBTQ friendly) signage and handouts and/or resources put on: doors/windows/bathrooms/clinic counters/pamphlet racks/websites
Ensure you have toys in the waiting area that are gender inclusive
Acknowledge and affirm at time of contact with patients their expressed gender variance
Negotiate preferred names and pronouns directly with patients and ensure these are visible on the chart or electronic medical record as "preferred" until legal changes exist
Negotiate safety and confidentiality with your patient before speaking with their parents, primary care practitioners or their school
Explore psychosocial, mental health, and wellness with all patients. Consider accessing validated gender assessment tools such as the Utrecht and body image scales
Obtain a sexual history asking about the use of protection (condoms/contraceptives) and rather than "boyfriend or girlfriend" ask about a partner
Ask the patient what names they prefer for their body parts and be sensitive to their comfort during any physical examinations
Negotiate support systems and encourage patients to use them
Know the resources and referral sources for general mental health (MH) access, specific gender MH assessments and gender specialty care like surgery, electrolysis in your area
Advocate for the child/youth/family within the health care system and community through participating in community/school education, media interviews, government relations

Reproduced with permission by Kirouac and Tan (2017)

Online resources for nurses regarding Gender Creative and Transgender Youth:

The Endocrine Society Clinical Practice Guidelines for the Endocrine treatment of Gender-Dysphoric/Gender-Incongruent Persons (2017)

https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines

The Paediatric Endocrinology Nursing Society Position Statement for Transgender Youth

www.pens.org

Gender Creative Kids CANADA: Resources for gender creative kids and their families, schools and communities

www.gendercreativekids.ca

Gender Spectrum: helping to create gender sensitive and inclusive environments for all children and teens

www.genderspectrum.org

National Centre for Transgender Equality (US)

www.transequality.org

The World Professional Association for Transgender Health: access to Standards of Care

www.wpath.org

Links to the Canadian Trans Youth Health Survey Reports and the USA/Canada Joint Study of Community Resources and Supports through the Stigma and Resilience Among Vulnerable Youth Centre (SARAVYC). Researchers with a focus on youth health equity

www.saravyc.ubc.ca

Case Scenario 3

Gender Creative and Transgender Youth

A 10-year-old natal male child is referred to the pediatric endocrine clinic by the child psychologist with a diagnosis of gender dysphoria. Upon arrival to the clinic, this child appears female with long curly hair and is wearing pink tights and a flower covered t-shirt. Parents are greeted by the receptionist who asks the family name and the child's preferred name. After a few minutes in the waiting room, the child and family are invited to the clinic room where the nurse proceeds to weigh and measure the child. These measurements are plotted on a "male" growth chart that has been photocopied to take out the color. Time is spent with parents and the child to learn the child's medical history, family history, and more specifically their gender preferences and desires for their future self. The nurse explains to the child that there will be a physical exam to help assess the level of puberty they are currently in. The child expresses that they identify as female and prefer female pronouns. Parents confirm that the child is presenting as female at school and in their community. The nurse assesses the child and learns that she is at Tanner stage 2 for testicular development. The child is upset about the examination and tells the nurse she does not want any further puberty

development as she is a girl. Time is spent explaining to parents and the child the role of a gonadotropin releasing hormone treatment to put puberty on hold and prevent further masculinization. The child is afraid of needles but is willing to try the treatment to prevent further puberty changes. The nurse reviews options of using analgesic creams, a vibrating device at and above the injection location, as well as distraction techniques at the time of injection. Parents and the child agree to try the gonadotropin releasing hormone treatment and plan an appointment in the upcoming weeks for the first injection. Upon return to the clinic following the successful first injection of the GnRH analogue, routine every three-month bloodwork is ordered for LH, FSH, and testosterone as well as physical examinations to ensure no further testicular growth. The option of an antiandrogen therapy such as spironolactone is offered to parents and the child. At this time, the family and the child would like to continue monitoring with the endocrine clinic every 3 months. The child has shared that she is looking forward to going through puberty like her friends, especially having breast development. The nurse explains that over the coming years the options of cross hormone therapy with estrogen will be further explored. The nurse reinforces that they are following treatment guidelines that are used across the world. The child and family appear reassured that the treatment approach is one that is used worldwide.

5.2.5 Conclusions

Infants, children, and teens attending any endocrine appointment or testing facility are likely to encounter the need for blood testing or injections. Many have not been offered any pre-treatment for these painful procedures to decrease the pain and anxiety they trigger. It is well known that these painful experiences can stay into adulthood, significantly affecting future encounters and access to health care as well as risk of chronic pain. Nurses are urged to consider all options to decrease the painful experiences of procedures in infants, children, and teens while assisting in reshaping their memories of pain to improve their quality of life.

Children and youth identifying as transgender face many challenges with mental health and acceptance by health care providers. Guidelines have been well developed to support transgender youth through an experienced multidisciplinary team as they transition to their preferred gender. All nurses should be familiar with the risks of this population and how to create gender friendly environments. Endocrine nurses can be instrumental in ensuring access to puberty blocking and cross hormone therapy for transgender youth while encouraging family and community supports.

5.3 Girls with Developmental Disability and Puberty

Puberty is a complex developmental period involving both physical and psychological maturation. This includes rapid growth, development of secondary sexual characteristics, maturation of reproductive functions, and bone mass accrual, as well as cognitive and psychological development. This process is the same for children with developmental/physical disabilities but raises a number of associated concerns for the girls with developmental disabilities (DD) and particularly for their families (Wolf and Long 2016; Kirkham et al. 2013).

Puberty and approaching menses can be very stressful for parents. They may share concerns about their daughters who are affected with DD as they increase in size and weight. How will their daughters manage the bleeding and hygiene measures required? How will the family cope with management of menstruation and related hygiene issues if their daughter isn't capable of independent self-care? Issues such as behavioral changes related to the pre-menstrual period, how to manage the pain of menstrual cramps, the risk of pregnancy, or whether puberty will affect their other medical issues (e.g., seizures) are typical concerns of parents of girls with DD (Tracy et al. 2016). Families sometimes may ask the health care team if going through puberty is necessary.

For the purpose of this chapter, "developmental disabilities" (DD) will include girls with

moderate to severe global developmental delay, autism spectrum disorder (ASD), moderate to severe cerebral palsy (CP) and neuromuscular conditions, and complex seizure disorders. When there are concerns specific to these diagnosis, these will be pointed out.

5.3.1 Pubertal Benefits

Families may be distressed with the onset of puberty in their child with DD and will ask the health care team if puberty is really necessary, or if it can be stopped entirely. There are many positive outcomes associated with puberty and it is important to review them (Zacharin et al. 2010).

First of all, there are structural and functional changes occurring in the brain including an increased ability to communicate and a greater desire to be independent (Fima 2006; Bourguignon and Juul 2012). Even for non-verbal, severely delayed children changes in cooperation and minimal understanding are reported by families. Physical strength also improves, and the girls may be able to help more with their own position changes. Overall mood is also reported to improve with the onset of puberty (Quint 2008).

Another important factor is the structural changes in bone formation during puberty. This bone formation becomes the base of children's bone mineral density for life. Puberty has been shown to increase bone mass by 40–50% (Lazar and Phillip 2012). Estrogen elevation associated with puberty is also important to the maturity of the cardiovascular system (Fima 2006; Freedman et al. 2002).

However, there are also many difficulties associated with puberty to consider, including hygiene management, comprehension of the physical changes, and the burden of physical care on parents, caregivers, and school support staff to consider. When parents are asked about their experiences in hindsight, they almost always report that their daughters tolerated the onset of menses better than was expected (Zacharin et al. 2010).

5.3.2 Pubertal Onset Differences

In general, girls with DD experience similar onset of puberty similar to non-affected girls. However, there are a few exceptions. Children with cerebral palsy tend to begin puberty earlier, but the timing of menarche is later than non-affected children. The median onset of menses for girls with cerebral palsy is 14 years compared to the typical onset at 12.8 years (Siddiqi et al. 1999). Children with neurodevelopmental disabilities are 20 times more likely to experience early pubertal change. It is not clearly understood why this happens, but it is generally believed to be related to the malformation of the central nervous system and its effect on the hypothalamic-pituitary-ovarian axis (Siddiqi et al. 1999).

Late puberty may also be more common in children with disabilities (Quint 2008) and girls with compromised nutrition (Wei and Crowne 2016). If early onset puberty causes concerns for self-esteem, self-care and hygiene, or risk of sexual abuse, then treatment with a gonadotropin releasing hormone (GNRH) agonist may be an option.

5.3.3 Assessment of Patients

There are many factors for the nurse to take into consideration when obtaining a medical history from DD girls and their families. The young woman should be included in the discussion as much as possible, while taking into consideration her cognitive and developmental level. As well as a typical medical history, the following special concerns need to be assessed (Kirkham et al. 2013; Tracy et al. 2016; Quint 2008):

Medications

- How does the child take her medications? Can she swallow pills? Does she have a feeding tube? It is important to remember that oral contraceptive pills (OCP) need to be swallowed unless access to chewable versions is available, and then they can be crushed and given in a g-tube.
- For children with a seizure disorder, it is important to consider what kind of anticonvulsant they are taking since some anticonvulsant

medications may not be compatible with OCP use due to increased liver clearance of estrogen.
- It is important to assess if the child is taking antipsychotic medication since some antipsychotic medications cause elevated prolactin levels, resulting in irregular periods and lactation.
- The nurse should also inquire whether the girl will be taking her own medication or will be supervised by the parent. For girls with a diagnosis of fetal alcohol syndrome, severe attention deficit hyperactivity disorder (ADHD), or mild-moderate cognitive impairment, impulsivity and poor memory, parents should be counseled to carefully supervise medication management.

Other specific concerns to address in medical history:
- History of previous surgeries since anatomic changes may effect periods (e.g., gastroschisis repair).
- Are they ambulatory, partially or totally wheelchair bound? For non-weight bearing children, bone accrual is very important to consider and any treatment that does not support good bone health is not recommended.
- Can the girl physically manage her own self-care related to hygiene? This may be a concern for girls with severe CP or severe cognitive delay. Studies show that girls who can independently manage toileting needs will learn to manage menses hygiene.
- Do they have issues with increased skin sensitivity (typical with autisn spectrum disorder)? A diagnosis of ASD raises a few concerns including increased skin sensitivity and sensitivity to color. For example, some teens will be very uncomfortable wearing menstrual pads and may remove them or be upset by the sight of blood.
- Other underlying medical concerns, such as chromosomal disorders, being significantly underweight, thyroid disorders, and epilepsy (found in 20–40% of people with intellectual disabilities (Bowley and Kerr 2000)).
- Is the girl verbal or non-verbal?
- Is bowel and bladder incontinence an issue since this can further complicate self-care (Tracy et al. 2016; Quint 2008).

Menses-related medical history assessment (Wolf and Long 2016; Quint 2008):
- Does the girl have pain with periods or if non-verbal, are there behaviors that might indicate this?
- How regular is the period? (every 21–45 days is within normal range for all girls).
- How long does the period last? (4–7 days is within normal range).
- How heavy is the bleeding? heavy bleeding would be changing pads every 1–2 h, clots bigger than 1 cm, gushing with standing up or overflowing pads at night in bed.

Social experiences:
- Does the child/adolescent require periodic or constant adult supervision?
- Is there a risk of abuse or pregnancy due to school or living arrangements?
- Is there a social group this girl can be exposed to? Social experiences play an important role in psychosexual development. Typical teens often get at least some of their information regarding puberty or menses through peers and social contacts. Girls with disabilities are known to have reduced social contacts and therefore may not gain as much knowledge (e.g., STIs) (Quint 2008; Murphy and Elias 2006; Grover 2011).

What are the primary concerns of the child/adolescent and parent(s)?
- Does regularity and predictability of periods matter or is the actual bleeding the biggest concern? Is treatment aimed towards pain control, bleeding control, hygiene concerns, behavior management, or birth control? There are many options for managing menses in this population. It is important to assess what the family and girl want to "control" and target your treatment recommendation(s).
- Reassure the adolescent and parent that the health care team will address specific concerns

related to menses management when the girl is assessed at Tanner 3. Once menarche has occurred, the medical options can be discussed.
- It is important to remember that many girls with severe physical and developmental issues manage menses well with little to no intervention, particularly if the periods are predictable and manageable.

5.3.4 Medical Treatment Options

5.3.4.1 LARC (Levonorgestrel IUD Implant)

LARC is an intrauterine device (IUD) placed within the uterus that contains progesterone. Progesterone is a naturally occurring hormone that prevents the buildup of the lining of the uterus. Overtime this may cause partial or total amenorrhea. About 65% of patients experience total amenorrhea while the remainder experience periods that are much lighter and typically without cramping. In the special needs patient, this device will be implanted under a brief anesthesia in the operating room (Savasi et al. 2009; Albanese and Hopper 2007).

The patient with a LARC will continue going through the hormonal cycle of menses, so this is sometimes not the best choice for patients with behavioral hormonal issues or seizures proven to be affected by hormones (catamenial) (Quint 2008).

Benefits of LARC:
- Reduced bleeding to complete amenorrhea
- Almost complete reduction of dysmenorrhea
- Little risk for bone depletion
- No risk for blood clots
- Lasts for 3–5 years
- Highest success for birth control

Stated side effects of the LARC:
- Cramping for short term after insertion
- Small amounts of vaginal bleeding (spotting) after insertion for up to 6 months
- Headache
- Mood changes
- Weight gain

LARC is a good choice for patients with:
- Seizure disorders
- Bone health concerns
- Very heavy menstrual bleeding or a bleeding disorder (Savasi et al. 2009; Albanese and Hopper 2007; Dizon et al. 2005)

5.3.4.2 Oral Contraceptive Control Pill or Patch

Oral contraceptive pill (OCP) or patch is a combination medication that contains estrogen and progesterone, which overrides the pituitary ovarian axis and results in anovulation. A low-dose monophasic pill can be used continuously, which may be useful for some patients (Grover 2011).

Benefits of OCP:
- Reduced blood flow with periods
- Reduced pain with periods
- Regular predictable periods
- Contraception
- Acne improvement
- Moods may be more stable

Possible side effects of OCP:
- Slightly increased risk of blood clots may even be higher for wheelchair bound teens
- Break through bleeding
- Nausea
- Headaches
- Mood changes
- Special consideration for those on anticonvulsants due to increased activation of cytochrome P450, which results in higher excretion of estrogen through the liver, that may require a higher dose of OCP (Quint 2008; Savasi et al. 2009; Albanese and Hopper 2007; Dizon et al. 2005)

Continuous use of OCP or patch:
- Once the pill or patch has been successfully introduced with a withdrawal bleed every 3 weeks, the adolescent may transition to continuous use. For example, 9 weeks of OCP back to back without taking a break or placebo pills. This will result in a planned withdrawal bleed every 10 weeks. Using the patch, you

may continue to put a new patch on weekly for 10 weeks and then take it off for the withdrawal bleed.

5.3.4.3 Depo Provera Injections

Depo Provera is an intramuscular injection of progesterone that is given every 12 weeks or more frequently. It reduces buildup of the lining of the uterus and eventually results in anovulation.

Benefits of depo provera:

- Reduced blood flow with periods
- Reduced pain with periods
- Contraception
- Eventual very light periods or none
- Treatment only every 12 weeks

Possible side effects of depo Provera:

- Weight gain
- Suppression of the hypothalamic-pituitary-ovarian axis results in depletion of estrogen and therefore reduction in the accrual of bone; therefore, it is not recommended for those at risk for reduced bone health because of decreased mobility
- Headache
- Breakthrough bleeding (Veale et al. 2017; Bonifacio and Rosenthal 2015; (World Professional Association for Transgender Health 2017))

5.3.5 Permanent Surgical Treatment

The option of surgical treatment as an intervention to manage menstruation varies from country to country. In general, hysterectomy or other forms of permanent sterilization is considered illegal, and possibly unethical. If all other strategies for menses management fail and the girl is experiencing significant distress, surgery may be considered after review with a specialist gynecologist and an appropriate ethics review (American College of Obstetricians and Gynecologists 2017).

- In recent years, there has been a movement towards a treatment referred to as growth attenuation therapy (GAT). Physicians may be asked about growth attenuation, which uses very high dose estrogen therapy and/or hysterectomy/sterilization and mastectomy. The goal of this therapy is to retain a girl in a "child-like state." Supporters of this approach propose that the outcomes of a smaller adult size will allow easier physical care of the adolescent/adult for the caregivers and therefore reduce hygiene concerns, and possibly reduce the possible risk of sexual abuse. However, at this time there is insufficient evidence to support this approach (Quint 2008; Savasi et al. 2009; Albanese and Hopper 2007; Dizon et al. 2005).

5.3.5.1 Pain Control

Painful menstrual periods are experienced by 10–45% of teens (Albanese and Hopper 2007; Dizon et al. 2005). For non-verbal girls, a change in behavior may be the only clue to whether they are experiencing period pain.

Non-steroidal anti-inflammatory drugs (NSAIDS) should be the first line of treatment, started the day before or the first day of bleeding, and given on a regular schedule during the onset of menses. Regular use of NSAIDS may reduce period flow by 30–50% (Quint 2008; Savasi et al. 2009; Albanese and Hopper 2007; Dizon et al. 2005).

At the start of menstrual period:

- Administer NSAIDs to prevent period cramps
- If periods are predictable, can start NSAIDs just before the onset of period and take regularly for the first few days.
- For period cramps due to prostaglandins, NSAIDs can suppress prostaglandins if taken consistently.
- For girls with period-related behavior concerns, treatment with NSAIDs has been shown to be helpful.

5.3.6 Nursing Strategies

The nurse should counsel the parent of a child with DD child regarding strategies to promote

adjustment to puberty and menstruation (Kirkham et al. 2013; Zacharin et al. 2010; Quint 2008; Grover 2011).

Prior to the onset of puberty:

- To start adjusting to the texture and sensation of pads, use mini-pads inside of panties for a brief time and gradually increase the time until they are comfortable with the sensation. Then, gradually work up to wearing larger size pads. Buy a few different brands and styles and be aware of perfumes and fragrances if the child has sensitivity to new smells or textures. If the texture causes a concern, try natural fiber or reusable pads (often available at health food stores).
- Mark the place on panties where the pad is to be stuck.
- Once the girl is comfortable wearing a pad, add a few spots of red food color to the pad; if the color causes distress sometimes describing the pad as a "bandage" can help.
- Girls wearing diapers often may want to use pads inside of the diaper. This provides some "normality" to their experience and also saves on the amount of diapers that are used.
- Allowing the girl in the bathroom to observe the mother or sister model the changing of pads may help them realize that this is normal for all women.

After the onset of puberty:

- Parents often describe behavior and mood changes around the time of periods. While this is possible, it may not always be an accurate interpretation. Emotional swings may also be a part of puberty or related to pain with periods. The best way to clarify this is to have parents, girls, or caregivers keep a calendar that includes period days, amount of bleeding, possible pain behaviors, as well as mood. Over a few months, a pattern may often become apparent. If seizures are a concern, they should also be reported in conjunction with periods on the calendar.
- Make a schedule for pad changes at school.
- Make a hygiene pack that can go to school or out with the girls including a change of bottoms, extra pads, and hygiene wipes.

5.4 Conclusions

The key to providing the right support during puberty to children with DD is to take a detailed and specific medical history. There is no method that is perfect for everyone. Different treatment options have different side effects and must be chosen carefully. It is also critical to listen to the family and the girls! They will tell you what they need help with the most and it may not always be what you assume. This is an area of practice that would greatly benefit from more outcome research, so that our practice can be more evidence based.

References

Albanese A, Hopper NW. Suppression of menstruation in adolescents with severe learning disabilities. Arch Dis Child. 2007;92(7):629–32.

American College of Obstetricians and Gynecologists. Sterilization of women: ethical issues and considerations. The American College of Obstetricians and Gynecologists [Internet]. 2017.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Bonifacio HJ, Rosenthal SM. Gender variance and dysphoria in children and adolescents. Pediatr Clin N Am. 2015;62(4):1001–16.

Bourguignon JP, Juul A. Normal female puberty in a developmental perspective. Endocr Dev. 2012;22:11–23.

Bowley C, Kerr M. Epilepsy and intellectual disability. J Intellect Disabil Res. 2000;44(Pt 5):529–43.

Dizon CD, Allen LM, Ornstein MP. Menstrual and contraceptive issues among young women with developmental delay: a retrospective review of cases at the Hospital for Sick Children, Toronto. J Pediatr Adolesc Gynecol. 2005;18(3):157–62.

Dorsen C. An integrative review of nurse attitudes towards lesbian, gay, bisexual, and transgender patients. Can J Nurs Res. 2012;44(3):18–43.

Eisenberg ME, Mehus CJ, Saewyc EM, Corliss HL, Gower AL, Sullivan R, et al. Helping young people stay afloat: a qualitative study of community resources and supports for LGBTQ adolescents in the United States and Canada. J Homosex. 2018;65(8):969–89.

Fima L. In: Fima L, editor. Pediatric endocrinology. 5th ed. New York: Marcel Dekker; 2006.

Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics. 2002;110(4):e43.

Grover SR. Gynaecological issues in adolescents with disability. J Paediatr Child Health. 2011;47(9):610–3.

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(11):3869–903.

Hofman PL, Lawton SA, Peart JM, Holt JA, Jefferies CA, Robinson E, et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. Diabet Med. 2007;24(12):1400–5.

Kirkham YA, Allen L, Kives S, Caccia N, Spitzer RF, Ornstein MP. Trends in menstrual concerns and suppression in adolescents with developmental disabilities. J Adolesc Health. 2013;53(3):407–12.

Kirouac N. PENS position statement on transgender youth. J Pediatr Nurs. 2015;31:230–1.

Kirouac N, Tan M. Gender creative or transgender youth and advanced nursing practice. Pediatr Endocrinol Rev. 2017;14(Suppl 2):441–7.

Koster MP, Stellato N, Kohn N, Rubin LG. Needle length for immunization of early adolescents as determined by ultrasound. Pediatrics. 2009;124(2):667–72.

Lazar L, Phillip M. Pubertal disorders and bone maturation. Endocrinol Metab Clin N Am. 2012;41(4):805–25.

McCarthy AM, Kleiber C, Hanrahan K, Zimmerman MB, Westhus N, Allen S. Factors explaining children's responses to intravenous needle insertions. Nurs Res. 2010;59(6):407–16.

McMurtry CM, Riddell RP, Taddio A, Racine N, Gordon MA, Asmundson JG, Noel M, Chambers CT, Shah V. Far from "just a poke": common painful needle procedures and the development of needle fear. Clin J Pain. 2015;31(10S):S3–7.

Murphy NA, Elias ER. Sexuality of children and adolescents with developmental disabilities. Pediatrics. 2006;118(1):398–403.

Noel M, Chambers CT, McGrath PJ, Klein RM, Stewart SH. The influence of children's pain memories on subsequent pain experience. Pain. 2012;153(8):1563–72.

Noel M, Pavlova M, McCallum L, Vinall J. Remembering the hurt of childhood: a psychological review and call for future research. Can Psychol. 2017;58(1):58–68.

Quint EH. Menstrual issues in adolescents with physical and developmental disabilities. Ann N Y Acad Sci. 2008;1135:230–6.

Savasi I, Spitzer RF, Allen LM, Ornstein MP. Menstrual suppression for adolescents with developmental disabilities. J Pediatr Adolesc Gynecol. 2009;22(3):143–9.

Siddiqi SU, Van Dyke DC, Donohoue P, McBrien DM. Premature sexual development in individuals with neurodevelopmental disabilities. Dev Med Child Neurol. 1999;41(6):392–5.

Strong KL, Folse VN. Assessing undergraduate nursing students' knowledge, attitudes, and cultural competence in caring for lesbian, gay, bisexual, and transgender patients. J Nurs Educ. 2015;54(1):45–9.

Taddio A, McMurtry CM, Shah V, Riddell RP, Chambers CT, Noel M, et al. Reducing pain during vaccine injections: clinical practice guideline. CMAJ. 2015;187(13):975–82.

Thrane SE, Wanless S, Cohen SM, Danford CA. The assessment and non-pharmacologic treatment of procedural pain from infancy to school age through a developmental Lens: a synthesis of evidence with recommendations. J Pediatr Nurs. 2017;31:e23–32.

Tracy J, Grover S, Macgibbon S. Menstrual issues for women with intellectual disability. Aust Prescr. 2016;39(2):54–7.

Veale JF, Watson RJ, Peter T, Saewyc EM. Mental health disparities among Canadian transgender youth. J Adolesc Health. 2017;60(1):44–9.

Wei C, Crowne EC. Recent advances in the understanding and management of delayed puberty. Arch Dis Child. 2016;101(5):481–8.

Wolf RM, Long D. Pubertal development. Pediatr Rev. 2016;37(7):292–300.

World Professional Association for Transgender Health (WPATH). The standards of care for the health of transexual, transgender, and gender non-conforming people. 2017. www.wpath.org.

Zacharin M, Savasi I, Grover S. The impact of menstruation in adolescents with disabilities related to cerebral palsy. Arch Dis Child. 2010;95(7):526–30.

Zunner BP, Grace PJ. The ethical nursing care of transgender patients: an exploration of bias in health care and how it affects this population. Am J Nurs. 2012;112(12):61–4.

Transition from Paediatric to Adult Services

6

Susie Aldiss

Contents

6.1 **Introduction** 102

6.2 **Issues Within Transitional Care** 103

6.3 **Key Principles of Transition** 104

6.4 **Interventions to Improve Transition** 107

6.5 **Models of Transitional Care Interventions** 107

6.6 **Service Delivery-Focused Interventions** 107
6.6.1 Transition Policies and Pathways 107
6.6.2 Transition Clinics and Young Adult Clinics 109
6.6.3 Enhanced Support/Follow-Up 110

6.7 **Healthcare Professional-Focused Interventions** 110
6.7.1 Named Transition Coordinator or Key Worker 110

6.8 **Young Person-Focused Interventions** 110
6.8.1 Skills Training/Education for Young People 110
6.8.2 Assessments of 'Readiness': Transition Checklists 111
6.8.3 Technology-Based Interventions 111

6.9 **Transition and Endocrinology** 115

6.10 **Conclusions** 115

6.11 **Critical Thinking Points** 115

References 116

S. Aldiss (✉)
School of Health Sciences, University of Surrey,
Surrey, UK
e-mail: s.aldiss@surrey.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_6

Abstract

The transition from child to adult services is a crucial time in the health of young people who may potentially fall into what has been described as a poorly managed 'care gap'. Health service provision, which fails to meet the needs of young people and families at this time of significant change, may result in deterioration in health or disengagement with services, which can have negative long-term consequences. There are two main challenges to providing transitional care: how care is organised and the impact this has on the continuing delivery of care to young people. In this chapter, the issues with transitional care are discussed along with the key principles of transition. Interventions to improve transition are presented along with examples from the literature which include: transition clinics, enhanced support/follow-up, transition coordinator, skills training/education for young people, and technology-based interventions. Endocrine care within the transitional process will also be touched upon, with particular reference to children and young people requiring growth hormone therapy, young people with a disorder of sex development, and young people who have undergone cancer treatment as a child. A successful transition process involves the provision of care that is uninterrupted, coordinated, and developmentally appropriate over a period of time before, during, and after a young person transfers to adult services.

Keywords

Transition · Transfer · Adolescent
Coordination · Long-term conditions
Young adult

Abbreviations

CQC	Care quality commission
DSD	Disorder of sex development
NICE	National Institute for Health and Care Excellence
ON TRAC	Taking responsibility for adolescent/adult care
UK	United Kingdom

Key Terms

- **Transition:** A purposeful and planned process of supporting young people and their families/carers to move from child to adult services. 'Transition' refers to the whole process including initial planning and preparation, the actual transfer between services, and continued support after a young person has moved to adult services.
- **Transfer:** Within the transition process 'transfer' occurs. This is the point at which the young person moves to adult services and is discharged from child services.

Key Points

- The transfer of young people from child to adult services is a crucial time in the health of young people who may potentially fall into a poorly managed 'care gap'.
- The young person should be at the centre of transitional care; transition should be developmentally appropriate taking into account the different needs of each young person.
- Transition should be a gradual process which starts in early adolescence and continues until the young person is well established in the adult care setting.
- Parents should be involved in the transition process and gradually prepared to transfer responsibility of health to the young person.

6.1 Introduction

An increasing number of children with long-term health conditions are now surviving into adulthood. Thus, there are a growing number of children with long-term health needs or complex disabilities who will require ongoing specialised care. The provision of health care for this group has been the focus of attention for some time, with numerous reports over the past decade highlighting the need for improvement in order to better meet the needs of young people.

The journey through adolescence to adulthood is a challenging time of psychological, physical, and social change. Young people with a long-term health condition can face even greater challenges as they deal with complex and important changes in the care they need and in the way it is provided. The role of the young person, and also their parents/carers, will evolve with the young person often wanting and indeed being expected to exercise greater independence in the management of their health condition. Health service provision, which fails to meet the needs of young people and families at this time of significant change, may result in deterioration in health or disengagement with services which can have negative long-term consequences. The transition of young people from child to adult services is a crucial period in the health of young people.

Transition services aim to bridge this 'care gap' between child and adult services. 'Transition' can be defined as 'a multi-faceted, active process that attends to the medical, psychosocial and educational/vocational needs of adolescents as they move from the child-focused to the adult-focused health care system' (Blum et al. 1993, p. 573). Within the transition process 'transfer' occurs, which refers the point at which the young person moves to adult health services and is discharged from child health services. On occasion, these two terms, transition and transfer are used interchangeably.

6.2 Issues Within Transitional Care

There are two main challenges to providing transitional care: how care is organised and the impact this has on the continuing delivery of care to young people. Unfortunately, many young people have a very different experience of transition, which does not meet the aspirations of Blum et al.'s (1993) definition. Numerous research studies have reported that some young people experience the transfer to adult care as disjointed and more of a one-off transfer, rather than a process of preparation in which they are involved, that is transition: such experiences seem to be comparable across young people with different diagnoses (for a review see Fegran et al. 2014). Lack of 'being prepared' was also a finding from the recent report on transition from the Care Quality Commission (CQC) in the United Kingdom (UK) (CQC 2014). Here only 54% of young people described preparation for transition that had enabled them to be involved in the process as much as they wanted to be and 80% of pre-transition case notes reviewed had no transition plans for health (CQC 2014).

Current approaches to transition are often described within three categories (Royal College of Nursing 2013):

1. An abrupt transfer to adult services
2. Staying in the paediatric area longer than is appropriate
3. Leaving medical supervision altogether, voluntarily or by default.

All three are associated with short- and long-term impact on young people with a long-term health condition as receivers of these services. Simple transfer can result in increasing anxiety for young people, this immediate change in a relationship with professionals, often one that is long standing, may leave them feeling isolated from their usual support mechanisms, and they may worry that the adult healthcare team will not be able to meet their needs. A review of qualitative literature on young people's experiences of transition by Fegran et al. (2014) described themes relating to loss of relationships with the child care team combined with insecurity and a feeling of being unprepared for what was ahead. So for some, remaining with a healthcare team they know may be their preferred choice. There is, however, the potential for delayed development into adulthood, and although they may feel safe in an environment and with people they know, some of their needs may not be met if they stay with a child health team too long. Disrupted care, or care that no longer meets their needs, can lead to disengagement from services and may result in deterioration in health.

Within the UK, it has been suggested that this lack of focus on young people as a group with particular healthcare needs in medical training and in the health service underpins the difficulty professionals face in improving transitional care (Gleeson and Turner 2012). The need for transi-

Box 6.1 Differences in Service Provision Between Child and Adult Health Care

- Age range
- Culture of care
- Recognition of growth and development
- Consultation dynamics
- Communication styles
- Role of parents
- Role of family
- Role of peers
- Educational issues
- Vocational issues
- Confidentiality issues
- Tolerance of immaturity
- Spectrum of diseases
- Impact of disease

tion has been created by the structure of healthcare services which focus on either children or adults. Child and adult health care are two very different systems of care, serving different populations with diverse requirements. The differences between these two care systems are summarised below in Box 6.1.

Healthcare professionals are mostly trained with a focus on the care of either adults or children and not young people. Young people are a distinctive group with different needs to children and adults. Core skills training in adolescent health care would help to shift current professional attitudes towards young people and result in professionals being able to offer more rounded support. Healthcare professionals working with young people should receive effective training about the stages of adolescence, how some long-term conditions may affect development, how to care for young people, and how best to communicate with them: core skills needed to provide transitional care.

From focus groups with professionals involved in transitional care, Aldiss et al. (2016) identified a number of factors that were associated with delayed transition. These included factors such as the patients' characteristics (e.g. age, health condition, having complex needs) as well as factors associated with services (such as the availability of equivalent services within adult care and the links between the child and adult team). The length of a relationship between the young person/family and clinical team was also found to impact on transition; when the team had known the young person since they were very young, transfer to adult services was more likely to be delayed. It is therefore imperative that healthcare professionals consider the population they are working with when planning transitional care and take into account factors which can lead to delayed transition, so that this can be avoided where possible.

6.3 Key Principles of Transition

There is a wealth of discussion in the literature regarding the key principles for transitional care and over the past decade, numerous documents have been produced outlining recommendations for practice (for a review of policy documents, see Hepburn et al. 2015). Within the UK, the latest of these documents is the guidance from the National Institute for Health and Care Excellence (NICE) published in February (2016). Gleeson and Turner (2012) outlined five key principles for transitional care, which are often reflected in other guidelines:

1. The process should consider the holistic nature of transitional care and address both clinical and also psychosocial and educational/vocational issues.
2. The process needs to be flexible and developmentally appropriate to meet the changing needs of young people.
3. The process has also to meet the needs of the parent/carer.
4. The process should span the period from early adolescence to young adulthood: a preparation phase in paediatric care; a transfer phase from paediatric to adult services; and an engagement phase in adult services.
5. Potential interventions to support the process should be considered with a focus on staffing, service delivery, and the young person and their parents/carers.

Transition should be a gradual process which starts in early adolescence (some professionals rec-

ommend that preparation for transition starts as early as 10 years old) and ends, not once the young person transfers to adult care, but once the young person is well established within the adult care setting. There is much debate about the best age to transfer young people to adult care and little consensus on when this might be. For many services, the age is arbitrary, fixed at maybe 16 or 18 years old, but a set age of transfer does not consider whether this is developmentally appropriate for that young person. Some young people may be ready to move to adult care sooner than others, having a set age of transfer creates a barrier and can delay the transfer for these young people. Conversely, not having a prescribed age of transfer can mean that services 'hold on' to young people for as long as possible resulting in them remaining in child care for longer than is appropriate (Aldiss et al. 2016). The ideal would be an approach with some flexibility enabling the young person to move to adult health care at a pace that suits them, where they are at the centre of the process.

A key element for successful transition is the relationship between the child and adult care providers. Where there is a good relationship and trust has been established, this usually results in a more positive experience of transition for the young person. This can be easier to achieve if the teams are geographically close to each other and can be more difficult when distance is involved and the child providers transfer young people to multiple care teams: documentation and sharing of information is important to ensure all relevant information about the young person is handed over to the new team.

In Box 6.2, a healthcare professional describes how the above key principles for transition are included in how transition is managed for the young people she works with, including transition being a gradual process, flexibility with the timing of transition, and enabling young people to establish a relationship with adult team prior to transfer.

Box 6.2 Healthcare Professional's Description of a Transition Service (Aldiss et al. 2016)

'In our transition clinic, from the age of fourteen, we discuss transition and we introduce the idea that they are going to be going through a transition process and that is very individual. From mostly sixteen, we see them in a transition clinic, which is jointly held with the adult diabetes team. The adult colleagues come over to our clinic and then from sixteen to eighteen, nineteen, depending on the child and the family, when they want to transition, they will be seen in that transition clinic. It is a very flexible, open clinic in that sense and it is held monthly. They then go to the young adult clinic… and they will see the same team member that they saw here. We have the adult nurse and the adult dietician and the adult diabetologist will come and attend, so we make sure that they have already met them over several years prior and then they go to the young adult diabetes team, which is up to the age of 25. It is a very gentle transition process. We also have several things in place, so we have a diabetes transition passport, which is something that we use with them. It is really to ensure that they understand their condition and it is giving them autonomy. Lots of them are diagnosed as babies or very young children and their parents were very much involved and it is just making sure that they them have much more ownership of their care and their treatment, so that is one thing that we are doing. We are introducing a transition day and graduation day, so it is going to be held twice a year, it is going to be for both the people coming into the transition and also people exiting the transition, so they will be held together. It will be an introduction to what transition is, it will be introducing to them to other various different people, but also taking them over to the adult service, so they can actually see where the adult clinic is, just so they have an idea of where they are going to, sort of, be going in the next couple of years. Also we are going to discuss some of the more adult puberty type of issues, so how to manage diabetes and exams, driving licences, jobs, all that kind of thing, as well as sex and alcohol and that kind of thing we are going to mention as well'.

Good communication between everyone involved, joint planning, and provision of information for young people and parents is essential for a good transition experience. Young people need information about their health condition, the plan for transition, and the adult service they will be transitioned to. This should be provided in an appropriate manner and include different formats where possible (such as verbal, written, and signposting to online resources). The timeline for transition should be shared so that families know what to expect and when transfer is expected to happen. What is expected of young people and parents throughout the transition process should be made clear as well as what they can expect from the professionals involved.

Transition can be a worrying and stressful time for parents. Parents are required to adjust their role, responsibilities, and behaviour to support their child's growing independence in preparation for adulthood. A review of parents' views and experiences of their child's healthcare transition highlighted that transition was characterised by ambiguity and uncertainty, leading to feelings of anxiety and distress (Heath et al. 2017). A strong source of anxiety related to a fear of poor health outcomes from relinquishing control of the health condition to the young person. Thus, it is imperative that transitional care involves parents and takes into account their needs. Parents can be key facilitators of their child's healthcare transition, supporting them to become experts in their own condition and care but in turn parents also need to be supported through this process.

Although what 'should' happen with transitional care is well documented, what is lacking in the literature and documents on transitional care is practical guidance on how professionals might start to make improvements to services in order to meet young people's/families' needs. Working with young people, parents, and professionals, Aldiss et al. (2015) developed benchmarks for transition which consist of eight key statements of best practice for transitional care (Box 6.3) along with associated indicators of best practice. The benchmarks offer a straightforward, practical tool for services to measure themselves against to see how they are doing, identify gaps in the service and provide a platform to share successful practice initiatives. This sharing of best practice is key; services need to learn from each other how to overcome common difficulties and offer each other practical support and encouragement sharing what works and what does not work.

Box 6.3 Best Practice in Transitional Care (from Benchmarks for Transition, Aldiss et al. 2015)

1. Young people are offered advice and information in a clear and concise manner about how to manage their health condition as an adult.
2. The young person as they progress through the transition process is gradually prepared and provided with personally understandable information and support.
3. The young person is supported through a smooth transition by knowledgeable and coordinated child and adult teams.
4. Young people are provided with care and in an environment that recognises and respects that they are a 'young person', not a child or adult.
5. Concise, consistent, and clear written document containing all relevant information about the young person's transition is provided to the teams involved in the transition process.
6. Parents are included in the transition process gradually transferring responsibility for health to the young person.
7. The young person's readiness for transition to adult care is assessed.
8. The young person's General Practitioner (primary care provider) is informed of the plan for transition and is able to liaise with other relevant teams to facilitate services requested/needed by the young person.

6.4 Interventions to Improve Transition

Transition programmes are needed to enhance personal growth, increase control and independence by promoting skills in communication, decision-making, and self-management. There is, however, no 'one-size fits all model of transition'. That approach may in fact be inappropriate, as it may not consider variation in the young people themselves, or their preferred style of engagement (Hislop et al. 2016). Personalised planning for transition seems more appropriate, where young people's preferences, combined with the knowledge healthcare professionals have of their patient population, could lead to more effective and efficient engagement with adult care. Reflecting on a comment made by Allen and Gregory (2009) is helpful when thinking about transitional care: 'rather than asking how best to manage transition, we might ask how best to meet the needs of young people with (a long-term condition) at this stage of their life course'. (p. 162).

The most effective way to achieve a smooth transition has become a topic of considerable debate. There are many examples of services where successful transitional care programmes have been implemented (for a review, see Crowley et al. 2011). What we are short of is evaluation, or empirical evidence from the proposed transitional models of care already in place. A recent Cochrane review on transition found few studies looked at effectiveness of interventions with only four fitting the inclusion criteria for the review (Campbell et al. 2016). The authors concluded that the current evidence is of limited quality and no firm conclusions about the effectiveness of interventions could be drawn: this could be why transitional care programmes are still not fully integrated into clinical services. Transitional care is complex and difficult to evaluate, there are not always clear measurable outcomes (Suris and Akre 2015). One issue surrounds the idea of 'usual care', which is usually used as the control for a comparison study. Usual care in relation to transitional care services is wide-ranging and inconsistent. Additional barriers to the development of robust evaluation studies are the diversity of the health conditions experienced by this patient population and the length of follow-up required to assess the efficacy of interventions over time.

6.5 Models of Transitional Care Interventions

Crowley et al. (2011) described three broad categories of intervention directed at the patient (such as education programmes, skills training), staff (such as a named transition coordinator), and service delivery (such as separate young adult clinics, after-hours phone support, enhanced follow-up). This section provides some examples of such interventions to improve transitional care, drawn from published literature, which could be used in isolation or combined in a multidimensional approach as appropriate for the population. The key features of these interventions are summarised in Table 6.1, with detail of enablers then described.

6.6 Service Delivery-Focused Interventions

6.6.1 Transition Policies and Pathways

In the past, 'transition in healthcare has been a process to get young people to adapt to us and the services we provide rather than us adapting to the needs of young people' (Gleeson and Turner 2012, p. 86). The existence of a transition policy is important to guide services but this needs to be developed in collaboration with young people, parents, and professionals who deliver transition. There needs to be some flexibility with timing of transfer in order to take into account the young person's readiness and what else is happening in their life to

Table 6.1 Key features of transitional care interventions

Intervention	Key features	Example from the literature
Transition policies and pathways	• Written guidance/pathway indicating the process of transitional care • Provides a framework for professionals to use when planning transition • Can help to standardise care for young people ensuring a more equitable access to services	Paone et al. (2006)
Transition clinics and young adult clinics	• Staffed by professionals from the child and adult teams • Enables the young person/family to build a relationship and gain trust in the adult team prior to transfer to adult services • Focuses on preparing the young person for adult services • Opportunity to promote peer interaction/support • Young people may feel less out of place in a young adult clinic than in a general clinic where patients in the waiting room may be older people	Harden et al. (2012)
Enhanced support/ follow-up	• Extra support provided for the young person which continues ideally until the young person is well-established within the adult service • Support provided via telephone/text message/email • Contact details for a named person providing the support are given to the young person • Helps the young person to navigate the adult care system	Steinbeck et al. (2014)
Named transition coordinator or key worker	• Named person takes responsibility for a young person's transition • Coordinator has an overarching view of the young person's transition • Ensures effective communication and information sharing between services, professional, and family • Improves continuity of care • Young person/family know who to contact regarding transition	Kelly (2014)
Skills training/education for young people	• Aims to prepare young people for life as an adult with a health condition and help them to develop skills for self-management • Should include education about the young person's health condition, treatment in the past and how the condition will affect them in future • Can be delivered in individual or group sessions • Group sessions enable peer support in addition to education	Mackie et al. (2014)
Assessments of 'Readiness'—transition checklists	• Readiness for transition should be frequently assessed through conversations held during clinic appointments • Checklists can be a useful trigger for engaging young people in conversation to help professionals to speak with young people about readiness • Can help to identify any gaps in a young person's skills, knowledge, or confidence needed to manage their health and transition to adult care • Can be used to track a young person's progress in self-management during the transition process	For a review see Zhang et al. (2014)
Technology-based interventions	• Interventions via internet/mobile apps or text messaging • Allow for remote delivery of an intervention • Uses methods of communication that young people are familiar with and use frequently • Potentially more convenient and easier to access than face-to-face interventions • Can be used to monitor young people, provide self-care advice, reminders or education related to health	Huang et al. (2014)

avoid transferring them at difficult times (e.g. during major exams, during a period of illness crisis/instability). Hospital wide policies and pathways can help to coordinate timing of transition for young people who access more than one service.

The ON TRAC (Taking Responsibility for Adolescent/Adult Care) model of care presents a clinical pathway and framework for transition. This model was originally developed in 1998 at Children's and Women's Health Centre of British Columbia, Canada; it provides a multidisciplinary approach to developmentally appropriate transition planning and skill building (Paone et al. 2006). The model is young people focused and family centred and includes stages of transitional care based on the developmental stages and capabilities of young people. The pathway serves as a healthcare provider's 'tool' to support the planning and preparation of young people with long-term conditions starting at 12 years of age. It outlines the timing, preparation and planning, transfer requirements, roles and tasks that can be embedded into clinical care in the child health, community, and adult settings (a shared care approach) to facilitate preparation for adult services and promote successful transfer. The ultimate goal of transition in the ON TRAC model is for all young people to reach their achievable level of independence, self-confidence, and self-esteem whilst transferring safely and securely into adult healthcare services and adulthood. For further information, see http://www.bcchildrens.ca/health-professionals/clinical-resources/transition-to-adult-care.

6.6.2 Transition Clinics and Young Adult Clinics

If possible, the young person and family should be given the opportunity to build a relationship and establish trust over a period of time with the adult team, prior to be being transferred. This can be achieved through joint clinics being held with members of both the adult and child teams. If these clinics are held in the adult environment, the young person can familiarise themselves with the new environment whilst still under the care of familiar professionals. Joint clinics need to be carefully managed; where there are large teams of professionals it may be overwhelming for the young person to have everyone in the consultation room at one time. Other strategies that can help to ease the way for young people into adult services include: having a 'cross-over' period where the young person has the chance to come back to see the child team following the first appointment within adult services to check all is going well with the transition, being accompanied by a member of the child team on the young person's first visit to the adult clinic and having an accompanied visit to the inpatient area if the young person is likely to require future admissions.

Some adult services offer dedicated young adult clinics, which are separate clinics for young people held within the adult setting. A young person would transition from child health services to the young adult service. This model has the advantage that young people may feel less out of place in the clinic waiting room where they are surrounded by their peers rather than older adults. Usually, these clinics are staffed by professionals from the adult service therefore when the young person moves into the adult clinic; there is some continuity, they can remain with health professionals who are familiar to them.

Harden et al. (2012) describe a model implemented for young people who have undergone a renal transplant which includes joint transition clinics as well as a young adult clinic. Between the ages of 15 and 18 years, patients are seen in a transition clinic staffed by a nephrologist and transplant nurse from the child team and adult team in addition to a youth worker from the adult team. Before transfer to the adult clinic, the young person has the chance to visit and look around the adult unit informally. The young person and family can progressively gain trust in the adult healthcare team before transfer. In addition, the adult team can obtain a thorough de-brief from the child health team, enabling a more effective and comprehensive care plan for the patient. By the age of 18, the young people are transferred to a young adult clinic, held in a student college and sports centre. The aim of holding the clinic in a non-clinical environment is to encourage peer interaction between the patients; this is aided by the youth worker coordinating activities such as

having lunch/coffee together and pool competitions in the games room. Timing of transfer to a standard adult clinic varies between the patients and in most cases is determined by them, taking into account their educational, employment, and social development. Harden et al. (2012) compared the rates of transplant loss between two groups of young people: group 1 transitioned to the adult service prior to the implementation of the model above and group 2 experienced the new service. In group 1, 67% of young people lost their transplant, compared to no transplant losses in group 2; Harden et al. (2012) suggest this model improved patient experience with the consequent effect of improving patient adherence to medication and engagement with health professionals.

6.6.3 Enhanced Support/Follow-Up

Enhanced support refers to the extra support provided to a young person as they move into the adult service which continues ideally until they are well established within the new service. The aims of enhanced support are to: improve the experience of transferring to adult services for the young person, help them to navigate the new system, reduce non-attendance, and reduce drop-out rates. Such support can be provided to young people moving to adult services in different ways. Steinbeck et al. (2014) describe an intervention which was implemented post-discharge from child health care and sought to promote better use of adult diabetic services. The intervention included a transition coordinator making the first adult diabetes service appointment and provisions of paper and electronic (USB memory stick) copies of information on services and health care for diabetes. This was followed by four standardised telephone calls at week one, three, six and 12 months. These calls aimed to provide support, help the young person to understand the transition process, and discuss the young person's general well-being, life events, transition difficulties, and contact with their adult diabetic services. The intervention described above involved telephone support but it is important that a young person's communication preferences are taken into account when planning such enhanced support, for example, they may prefer text message or email contact instead of or in addition to telephone support.

6.7 Healthcare Professional-Focused Interventions

6.7.1 Named Transition Coordinator or Key Worker

Good communication between the family and professionals involved in transition is key in the provision of appropriate care and support. It is frustrating and worrying for families when they do not know who to contact regarding transition and are not kept updated on the process. A named person who takes responsibility for a young person's transition can help to resolve some of these issues; a 'key worker' or transition coordinator (see for example Kelly 2014). This is a role usually undertaken by a nurse. The key worker/coordinator has an overarching view throughout the young person's transition process. They play an important role in pulling the different elements of transitional care together, ensuring there is effective communication between services, professionals, and the family. Someone taking on this role is especially vital for young people with complex needs where many services and numerous professionals are involved. In the model for young people with complex health needs described by Kelly (2014), the transition nurse coordinates regular multi-agency transition progress meetings with young people so that information is shared and communicated effectively. The role bridges the gap between child and adult services providing continuity until the young person is established within adult services.

6.8 Young Person-Focused Interventions

6.8.1 Skills Training/Education for Young People

Part of the role of transitional care is to prepare young people for life as an adult with a health condition. The young person needs to understand their health condition; to do this they need information

about their treatment when they were younger and how the condition may affect them in the future. Practical information such as how to make appointments, how to get a prescription, and how to contact the healthcare team should be provided along with opportunity to practice these skills before moving to adult care. It is important that the information provided includes 'lifestyle' advice (e.g. about healthy diet, alcohol, smoking, recreational drugs, exercise, sexual health, staying well) as well as information relating to future career/education. Approaches to providing information for young people varies between services, some services run specific education sessions/workshops and others give information routinely in clinic, building up knowledge and skills over time. The advantage of running information/skills training events is that young people can meet others with the same health condition; therefore, peer support is also provided. Such group sessions would also need to be complemented by an individual session(s) for young people where they are able to gain information and ask questions specific to them and their health.

Within children's services, much of the conversation in healthcare consultations is often led by parents. In adult services, the young person will be expected to take the lead. The young person needs to be helped to gain confidence when talking with health professionals without their parent(s) being there. It is important that the young person has the opportunity to practice speaking directly to health professionals whilst they are still seen in children's services with professionals who are more familiar to them. Time without parents present in a consultation also allows the young person to raise any confidential issues they may not wish their parents to know about.

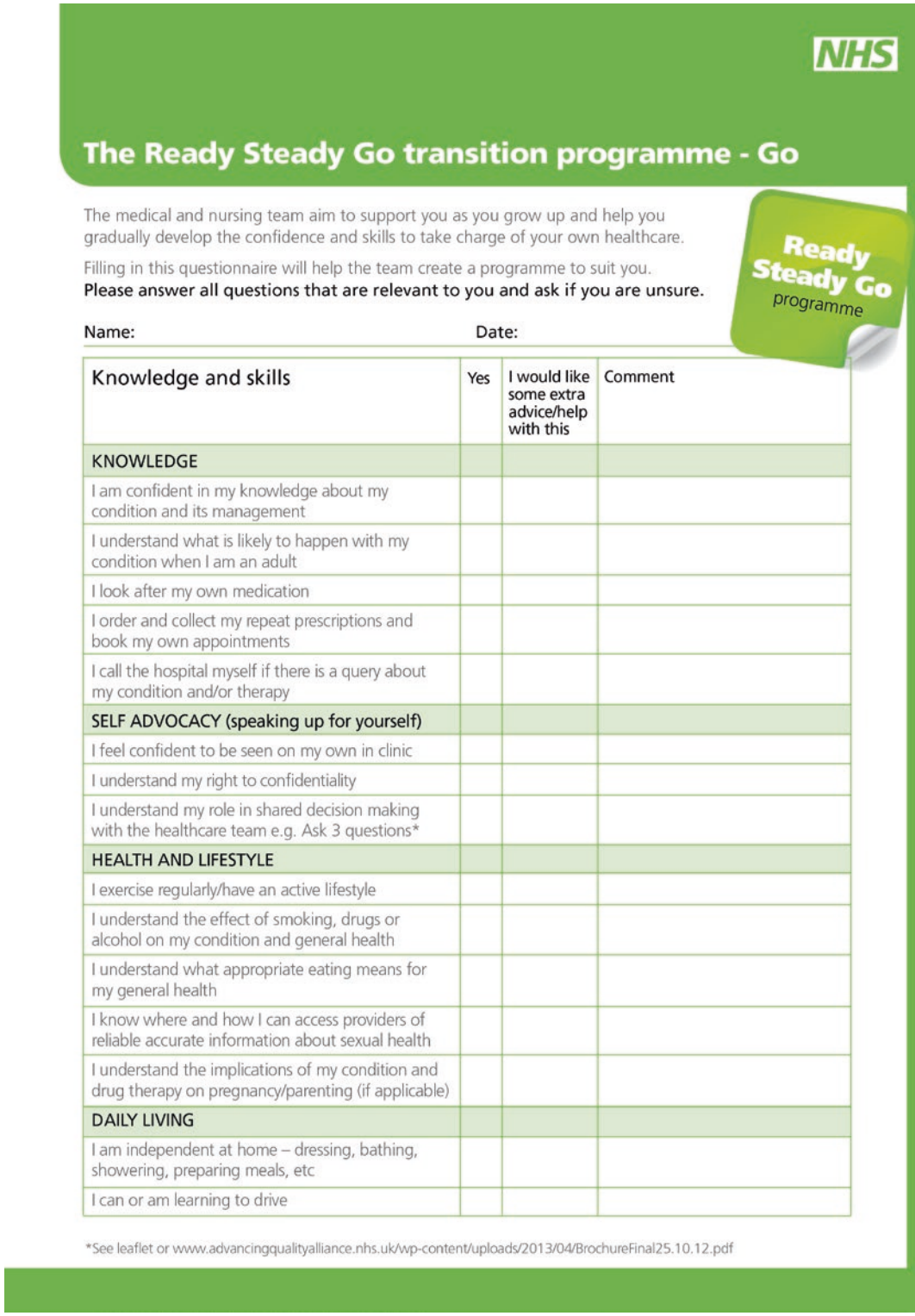
Mackie et al. (2014) describe an intervention delivered by an experienced cardiology nurse that involved a one-to-one teaching session aiming to improve knowledge and self-management skills in preparation for transition to adult care. The elements of this session were tailored to the young person and included: discussion about transition and its importance, issues of confidentiality, issues related to their cardiac condition, review of cardiac anatomy as relevant, discussion of potential future complications, advice about lifestyle issues (smoking, alcohol, and sexual health), details of adult care team contact names and an introduction to relevant websites. Case studies were used to address health behaviour and written materials were supplied. A 'MyHealth' passport was also created, including the name of the young person's cardiac condition, previous cardiac interventions, and names and purposes of medications. Follow-up emails or text message contact with the nurse were encouraged. An evaluation of this intervention found significant improvement in self-management and cardiac knowledge scores compared to controls not receiving the intervention (Mackie et al. 2014).

6.8.2 Assessments of 'Readiness': Transition Checklists

Readiness for transition should be frequently assessed through conversations held during clinic appointments. A number of checklists/questionnaires are available to assess a young person's readiness to transfer to adult services and provide an indication of the knowledge and skills young people need to acquire to function well in the adult care setting and adult life (Zhang et al. 2014). Figure 6.1 provides an example of a checklist from the Ready Steady Go Transition Programme (www.uhs.nhs.uk/readysteadygo). Such checklists can be a useful trigger for engaging young people in conversation to help professionals to speak with young people about readiness and identify any gaps in skills, knowledge, or confidence needed to manage their health and transition to adult care. They can be used to track a young person's progress in self-management during the transition process. Parents can also be asked for their opinion and feedback about whether or not the young person is ready for transition. It is important to note that checklists rarely assess mastery of knowledge and skills, it is important to check a young person's actual competency (which may be different to their perceived competency).

6.8.3 Technology-Based Interventions

Advances in technology have offered healthcare professionals new opportunities to engage



NHS

The Ready Steady Go transition programme - Go

Ready Steady Go programme

The medical and nursing team aim to support you as you grow up and help you gradually develop the confidence and skills to take charge of your own healthcare.

Filling in this questionnaire will help the team create a programme to suit you.
Please answer all questions that are relevant to you and ask if you are unsure.

Name: Date:

Knowledge and skills	Yes	I would like some extra advice/help with this	Comment
KNOWLEDGE			
I am confident in my knowledge about my condition and its management			
I understand what is likely to happen with my condition when I am an adult			
I look after my own medication			
I order and collect my repeat prescriptions and book my own appointments			
I call the hospital myself if there is a query about my condition and/or therapy			
SELF ADVOCACY (speaking up for yourself)			
I feel confident to be seen on my own in clinic			
I understand my right to confidentiality			
I understand my role in shared decision making with the healthcare team e.g. Ask 3 questions*			
HEALTH AND LIFESTYLE			
I exercise regularly/have an active lifestyle			
I understand the effect of smoking, drugs or alcohol on my condition and general health			
I understand what appropriate eating means for my general health			
I know where and how I can access providers of reliable accurate information about sexual health			
I understand the implications of my condition and drug therapy on pregnancy/parenting (if applicable)			
DAILY LIVING			
I am independent at home – dressing, bathing, showering, preparing meals, etc			
I can or am learning to drive			

*See leaflet or www.advancingqualityalliance.nhs.uk/wp-content/uploads/2013/04/BrochureFinal25.10.12.pdf

Fig. 6.1 Example of a transition checklist—Ready Steady Go Transition programme—'Go' questionnaire 'Ready Steady Go' and 'Hello to adult services' developed by the Transition Steering Group led by Dr. Arvind Nagra, paediatric nephrologist and clinical lead for transitional care at Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust based on the work of: (1) Whitehouse S, Paone MC. Bridging the gap

The Ready Steady Go transition programme - Go

Knowledge and Skills	Yes	I would like some extra advice/help with this	Comment
DAILY LIVING (CONTINUED)			
I know how to plan ahead for being away from home, overseas, trips e.g. storage of medicines, vaccinations			
I understand my eligibility for benefits (if applicable)			
SCHOOL/CAREER/YOUR FUTURE			
I have had work/ volunteering experience			
I have a Career Plan (please specify)			
I am aware of the potential impact (if any) of my condition on my future career plans			
I know how and what to tell a potential employer about my condition (if applicable)			
I know who to contact for careers advice			
LEISURE			
I can use public transport and access my local community, e.g. shops, leisure centre, cinema			
I see my friends outside school hours			
MANAGING YOUR EMOTIONS			
I know how to deal with unwelcome comments/ bullying			
I know someone I can talk to when I feel sad/fed-up			
I know how to cope with emotions such as anger or anxiety			
I would like more information about where I can get help to deal with my emotions			
I am comfortable with the way I look to others			
I am happy with life			
TRANSFER TO ADULT CARE			
I understand the meaning of 'transition' and transfer of information about me			
I know the plan for my care when I am an adult			
I would like more information about an orientation visit to the adult service I will transfer to for my adult care			

Please list anything else you would like help or advice with:

Thank you

Fig. 6.1 (continued) from youth to adulthood. Contemporary Pediatrics. 1998;13–16. (2) Paone MC, Wigle M, Saewyc E. The ON TRAC model for transitional care of adolescents. Prog Transplant. 2006;16:291–302. (3) Janet E, McDonagh et al. J Child Health Care. 2006;10(1):22–42." Further information can be found at www.uhs.nhs.uk/readysteadygo

young people in personal health care and provide support to patients with long-term conditions, which includes the transition period. Mobile phone and tablet mobile technologies featuring software programme apps are already well used by young people for social networking or gaming. They have also been utilised in health care to support personal condition management, using condition-specific and patient-tailored software. In addition to the utilisation of apps, text messaging presents a method of supporting and communicating with young people undergoing transition to adult care. Engaging with young people through technology has many advantages including being easy to access, responsive, convenient, and interactive. Remote delivery as opposed to face-to-face delivery of an intervention potentially reduces cost and increases availability and efficiency. It is essential when developing interventions involving technology that the end users, in this case young people and healthcare professionals, are involved in the development and testing phases to ensure an intervention that is acceptable and works in practice.

The MD2Me intervention (Huang et al. 2014) is a generic internet and mobile phone delivered disease management intervention which has been evaluated with young people with inflammatory bowel disease, cystic fibrosis, and diabetes. The intervention targets the self-management constructs of monitoring disease symptoms, responding to monitoring with appropriate treatments and actively working with healthcare providers to manage care. Young people log into a secure website weekly to receive theme-based materials about common disease management and communication skills and lifestyle tips (see Fig. 6.2 for a screenshot). Case studies are provided to

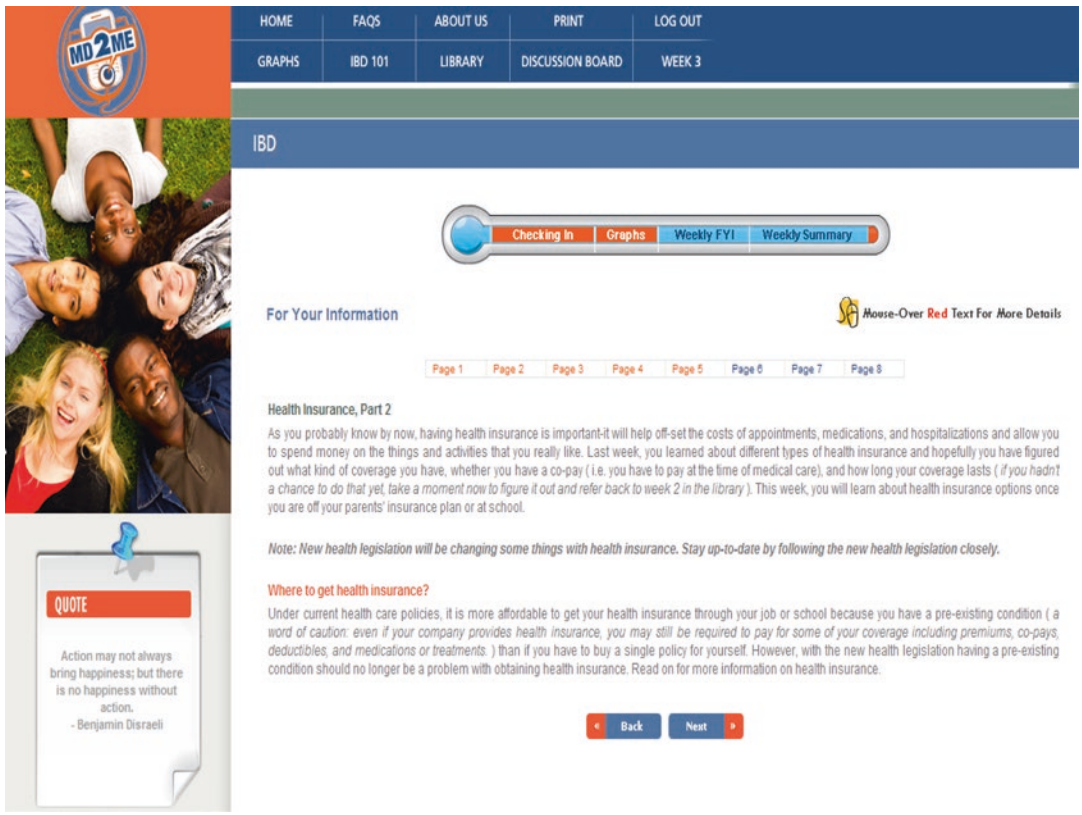


Fig. 6.2 Screenshot of MD2Me Website

increase usability. Tailored text messages and queries are delivered (three to five messages per week) to ensure that participants receive and understand the intervention messages. To encourage more patient-initiated communication, young people can also send text messages to report health concerns to the healthcare team. The intervention was evaluated positively by young people and indicates the potential for generic technology-based interventions which are not disease specific, therefore offering a cost-effective approach to improving transitional care outcomes.

6.9 Transition and Endocrinology

Transitional care is especially important in young people with an endocrine condition. In particular, children who have received growth hormone therapy (see Chap. 2 "GH Therapy in Childhood") need to be re-tested once linear growth is complete, (see Chap. 15) in order to see if growth hormone therapy is still required in adulthood (see Chap. 25 "GH Therapy in Adulthood"), particularly if the young person has the diagnosis of complete hypopituitarism. Paediatric and adult endocrinologists need to work together in order to provide a seamless transition along with the multidisciplinary team, particularly as growth hormone therapy regimes are vastly different in adulthood compared to childhood (Clayton et al. 2005).

The number of cancer survivors is increasing; young people who have undergone treatment for cancer (see Chap. 58) need continued follow-up, sometimes lifelong, and transition guidelines are essential: survivors are at risk of chronic health conditions and require long-term follow-up care (Mulder et al. 2016).

Young people with a disorder of sex development (DSD) (see Chap. 3) present many challenges, particularly concerning disclosure of the condition to the young person, and the requirements for potential genital examinations and potential vaginal treatments (see Chap. 35) Some young people may be diagnosed during adolescence and spend a short time in paediatric care before transitioning to adult services, particularly patients with gonadal dysgenesis with a Y chromosome where gonadectomy may be advised. It is imperative to include a psychologist within the multidisciplinary team make up, to help underpin the whole transition process, which can take years to complete in a young person with a DSD (Crouch and Creighton 2014).

6.10 Conclusions

Despite professional consensus on the key principles for transitional care, transition programmes are still not fully integrated into health services. There remains much variability in the provision of transitional care for young people. The need for change in order to best meet the needs of young people and parents during transition is very evident in existing literature. A range of approaches to improving the processes and structure of transitional care have been proposed although it is not yet clear how effective these approaches might be in improving health outcomes and the experience of transition for young people. Whatever solution is adopted requires a comprehensive programme that takes into account the young person's psychosocial, lifestyle, and educational/vocational needs in addition to any health needs. Sharing of best practice is key; services need to share successes and failures and learn from each other how to overcome common difficulties in improving transitional care.

6.11 Critical Thinking Points

How and when is the topic of transition introduced to young people and parents in the services you work in? Do you think this is appropriate?

What do you know about the experiences of transition for young people and parents in the service you work in? Is there a mechanism in place for young people and parents to feedback their experiences?

What might the key challenges/barriers be to implementing a seamless transition experience for young people in the service you work in? How might these barriers be overcome?

Are you aware of how transition is implemented in other services within the organisation you work in? How might services improve on sharing best practice and experiences of what works or does not work with regard to transition?

References

Aldiss S, Ellis J, Cass H, Pettigrew T, Rose L, Gibson F. Transition from child to adult care—'it's not a one-off event': development of benchmarks to improve the experience. J Pediatr Nurs. 2015;30:638–47.

Aldiss S, Cass H, Ellis J, Gibson F. "We Sometimes Hold on to Ours"—Professionals' views on factors that both delay and facilitate transition to adult care. Front Pediatr. 2016;4:125. https://doi.org/10.3389/fped.2016.00125.

Allen D, Gregory J. The transition from children's to adult diabetes services: understanding the 'problem'. Diabet Med. 2009;26(2):162–6.

Blum R, Garell D, Hodgman C, Jorissen T, Okinow N, Orr D, Slap G. Transition from child-centred to adult health-care systems for adolescents with chronic conditions: a position paper of the Society for Adolescent Medicine. J Adolesc Health. 1993;14:570–6.

Campbell F, Biggs K, Aldiss S, O'Neill PM, Clowes M, McDonagh J, While A, Gibson F. Interventions to improve transition of care for adolescents from paediatric services to adult services. Cochrane Database Syst Rev. 2016;(4):CD009794. https://doi.org/10.1002/14651858.CD009794.pub2.

Care Quality Commission. From the pond into the sea: children's transition to adult health services. 2014. http://www.cqc.org.uk/content/teenagers-complex-health-needs-lack-support-they-approach-adulthood. Accessed 23 Jan 2017.

Clayton P, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152:165–70.

Crouch NS, Creighton SM. Transition of care for adolescents with disorders of sex development. Nat Rev Endocrinol. 2014;10(7):436–2.

Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between child and paediatric healthcare: a systematic review. Arch Dis Child. 2011;96:548–53.

Fegran L, Hall E, Uhrenfeldt L, Aagaard H, Ludvigsen M. Adolescents' and young adults' transition experiences when transferring from paediatric to adult care: a qualitative metasynthesis. Int J Nurs Stud. 2014;51:123–35.

Gleeson H, Turner G. Transition to adult services. Arch Dis Child Educ Pract Ed. 2012;97:86–92.

Harden P, Walsh G, Bandler N, Bradley S, Lonsdale D, Taylor J, Marks S. Bridging the gap: an intergrated paediatric to adult clinical service for young adult with kidney failure. BMJ. 2012;344:e3718.

Heath G, Farre A, Shaw K. Parenting a child with chronic illness as they transition into adulthood. A systematic review and thematic synthesis of parents' experiences. Patient Educ Couns. 2017;100(1):76–92.

Hepburn CM, Cohen E, Bhawra J, Weiser N, Hayeems R, Guttmann A. Health system strategies supporting transition to adult care. Arch Dis Child. 2015;100:559–64.

Hislop J, Mason H, Paar J, Vale L, Colver A. Views of young people with chronic conditions on transition from pediatric to adult health services. J Adolesc Health. 2016;59:345–53.

Huang JS, Terrones L, Tompane T, Dillon L, Pain M, Gottschalk M, Norman G, Bartholomew K. Preparing adolescents with chronic disease for transition to adult care: a technology program. Pediatrics. 2014;133:e1639–46.

Kelly D. Theory to reality: the role of the transition nurse co-ordinator. Br J Nurs. 2014;23:888–94.

Mackie AS, Islam S, Magill-Evans J, Rankin KN, Robert C, Schuh M, Nicholas D, Vonder Muhll I, McCrindle B, Yasui Y, Rempel G. Healthcare transition for youth with heart disease: a clinical trial. Heart. 2014;100:1113–8.

Mulder RL, van der Pal HJH, Levitt GA, Skinner R, Kremer LCM, Brown MC, Bardi E, Windsor R, Michel G, Frey E. Transition guidelines: An important step in the future care for childhood cancer survivors. A comprehensive definition as groundwork. Eur J Cancer. 2016;54:64–8.

National Institute for Health and Care Excellence. Transition from children's to adults' services for young people using health or social care services. 2016. https://www.nice.org.uk/guidance/ng43. Accessed 23 Jan 2017.

Paone MC, Wigle M, Saewyc E. The ON TRAC model for transitional care of adolescents. Prog Transplant. 2006;16(4):291–302.

Royal College of Nursing. Adolescent transition care: RCN guidance for nursing staff. 2013. https://www.rcn.org.uk/library/subject-guides/children-and-young-people-transition-to-adult-services. Accessed 23 Jan 2017.

Steinbeck KS, Shrewsbury VA, Harvey V, Mikler K, Donaghue KC, Craig ME, Woodhead HJ. A pilot randomized controlled trial of a post-discharge program to support emerging adults with type 1 diabetes mellitus transition from pediatric to adult care. Pediatr Diabetes. 2014;16(8):1–6.

Suris J, Akre C. Key elements for and indicators of a successful transition: an international Delphi study. J Adolesc Health. 2015;56:612–8.

Zhang L, Ho J, Kennedy S. A systematic review of the psychometric properties of transition readiness assessment tools in adolescents with chronic disease. BMC Pediatr. 2014;14:4. https://doi.org/10.1186/1471-2431-14-4.

Key Reading

1. Aldiss S, Ellis J, Cass H, Pettigrew T, Rose L, Gibson F. Transition from child to adult care—'it's not a one-off event': development of benchmarks to improve the experience. J Pediatr Nurs. 2015;30:638–47.
2. Campbell F, Biggs K, Aldiss S, O'Neill PM, Clowes M, McDonagh J, While A, Gibson F. Interventions to improve transition of care for adolescents from paediatric services to adult services. Cochrane Database Syst Rev. 2016;(4):CD009794. https://doi.org/10.1002/14651858.CD009794.pub2.
3. Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between child and paediatric healthcare: a systematic review. Arch Dis Child. 2011;96:548–53.
4. Fegran L, Hall E, Uhrenfeldt L, Aagaard H, Ludvigsen M. Adolescents' and young adults' transition experiences when transferring from paediatric to adult care: a qualitative metasynthesis. Int J Nurs Stud. 2014;51:123–35.
5. Heath G, Farre A, Shaw K. Parenting a child with chronic illness as they transition into adulthood. A systematic review and thematic synthesis of parents' experiences. Patient Educ Couns. 2017;100(1):76–92.

Part II

Endocrine Disorders and Genetics in Childhood

Kate Davies and Margaret F. Keil

Genetics and Family History

7

Kelly Mullholand Behm

Contents

7.1 **Introduction** 125

7.2 **Historical Eras Linking Genetics and Endocrinology** 126

7.3 **Basic Genetics Review** 127
7.3.1 DNA (The Genetic Alphabet) 127
7.3.2 Genes (Genetic Sentences) 128
7.3.3 Chromosomes and Genomes (Genetic Chapters and Books) 129

7.4 **The Genetic Code** 129

7.5 **Template, Transcription, Translation** 130

7.6 **Exons and Introns** 130

7.7 **Gene Expression** 131

7.8 **Gene Locus and Alleles** 132

7.9 **Genotype and Phenotype** 133

7.10 **Inheritance** 134
7.10.1 Mendelian Inheritance 134
7.10.2 Non-Mendelian Patterns of Inheritance 135

7.11 **Epigenetics** 137

7.12 **Mutations** 138

7.13 **Chromosomal Abnormalities** 140
7.13.1 Chromosomal Structural Abnormalities 140
7.13.2 Chromosomal Copy Number Abnormalities 141

K. M. Behm (✉)
Orlando, FL, USA

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_7

7.14 **Interpreting Genetic Test Results** 141
7.14.1 Chromosome Anatomy 142
7.14.2 Cytogenic Testing 142
7.14.3 Molecular Genetic Testing 148
7.15 **Family History** 152
7.16 **Legal/Ethical Issues** 153
7.17 **Nursing Implications** 153
7.17.1 Attitude 153
7.17.2 Disclosure 153
7.17.3 Care Coordination 156
7.18 **The Future** 156
7.19 **Conclusions** 156
7.20 **Additional Resources** 156
7.20.1 Online Software Applications and Tools 157
7.20.2 Online Information on Genetic Concepts 157
7.20.3 Professional Organizations for Nurses Interested in Genetics 158
References 158

Abstract

This chapter describes principles of genetics and family history that are relevant to the practice of clinical endocrinology. It begins with a review of historical eras that provides context for how two seemingly distinct specialties have become intricately interwoven. Genetics concepts are then explained in a progression from basic to complex, each section building on the previous, with clinical examples included to help readers develop a comprehensive understanding without becoming overwhelmed. Topics covered include DNA and RNA structure and function, the genetic code, transcription, translation, exons, introns, gene expression, gene locus, alleles, genotype, phenotype, Mendelian and non-Mendelian patterns of inheritance, epigenetics, gene mutations, chromosomal structural and copy number abnormalities, and cytogenetic and molecular genetic testing methodologies and interpretation.

The Mendelian inheritance section outlines the three laws of Mendelian inheritance and associated inheritance patterns including homozygous and heterozygous, autosomal and pseudoautosomal, dominant and recessive. Non-Mendelian patterns of inheritance described include co-dominance, linkage, sex-linked, multiple alleles, complex polygenic or multifactorial, and mitochondrial.

Gene mutations discussed include point, missense, nonsense, insertion, deletion, duplication, frameshift, substitution, and repeat expansions. Chromosomal abnormalities described include translocations, deletions, duplications, inversions, isochromosomes, dicentric, ring, and aneuploidies resulting from meiotic and mitotic nondisjunction.

The genetic testing section covers karyotyping, fluorescent in situ hybridization, microarrays, gene expression analysis, direct sequencing analysis, and methylation analysis. The section on family history provides information about publicly available tools for collecting genetic and endocrine history data, as well as a detailed description of how to create and use pedigrees to aid in clinical decision-making and communication with patients and their families.

The chapter concludes with a practical discussion of nursing implications, a recommended reading section, and an extensive list of supplemental educational materials and resources. Supplemental materials include a genetics glossary, a list of online resources for information on genetics concepts introduced within the chapter, a list of genetics-based peer-reviewed journals, a list of professional organizations and societies for nurses interested in genetics, and a list of current textbooks on genetics.

The recommended reading section contains a list of online and print publications providing additional in-depth information on genetics in human endocrinology, nursing competencies in genetics, using analogies in patient education, legal and ethical implications of genetics in the clinical setting, issues surrounding disclosure of genetic diagnoses, clinical case studies, interactive pedigree software, epigenetics, molecular genetics testing, gene therapy, additional internet genetics resources, and the future of genetics in endocrinology.

Keywords

Genetics · DNA · Expression · Inheritance · Mutation · Testing · Pedigree

Abbreviations

2n	Diploid
3′	3-prime
3-M	Syndrome causing short stature, unusual facial features, and skeletal abnormalities first identified by researchers named Miller, McKusick, and Malvaux
5′	5-prime
A	Adenine
aCGH	Array comparative genomic hybridization
ACTH	Adrenocorticotropic hormone
AR	Androgen receptor
arr	Array
bp	Base pairs
BWS	Beckwith–Wiedemann syndrome
C	Cytosine
CAG	Cytosine-adenine-guanine nucleotide sequence
CDKN1B	Cyclin dependent kinase inhibitor 1B
cDNA	Complementary DNA
CGH	Comparative genomic hybridization
CH_3	Methyl group
CH_3CO	Acetyl group
CNV	Copy number variants or copy number variations
CpG	Cytosine-phosphate-guanine (cytosine and guanine separated by a phosphate)
CYP212A	Cytochrome P450 family 21 subfamily A member 2
del or dn	Deletion
der	Derivative chromosome
dp	Duplication
DNA	Deoxyribonucleic acid
FGD	Familial glucocorticoid deficiency
FGFR3	Fibroblast growth factor receptor 3
FISH	Fluorescent in situ hybridization
FMR1	Fragile X mental retardation 1
G	Guanine
GEM	Gene expression microarray
GH	Growth hormone
GNAS	Guanine nucleotide-binding protein alpha subunit or g-protein alpha subunit
HDSNP-array	High-density single nucleotide polymorphism array
i	Isochromosome
ins	Insertion
inv	Inversion
kb	Kilobase pairs
mat	Maternally derived chromosome
Mb	Megabase pairs
MEN1	Multiple endocrine neoplasia type 1 or menin 1
MEN4	Multiple endocrine neoplasia type 4

MIDD	Maternally inherited diabetes and deafness or mitochondrial diabetes and deafness
miRNA	MicroRNAs
MODY5	Maturity-onset diabetes of the young type 5
mRNA	Messenger RNA
mtDNA	Mitochondrial DNA
n	Haploid
NGS	Next-generation sequencing
p	Short arm of a chromosome
PCOS	Polycystic ovarian syndrome
PCR	Polymerase chain reaction
PHEX	Phosphate regulating endopeptidase homolog X-linked
PTPN11	Protein tyrosine phosphatase, non-receptor type 11
q	Long arm of a chromosome
RCAD	Renal cysts and diabetes syndrome
RNA	Ribonucleic acid
rRNA	Ribosomal RNA
SHOX	Short stature homeobox
SNP	Single nucleotide polymorphism
SNP-array	Single nucleotide polymorphism array
SOS1	Son of sevenless homolog 1 or SOS Ras/Rac guanine nucleotide exchange factor 1
SOX3	SRY-box 3 or SRY-related HMG-box 3 (Sex-determining region Y-related high-mobility-group box transcription factor 3)
SRY	Sex-determining region Y
T	Thymine
t	Translocation
tRNA	Transfer RNA
TSH	Thyroid stimulating hormone
U	Uracil
VHL	Von Hippel-Lindau
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
wt	Wild type allele
Xce	X chromosome controlling element
Xic	X-inactivation center
Xist	X inactive specific transcript

Key Terms[1]

- **Autosomal dominant inheritance:** caused by a mutation in a gene located on an autosomal chromosome and occurs when one autosomal allele masks the expression of another allele
- **Autosomal recessive inheritance:** also caused by a mutation in a gene located on an autosome, but in this case, two copies of the recessive gene are needed for the trait to be expressed
- **Chromosomes:** linear end-to-end arrangement of DNA found in tightly coiled packets in the nucleus of every cell
- **Deletion:** a piece of a chromosome breaks off and is lost
- **DNA:** deoxyribonucleic acid; a double chain of linked nucleotides having deoxyribose as their sugars; the fundamental substance of which genes are composed
- **Epigenetics:** heritable changes in gene function that do not involve changes in the DNA sequence
- **Frameshift mutation:** the addition or deletion of a nitrogen base, causing the gene sequence to read out of sequence
- **Functional genomics:** the study of patterns of gene expression and interaction in the genome
- **Gene expression:** the timing, frequency, rate, and efficiency of protein production for a specific gene
- **Genes:** sections of DNA containing coding sequences for making proteins and regulatory sequences for controlling transcription
- **Genome:** the complete set of genes for an organism
- **Genotype:** the pair of alleles a person has at a specific location in the genome
- **Germ mutation:** occur in gametes (reproductive cells)
- **Haplosufficient:** a single copy of a normal gene allele is enough to produce normal function
- **Hemizygous:** there is only one copy of a gene for a specific trait resulting in a recessive phenotype (X-linked genes in human males are hemizygous)

[1] Key terms definitions were derived from National Human Genome Research Institute (2014).

- **Heterozygous:** having differing gene alleles for a trait in an individual, such as Aa
- **Inversion:** a piece of a chromosome breaks off and reattaches itself in reverse order
- **Knockout:** inactivation of one specific gene
- **Locus (gene locus):** the specific place on a chromosome where a gene is located (plural, loci)
- **Mendelian inheritance:** hereditary process which follows Mendel's laws of segregation, independent assortment, and dominance
- **Mitochondrial inheritance:** the passage of mitochondrial DNA from the mother to the offspring through the cytoplasm of the egg
- **Molecular genetics:** the study of the molecular processes underlying gene structure and function
- **Mutant allele:** an allele differing from the allele found in the standard, or wild type
- **Mutations:** less common differences in the sequence of DNA, occurring in less than 1% of the population and having a deleterious effect
- **Nonsense mutation:** a mutation that alters a gene to produce a nonsense codon
- **Null mutation:** a mutation that results in complete absence of function for the gene
- **Phenotype:** the detectable outward manifestations of a specific genotype; the observable effect of an allele, such as eye color or how an individual reacts to a drug
- **Point mutation:** a change in a single nitrogen base in DNA; a mutation that can be mapped to one specific locus
- **Polymorphism:** common variations in the sequence of DNA, occurring in at least 1% of the population; the occurrence in a population of several phenotypic forms associated with alleles of one gene or homologs of one chromosome; useful for genetic linkage analysis
- **Proband:** the family member in which a disease-causing mutation is known to exist; an affected family member coming to medical attention independent of other family members
- **Recessive allele:** an allele whose phenotypic effect is not expressed in a heterozygote
- **RNA:** ribonucleic acid; a single-stranded nucleic acid like DNA but having ribose sugar rather than deoxyribose sugar and uracil rather than thymine as one of the bases
- **SNP (pronounced "snip"):** single nucleotide polymorphism; a type of polymorphism involving variation of a single base pair; the most common type of genetic variation among people
- **Somatic mutation:** occurs in body cells rather than reproductive cells
- **Trait:** the manifestation or phenotype of a specific gene
- **Wild type:** the most common allelic form of a gene; the genotype or phenotype that is found in nature
- **X-linked recessive inheritance:** caused by a gene on the X chromosome rather than on an autosome

Key Points

The content of this chapter will enable the reader to:

- Define at least five genetics concepts not previously known to the reader
- Differentiate between Mendelian and non-Mendelian patterns of inheritance
- Describe the relationship between gene expression and epigenetics
- Give endocrine examples of gene mutations and chromosomal abnormalities
- Explain cytogenetic and molecular genetic test results to patients and families
- Collect a fourth-generation family health history and draw a pedigree depicting genetic relationships

7.1 Introduction

One does not need to be trained as a molecular geneticist to appreciate the intersection of genetics and endocrinology. However, a basic working knowledge of genetics *is* essential in guiding

patients to an understanding of the "why?" underlying the disruption to their endocrine physiology. Although not all endocrine disorders with a genetic root cause are inherited, understanding inheritance patterns where they *do* apply is important, as is being able to explain basic principles of non-inherited (acquired) changes resulting from epigenetics, somatic cell line mutations, and errors in mitotic cell division.

Explaining these phenomena to affected patients and their families is not solely the purview of the clinical geneticist. For example, an endocrine health care provider should not deliver the news of a Turner syndrome or non-classical congenital adrenal hyperplasia diagnosis, and then send the overwhelmed and bewildered patient/family off to a consult with the genetics clinic armed *only* with instructions to take the endocrine medications as prescribed and to make a follow-up appointment for a few months down the road. These individuals need to receive basic genetic education from their endocrine provider throughout the entire endocrine workup, beginning with the family history segment of the new patient interview, and continuing through the diagnostic testing process, confirmation of diagnosis, and subsequent follow-up appointments. In addition, maintaining and sharing knowledge of current authenticated patient education resources and support organizations specific to endocrine diagnoses of genetic origin will prevent these individuals from suffering unnecessary fear and anxiety from misinformation that exists on the internet and within their cultural milieu.

The purpose of this chapter is to review principles of genetics and family history that are relevant to the practice of clinical endocrinology. Examples of how these principles might apply to actual patient scenarios are interspersed throughout the chapter to assist in the translation from abstract fact to clinical reality. A list of additional resources and suggestions for further reading and personal education is provided after the main chapter content, as well as a glossary of genetics terminology.

7.2 Historical Eras Linking Genetics and Endocrinology

Putting what we currently know about genetics into historical context brings increased understanding of clinical implications. There are three scientific eras where genetics and endocrinology intersect: the physiologic era, the assay era, and the molecular genetic era (Asa and Mete 2018; Fisher 2004; Marty et al. 2011).

The physiologic era took place pre-Watson and Crick, running from the time of Mendel (mid-1800s) to 1953. In this era, physiologic, biochemical, and cellular anomalies were known, but the specific molecular alteration in a gene as the root cause of the anomaly had not yet been identified. Important scientific milestones of this era included the rediscovery of Mendelian principles of genetic inheritance in the early 1900s, the discovery of insulin in the early 1920s, the discovery of the relationship between genes and proteins in sickle cell anemia, and finally, Watson and Crick's discovery of the three-dimensional double-stranded structure of DNA in 1953, which ushered in the next scientific era (Asa and Mete 2018; Fisher 2004; Marty et al. 2011).

The assay era occurred post-Watson and Crick, from 1953 to 1990, ending just before the Human Genome Project. Scientific discoveries in this era were explosive, focusing on DNA, RNA, mapping, sequencing, and recombination. Important scientific milestones of this era included: discovery of 46 human chromosomes in the mid-1950s, discovery of DNA polymerase I enzyme which led to creation of DNA in a test tube in the late 1950s, development of the plasma insulin immunoassay around 1960, cracking of the genetic code as triplet messenger RNA (mRNA) codons specifying amino acids in the mid-1960s, isolation of the first restriction enzyme, HindII, that could cut DNA molecules within specific recognition sites around 1970, production of the first recombinant DNA (rDNA) molecule in the early 1970s, development of a DNA sequencing method around 1975, production of the first human hormone using rDNA technology in the late 1970s, and finally, the

beginning of the Human Genome Project in 1990, which ushered in the current scientific era (Asa and Mete 2018; Fisher 2004; Marty et al. 2011).

The molecular genetic era began with the commencement of the Human Genome Project in 1990 and continues to the present day, and it is the discoveries of this era that have made the genetic diagnosis of many endocrine disorders possible. The genes for insulin and growth hormone were both discovered in the early 1990s, and the final human genome sequence (the complete human DNA sequence) was published in 2003 after the Human Genome Project concluded (Asa and Mete 2018; Fisher 2004; Marty et al. 2011). In terms of significance, this last accomplishment was the equivalent of putting a man on the moon. The discoveries of this era have further defined the fields of genetics and molecular genetics. Genetics is the study of genes and inheritance. Molecular genetics is the study of molecular processes underlying gene structure, function, and behavior; it is analyzing and manipulating individual genes at the DNA level.

7.3 Basic Genetics Review

DNA, genes, chromosomes, genetic code, and genome are terms one may have heard, but not thought to put together in a way that makes practical sense. The analogy of learning to read, i.e., identifying letters in the alphabet, putting those letters together to form words, then linking words to make sentences, sentences to make chapters, and chapters to create a book, can be useful in understanding the connections between basic genetic terminology. This foundation can then be built upon to understand more complex genetic concepts.

7.3.1 DNA (The Genetic Alphabet)

The acronym DNA stands for deoxyribonucleic acid. DNA consists of two parallel linear strands of repeating units called nucleotides. The nucleotides in each parallel strand are joined by weak chemical bonds in a double helix formation that resembles a twisted ladder. Nucleotides are composed of one deoxyribose sugar-phosphate molecule and one chemical base. The sugar-phosphate portion of each nucleotide forms the outer rails of the ladder, while the base portion faces the center of the ladder. Each center-facing base is joined by a chemical bond to another base connected to the opposite rail of the ladder. The bases are designated by letters: A for adenine, C for cytosine, T for thymine, and G for guanine. During DNA transcription, enzymes forming RNA (a single-stranded ribonucleic acid containing the sugar ribose) substitute the base uracil, designated by the letter U, for the DNA base thymine. When two bases on opposite sides of the ladder are chemically joined together in the center with a weak hydrogen bond to form a rung, they are referred to as base pairs (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

This genetic "alphabet" thus contains only five letters representing the five nucleotide bases in DNA and RNA. These bases follow specific rules for pairing with each other to form those "ladder rungs." A and G are purine bases, and T, C, and U are pyrimidine bases. Purines bond to pyrimidines so that A always pairs with T, and C with G in DNA, while A pairs with U in RNA. [One might think of the words "at" and "Catgut" (for A-T and C-G) and the phrase "Hey You!" (for A-U) to remember which bases pair with each other.] Humans have approximately three billion base pairs (six billion bases) contained in the DNA found in most of our cells (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The individual strands within double-stranded DNA are complementary and run in opposite directions due to the rules of base pairing. The direction of the strands is indicated as either 5′ to 3′ or 3′ to 5′. The 5′ and 3′ designations refer to the number of carbon atoms in the sugar-phosphate backbone (National Human Genome Research

Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). The direction of each strand is important for the processes of transcription and translation, which will be discussed later. Figure 7.1 illustrates the basic structure of DNA described in this section.

7.3.2 Genes (Genetic Sentences)

A gene is a segment of DNA containing a specific sequence of base pairs that provide instructions for making proteins, like sentences and paragraphs made from the nucleotide "alphabet." Humans have approximately 35,000 genes. The smallest genes are about 100 base pairs in length. The largest genes are over one million base pairs long. Base sequence variations occur in only about three million base pairs, 1% of our DNA, yet it is this minute 1% variation that is responsible for the differences that make each individual unique (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

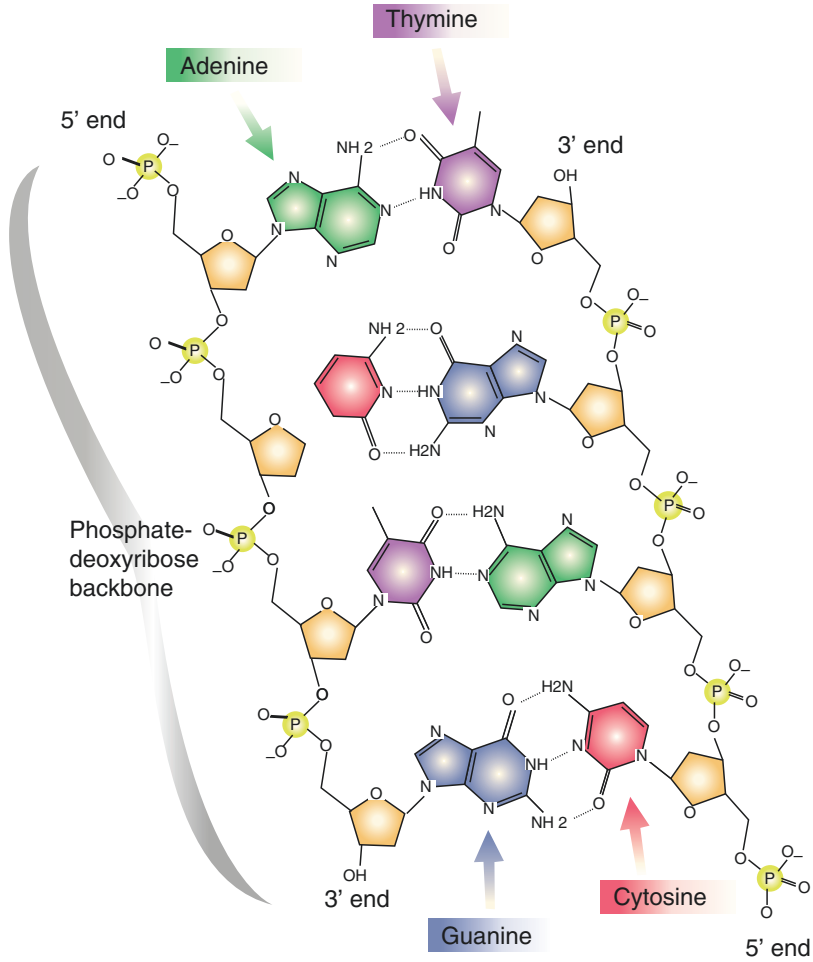


Fig. 7.1 DNA structure (Reproduced from https://www.news-medical.net/image.axd?picture=2016%2F11%2FDNA_structure_-_Zvitaliy_Enlarge_image_.jpg)

7.3.3 Chromosomes and Genomes (Genetic Chapters and Books)

DNA, with its nucleotide base pair "alphabet" sequenced into "sentences" of genes, is contained within tightly coiled packages called chromosomes that are found in the nucleus of every cell. Humans have two types of chromosomes, autosomal chromosomes and sex chromosomes. Autosomal chromosomes are usually referred to as autosomes. There are 22 autosomes (labelled 1 through 22, numbered from the largest to the smallest) and two sex chromosomes (labelled X and Y). The complete set of an organism's DNA (in humans, all the genes within a set of chromosomes) is referred to as a genome (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). Each chromosome is like a chapter of gene "sentences" in a genome "book."

Each egg or sperm cell contains one "book" or genome in its "library," that is, *one* copy of each of the 22 autosomes and *one* of the two sex chromosomes for a total of 23 chromosomes. This is called the haploid state (one copy). Once an egg is fertilized by a sperm, the resulting zygote has two "books" or genomes in its "library," that is *two* copies of the 22 autosomes, and *two* sex chromosomes, for a total of 46 chromosomes in all its cells. This is called the diploid state (two copies). Eggs and sperm are also referred to as gametes. Cells that develop into gametes are also called germ cells. All other cells are referred to as somatic cells. Germ cells contain one genome, and somatic cells contain two genomes.

If there is a spelling error in a sentence, or if a sentence, paragraph, or chapter is missing, incomplete, or out of order, a book may not make sense to the reader, or it may take on a completely different meaning than its author intended. It is the same with our genome when genetic errors occur. Genetic errors are often referred to as mutations although there are errors that do *not* result from mutation. Mutations that occur in germ cells are called germline mutations, whereas mutations that occur in all other cells are called somatic mutations (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.4 The Genetic Code

Before one can understand how mutations or other genetic errors occur and what effects they have, one must know what "normal" looks like, just as to recognize that a word has been misspelled, one must already know its correct spelling. We have already established that genes are sections of DNA with a specific sequence of nucleotides whose bases are identified by letters, and that those bases exist in pairs. When a DNA sequence in a gene is transcribed into mRNA, a series of three base pairs forms a codon, which is like a "word" in a gene "sentence." The resulting codons are then translated into amino acids (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The genetic code refers to the list of 64 possible codons (3 base pair combinations) that code for 20 amino acids as well as start and stop sequences. Amino acids are strung together to make proteins. Proteins are molecules that play a critical role in the structure, function, and regulation of the body's cells, tissues, and organs. Proteins are either structural (such as hair and muscle) or functional/regulatory (such as enzymes and transcription factors). Genes thus contain the instructions for making proteins, and act or "express" themselves by dictating the order of amino acids used to make those proteins (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Genetic errors can occur when the order of the base pairs in a codon is disrupted (like a misspelled word), resulting in a premature stop codon (sometimes called a nonsense codon) that causes a shortened protein that doesn't function normally, or a codon for a completely different amino acid resulting in a completely different

protein product than what the gene intended to produce (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). An example of genetic code function is provided in Fig. 7.2.

7.5 Template, Transcription, Translation

Polymerase enzymes are regulatory proteins that synthesize DNA or RNA after the enzyme helicase unwinds the double strands of DNA. Once the strands are separated, the nucleotide sequence in each strand becomes a template for replication or transcription. When DNA duplicates itself, the process is called replication, and DNA polymerase regulates the replication into new double-stranded DNA. When the DNA template is being used to make proteins, the first step in the process is called transcription. Transcription occurs when RNA polymerase copies the DNA template into single-stranded mRNA. Once the DNA template has been transcribed into mRNA, the mRNA copy is referred to as the transcript. It is this transcript that contains the codons for amino acids that make up proteins. Translation is the process of translational RNA (tRNA) reading the transcript of mRNA and translating it into individual amino acids that are linked together in a chain to form a polypeptide, the main structure of a protein (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.6 Exons and Introns

DNA in genes contains coding regions for proteins as well as non-coding regions that are transcribed into RNA but not translated into proteins. The coding regions are called exons, and the non-coding regions are called introns. One way to recall the difference is to remember that introns are "in-between" each coding region of a gene. There are additional non-coding regions of DNA that separate the genes from one another. Many non-coding regions of DNA between genes are functional elements that help regulate patterns of gene expression, while the purpose of other non-coding regions is not yet fully understood. Only about 2% of the genome contains genes (DNA sequences encoding proteins) (National Human

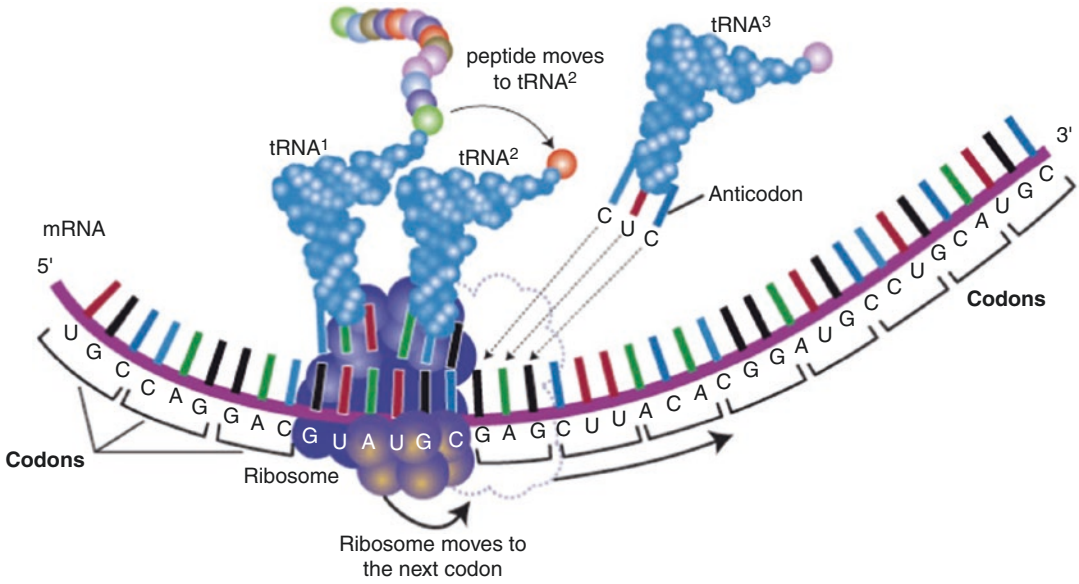


Fig. 7.2 mRNA codons translated into amino acids for protein synthesis (Reproduced from http://cdn.differencebetween.net/wp-content/uploads/2017/12/Difference-Between-Anticodon-and-Codon.jpg)

Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The non-coding regions of a gene include a regulatory region at one end that initiates transcription (the 5′ end), and a termination region at the other end that ends transcription (the 3′ end). In between the two ends is the protein encoding sequence (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). (Remember that the 5′ and 3′ designations merely refer to the number of carbon atoms in the sugar-phosphate backbone.)

When the double strands of DNA are separated, the strand oriented in the 5′ to 3′ direction is known as the sense (coding) strand, while the 3′ to 5′ strand is known as the antisense (anticoding) strand. The 5′ end includes a regulatory region (sometimes referred to as a regulatory box) with a sequence called a promoter. Because this region is located *before* the first exon of a gene begins, it is referred to as "upstream" of the gene. Upstream of the promotor sequence are untranslated enhancer sequences where transcription factors (sequence-specific DNA binding proteins) bind to turn the gene on and control the rate of DNA transcription. The promotor sequences begin as leader sequences called TATA or CCAAT boxes that provide a signal to RNA polymerase telling the enzyme which DNA sequence is ready for transcription. The leader sequences are followed by an initiation codon sequence (ATG on DNA or AUG on RNA) that starts transcription (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The 3′ end includes an untranslated regulatory region with a stop codon sequence (TAG, TAA, TGA on DNA or UAG, UAA, UGA on RNA) that ends transcription. Because this region is located *after* the last exon of a gene ends, it is referred to as "downstream" of the gene. Remember, untranslated doesn't mean untranscribed. Transcribed means DNA is copied into RNA, but that RNA may or may not be translated into an amino acid depending on whether it has a coding or non-coding sequence. Translation occurs when DNA is copied to RNA with a coding sequence leading to an amino acid (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The initial mRNA transcript (called precursor mRNA) contains the transcribed sequence of both the exons and introns in the sense strand of the DNA template. The introns must be spliced out to produce a mature mRNA transcript before it can exit the nucleus. Introns are identified by specific splice recognition site sequences of two nucleotides (dinucleotides) at each end. Introns begin with the sequence GT (GU on RNA) and end with the sequence AG. Once the introns are spliced out, the mature mRNA transcript contains the sequences of all the exons in the sense strand of DNA and is ready for translation. The stop codon at the 3′ end of the DNA sense strand template mentioned previously is followed by other untranslated sequences that cause capping and tailing of the mature mRNA transcript so that it can exit the nucleus for translation by tRNA mediated by ribosomes in the cytoplasm (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.7 Gene Expression

Although most of our cells have the same genes, not all genes are active in every cell at the same time.

Genes may be "switched on" (active or expressed) sometimes and "switched off" (inactive or suppressed) at other times. To understand how gene expression occurs, it is important to remember that genes are sequences of DNA that code for proteins; therefore, gene expression refers to the timing, frequency, rate, and efficiency of protein production for that gene (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

All DNA exists coiled tightly around histone proteins to form chromatin. Chromatin protects DNA from damage by making it denser and more compact. It also reacts to regulatory proteins, which among other functions, modify its structure to control gene expression and DNA replication. In general, an open chromatin structure is a transcriptionally active state leading to gene activation (expression), while a closed chromatin structure is a transcriptionally inactive state leading to gene inactivation (suppression). Regulatory proteins include transcription factors, activators, repressors, acetyltransferases, deacetylases, methylases, coactivators, corepressors, kinases, and others (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Regulatory proteins regulate the activity of other genes by exerting control of gene expression through four primary mechanisms: (1) attaching to specific DNA binding sites directly (transcription factors, activators, and repressors), (2) modifying chromatin to open its conformation to reveal DNA binding sites for transcription (histone acetyltransferases) or closing its conformation to preventing such access (histone deacetylases and methylases), (3) binding to transcription factors, activators, and repressors to promote or inhibit gene expression (coactivators and corepressors), or (4) chemically altering transcription factors and activators through phosphorylation (kinases) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Homeobox genes are a family of genes that act during early embryonic development to control the formation of many body structures by coding for regulatory proteins mentioned previously. Homeobox genes exist on every chromosome and usually appear in clusters. Homeobox genes contain a DNA sequence that codes for a 60-amino acid polypeptide chain known as the homeodomain. The homeodomain is the part of the protein that binds directly to sequence-specific binding sites in the regulatory regions of the target genes (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.8 Gene Locus and Alleles

DNA sequence variations (differences in the order of the nucleotides) occur normally throughout the genome, and the resulting different forms or variants of the same gene are called alleles. Alleles are the cause of normal hereditary variation. The alleles of a gene coding for a functional protein product that are most common or prevalent in a population are called its "wild type," and are usually designated with a plus sign (+) or the abbreviation "wt." Other alleles are considered mutant alleles and are usually designated with a minus sign (−). Only two alleles exist for most genes, but no matter how many alleles exist for a gene, everyone inherits only two of them, one from each parent (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Zygosity refers to similarity between alleles. The inherited alleles for a gene can be identical (homozygous) or different (heterozygous). Locus refers to the location or position of a gene's DNA sequence on a chromosome, and homology refers to similarity in genetic content between chromosomes. Both chromosomes of a homologous pair (a set of matching maternal and paternal chromosomes) have the same loci (gene positions) all the way along their length but may have different alleles at some of the loci. This means that each chromosome in a homologous pair may contain a different variant of a specific gene, but the gene will be in the same position on both chromosomes. Each chromosome of a homologous pair is called a homolog (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

All autosomes usually exist in cells as homologous pairs having one homolog from each parent. Sex chromosomes are different. Female sex chromosomes (XX) are homologous, while male sex chromosomes (XY) are not. Since the Y chromosome does not have a homolog, most of the genes on the Y chromosome are unique to that sex chromosome. And although X chromosomes in the cells of females are homologous,

most of the genes on one of the X homologs are inactivated to compensate for human males only having one X chromosome. Since X and Y are non-homologous chromosomes, most the genes present on the X chromosome differ from those that exist on the Y chromosome. However, there is an area on the distal end of the short arm of both X and Y called the pseudoautosomal region. Genes in the pseudoautosomal region are present on *both* X and Y chromosomes, and therefore behave like genes on autosomes. Genes in the pseudoautosomal region of the X chromosome also escape inactivation. As a result, both females (who have two X chromosomes) and males (who have one X and one Y chromosome) usually have two functional alleles in each cell for genes from these regions (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). These concepts are illustrated in Fig. 7.3.

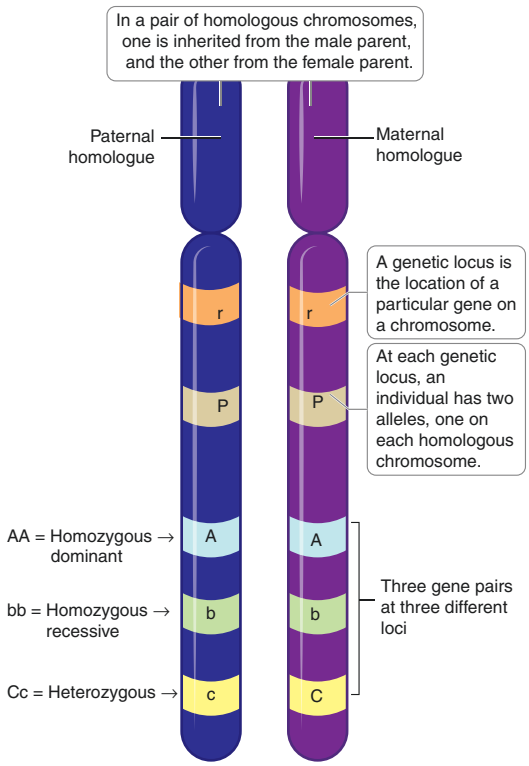


Fig. 7.3 Gene alleles, locus, and zygosity (Reproduced from https://i.stack.imgur.com/16QyG.jpg)

7.9 Genotype and Phenotype

Genotype refers to the pair of alleles an individual has at a specific location (locus) in the genome. Remember that zygosity refers to the degree of similarity between alleles in a genotype. When a pair of alleles for a gene are the same, the genotype is said to be homozygous. When a pair of alleles for a gene are different (heterozygous genotype), one of the alleles can override the other. In this situation, the overriding allele is referred to as the dominant allele, while the other is referred to as recessive. Genotypes can also be homozygous for either the dominant allele or the recessive allele. Genotypes are usually described by labelling the dominant allele with a capital letter and the recessive allele with a lower-case letter. Hemizygous genotypes occur when there is only one allele present for a gene and the other is absent (genes on the X chromosome in cells that contain only one X chromosome in individuals with Turner syndrome), or only one allele exists for that gene (most genes on the Y chromosome in human males) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Phenotype is the observable effect of the expression of a pair of gene alleles. Phenotype is sometimes referred to as a trait, but this is inaccurate, as there can be more than one phenotype for a given trait. For example, phenotype might mean brown or blue regarding the trait of eye color; or it might mean non-responder regarding the trait of drug response. Phenotypes can represent discontinuous or continuous variation. Discontinuous variation is monogenic, meaning it refers to discrete phenotype alternatives caused by differences in alleles of only one gene. For example, being albino versus pigmented. Continuous variation occurs when a spectrum of differences exist that are not usually traceable to just one gene. This means that the phenotypic differences occur in a continuum rather than as distinct alternatives. Continuous variations are caused by a combination of genes (polygenic) or by the interaction of genes and environment (epigenetic) rather than by just one gene. Examples include height, weight, skin color, or hair color

(National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

When referring to the number of normal alleles in a genotype required for the gene to produce enough protein product to maintain normal function, the gene involved is described as haplosufficient or haploinsufficient (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). (This is different from zygosity because zygosity refers to the genotype itself, whereas sufficiency or insufficiency refers to the mechanism through which a genotype produces a phenotype.)

Haplosufficient genes are those in which a single functional allele can compensate for a non-functioning or absent second allele and is thus able to produce sufficient protein product to maintain the gene's normal function. Null alleles of a gene fail to code for a functional protein, and in haplosufficient genes, are usually not expressed if a functional allele is also present. Genes in homologous regions of the X chromosome and most genes on the Y chromosome are examples of haplosufficient genes. One such example is the *SRY* gene located only on the Y chromosome. A single normal *SRY* allele from the Y chromosome is responsible for normal development of male genitalia (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Haploinsufficiency is when a single functional allele of a gene is unable to compensate for a non-functioning or absent second allele and is therefore is insufficient to maintain the gene's normal function. Genes in all autosomes and in the pseudoautosomal regions of the X and Y chromosomes are examples of haploinsufficient genes. One such example is the *SHOX* gene. *SHOX* is the short stature homeobox gene on the X chromosome. Two normal alleles of this gene, one from each sex chromosome, must be present in all cells in both males and females for normal growth and maturation of the skeleton, particularly in the arms and legs. If only one functional allele is present, the amount of *SHOX* protein produced is reduced, and this shortage causes disruption of bone growth beginning in embryonic development. Mutations and deletions in the *SHOX* gene are responsible for the short stature and bone abnormalities observed in Turner syndrome, Léri-Weill dyschondrosteosis, and Langer mesomelic dysplasia (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.10 Inheritance

Patterns of inheritance can be categorized as Mendelian or non-Mendelian. Mendel described the basic patterns of what is now known as Mendelian inheritance before the existence of genes as the mechanism for inheritance had been discovered. Phenotypic expression of an inherited Mendelian trait depends on the genotype at specific locus. Mendelian traits are inherited in a predictable manner following the laws of segregation, independent assortment, and dominance. Genes on autosomes and the pseudoautosomal regions of the sex chromosomes usually follow Mendelian laws of inheritance (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.10.1 Mendelian Inheritance

The law of segregation states that the two alleles for one specific trait (one allele on each chromosome of a homologous pair) separate in meiosis during gamete formation (formation of eggs or sperm) so that each gamete has only one allele for that trait. When two gametes randomly fuse at fertilization, the new genotype in the resulting zygote once again contains two alleles for that trait, one from each parent (National Human Genome Research Institute 2015; National

Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The law of independent assortment states that alleles for two or more *different* traits separate independently from each other during gamete formation, so that an allele for one trait is inherited by offspring independently from the allele for any other trait (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The law of dominance states that there is a dominant allele and recessive allele for each trait. As mentioned previously, dominant alleles are designated by a capital letter and recessive alleles by a lower-case letter. Inherited genotypes are either heterozygous (Aa), homozygous dominant (AA), or homozygous recessive (aa). Heterozygous and homozygous dominant genotypes produce the dominant phenotype for a trait. In the absence of mutation, only homozygous recessive genotypes produce the recessive phenotype for a trait (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Clinical examples of Mendelian inheritance include achondroplasia, multiple endocrine neoplasia, 21-hydroxylase deficiency, Léri-Weill dyschondrosteosis, and Langer mesomelic dysplasia. Achondroplasia can be inherited in an autosomal dominant manner from one affected parent because one mutant allele of the *FGFR3* gene on chromosome 4 is sufficient to cause the phenotype (heterozygous dominant genotype). Inheritance of two mutant alleles from two affected parents is fatal (homozygous dominant genotype) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Multiple endocrine neoplasia type 1 usually results from autosomal dominant inheritance of mutations in both *MEN1* gene alleles on chromosome 11 (homozygous dominant genotype). All three forms of congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency (classic salt-wasting, classic simple virilizing, and non-classic) are caused by autosomal recessive inheritance of two mutant *CYP21A2* gene alleles on chromosome 6 (homozygous recessive genotype) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Léri-Weill dyschondrosteosis has a pseudoautosomal dominant pattern of inheritance. The allele for the *SHOX* gene is mutated or missing on the pseudoautosomal region of only one of the two sex chromosomes. Langer mesomelic dysplasia has a pseudoautosomal recessive pattern of inheritance. In this disorder, both alleles for the *SHOX* gene on the pseudoautosomal regions of the sex chromosomes are missing or altered, and the phenotype is more severe (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Lethal genes are those for which one allele is fatal if a genotype with that allele is inherited. Huntington Disease is caused by autosomal dominant inheritance of a lethal mutant *HTT* gene allele on chromosome 4 (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.10.2 Non-Mendelian Patterns of Inheritance

Non-Mendelian patterns of inheritance include co-dominance, linkage, sex-linked inheritance, multiple alleles, complex inheritance that is polygenic or multifactorial, and mitochondrial inheritance.

Co-dominant inheritance occurs when the effects of both alleles are present in the phenotype so that both traits appear together, and neither is dominant over the other. Human blood type is the most common example. Linkage

refers to traits that tend to be inherited together rather separately because the gene alleles for those traits are close enough together on the chromosome to avoid the crossing-over and recombination that occurs during meiosis (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Sex-linked traits are those associated with genes on the non-homologous regions of the X and Y chromosomes. (Remember, genes on non-homologous regions of sex chromosomes contain only one allele in their genotypes, while genes in the pseudoautosomal regions contain two alleles in their genotypes. As noted previously, pseudoautosomal regions of sex chromosomes demonstrate Mendelian inheritance patterns. Sex-linked inheritance can be X-linked or Y-linked (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

X-linked inheritance can be X-linked dominant or X-linked recessive. Hereditary hypophosphatemic rickets (X-linked hypophosphatemic rickets) results from a mutation in the *dominant PHEX* gene allele on the X chromosome. It can occur in both males and females but is usually fatal in males. Fragile X syndrome results from a mutation in the *recessive FMR1* gene allele the X chromosome. It also occurs in both males and females, with males being more severely affected. Individuals with complete androgen insensitivity syndrome have both X and Y chromosomes, but they have inherited a *recessive* androgen receptor gene (*AR* gene) allele on their X chromosome and develop external female genitalia but no uterus (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Individuals with *SRY*-related Swyer syndrome (46,XY pure gonadal dysgenesis) also have both X and Y chromosomes in all their cells but have a mutated *SRY* gene allele on their Y chromosome, causing development of both female external genitalia and female reproductive organs, although the gonadal tissue is non-functional. Most cases develop due to new mutations, but sometimes an individual will inherit the mutation from an unaffected father who is mosaic for the mutation. Mosaicism occurs when the mutation exists in some cells but not in others. Because the mutation is in a gene on the Y chromosome, this is an example of Y-linked inheritance (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The term "multiple alleles" describes a situation in which a gene has *more than* two possible alleles, and the alleles have relative dominance to each other. In Mendelian inheritance, *only* two alleles exist for a gene, and one has absolute dominance over the other (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

While monogenic disorders result from mutations in one gene and follow Mendelian patterns of inheritance, complex disorders do not. Complex disorders are often familial but do not have a specific identifiable pattern of inheritance. Complex inheritance is multifactorial, involving the additive effect of many susceptibility genes interacting with each other and with the environment, and is not completely understood. A susceptibility gene is one that confers a risk to develop a disease but is not sufficient by itself to cause the disease. Susceptibility genes can contribute to age of onset and severity of disease or protect against developing the disease. Type 1 diabetes mellitus is an example of a disorder with complex inheritance (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Polygenic inheritance refers to traits in which the phenotype is determined by several different genes. Human stature (height) is an example of this (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Mitochondrial inheritance describes the passing of mitochondrial DNA (mtDNA) from a

mother to her offspring through the cytoplasm of her egg cells. All other Mendelian and non-Mendelian inheritance patterns refer to nuclear DNA (DNA that is packaged into chromosomes within the nucleus of cells). Paternal lineage can only be traced through Y-linked DNA in males, while maternal lineage can be traced through mtDNA in both males *and* females. There are 37 genes on mtDNA, 13 of which code for proteins that function as enzymes involved in the energy producing processes within the mitochondria, and the rest provide templates for the synthesis of transfer RNA (tRNA) and ribosomal RNA (rRNA). A clinical example is mitochondrial diabetes and deafness (MIDD), a disorder that results from mutations in at least three mtDNA genes coding for tRNA molecules responsible for synthesis of proteins in the mitochondria of pancreatic beta cells. The mutations impair the ability of the mitochondria to signal insulin release in response to rising glucose levels. The mechanism for the associated deafness is not yet known (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.11 Epigenetics

Epigenetics is the study of heritable changes that occur *without* a change in DNA sequence. The word "epi" is of Greek origin and means "over" or "above," so epigenetics literally means "above" the genome. The epigenome includes chemical compounds and proteins that mark or tag the genome to provide instructions for turning genes on or off and modifying the way cells produce or use proteins, rather than changing the DNA sequence itself. The epigenome can also change throughout a human's lifespan. Epigenetic changes are passed along as somatic cells divide (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Lifestyle and environmental factors such as diet, medications, smoking, and exposure to pesticides and pollutants can expose a person to chemical tags on the DNA backbone or on histone tails that change the epigenome. Researchers have linked changes in the epigenome to diabetes, autoimmune diseases, and other disorders. Epigenetics explains why although most of all cells in the human body contain the same genes, different cell types behave differently. They behave differently because their epigenetic tags are arranged differently. Epigenetics may also explain differences seen in identical twins (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Epigenetic inheritance involves chemical and structural mechanisms that control gene expression (activation and deactivation of genes), such as chromatin remodelling, X chromosome inactivation, and genetic imprinting. Mechanisms involved in chromatin remodelling via histone modification include methylation and acetylation. During methylation, methyltransferases add methyl groups (CH_3) to histones that close the chromatin structure inducing a transcriptionally inactive state that acts as an off-switch repressing gene expression. During acetylation, acetyltransferases add acetyl groups (CH_3CO) to histones that open the chromatin structure inducing a transcriptionally active state that acts as an on switch activating gene expression. Inappropriate methylation (deactivation) causes a loss of necessary function while inappropriate *de*methylation (removal of a methyl group from the histone causing unintended activation) causes a gain of undesirable function. Similar problems occur when acetylation goes awry (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

X chromosome inactivation is an epigenetic form of X chromosome dosage compensation. Dosage refers to the number or "dose" of X chromosomes in a cell. Because cells in human males have one X chromosome while those in human females have two, the species compensates for the extra "dose" females receive by having each cell inactivate (turn off) one of them. This allows males and females to have equal expression of

the genes carried on the X chromosome (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The gene that controls which X chromosome remains active is called the X-controlling element (*Xce*), but the mechanism by which it does so is not yet known. The X-chromosomal region that controls the initiation and continuation of X-inactivation is called the X-inactivation center (Xic). The *Xist* gene controls Xic initiation of inactivation (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The exception to this rule is in genes located in the distal region of the short arms of chromosomes X and Y, called the Xp and Yp regions, which demonstrate pseudoautosomal inheritance. In other words, these regions escape X-inactivation and the genes in these regions are inherited in the same manner as genes found on autosomes. This means that two copies of a gene allele are required for expression in these regions instead of the one copy that is required for other genes on the X and Y chromosomes (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Imprinting refers to sex-specific differences in epigenetic methylation patterns. Gene expression is determined by the methylation pattern in the parent of origin (tied to whether it is inherited from mother or father). Unlike histone modification where the methyl groups are attached to the histone tails, during imprinting, the methyl groups are added directly to the DNA without changing the sequence. Cytosine nucleotide bases located next to guanine bases are referred to as CpG dinucleotides. Clusters of CpG repeats are called CpG islands. A different methyltransferase from that used in histone modification adds a methyl group to the cytosine in these islands scattered throughout the genome to inactivate certain genes in only one parent. In some genes, only the copy of the gene from the mother gets turned on, while in others, only the copy from the father. The copy from the opposite parent is turned off. The pattern of methylation is transmitted during replication. Clinical examples include Prader-Willi syndrome and Angelman syndrome which both involve imprinted genes on chromosome 15 (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.12 Mutations

Genetic alterations in the DNA sequence that occur in *at least* 1% of the population and are common enough to be considered normal variation are referred to as polymorphisms. Polymorphisms are generally considered neutral or not harmful. A single nucleotide polymorphism (SNP) is the smallest possible change in DNA, affecting only one nucleotide. Single nucleotide polymorphisms commonly occur in both coding (exons) and non-coding (introns) regions (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Permanent changes in the DNA sequence that are harmful and rare, occurring in *less than* 1% of the population, are called mutations. Mutations range in size from one nucleotide to large chunks of a chromosome involving many genes. Mutations can be classified as either hereditary (germline) or acquired (somatic). Hereditary mutations are germline mutations because the DNA error occurs in germ cells (egg and sperm, also called gametes). A germline mutation is passed from parent to offspring and remains present in every cell of the offspring's body for the entire lifespan. De novo mutations are defined as new DNA sequence variants that are present in an offspring but absent from both parents. A de novo germline mutation is a new mutation in an egg or sperm cell of a parent or a new mutation that occurs immediately after fertilization before cell division begins. De novo germline mutations can result from DNA errors that occur during meiotic cell division. The muta-

tion is not present in any of the parent's other cells, so the parent is unaffected. The disorder in the offspring caused by the new mutation may be the first appearance of that disorder in the family (there may not be any prior family history of the disorder) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Acquired mutations are called somatic mutations because they occur in somatic cells (cells that are not egg or sperm cells). All acquired mutations are mutations that cannot be passed on to offspring, are not present in every cell of the body, and can occur at any time from the embryonic period until the end of the individual's lifespan. DNA errors causing acquired mutations can result from environmental damage to the DNA, errors that occur during DNA replication in mitotic cell division, and problems with DNA repair mechanisms (DNA repair enzymes that find and fix most DNA errors before they can accumulate) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). Types of gene mutations with clinical examples are provided in Table 7.1 (Lania et al. 2001; Vassart and Costagliola 2011; Lin et al. 2007; Bashamboo et al. 2016; Birla et al. 2014; Bøe Wolff et al. 2008; Gagliardi et al. 2014; Tonelli et al. 2014; Yamaguchi et al. 2013; Baculescu 2013; Akbas et al. 2012).

Table 7.1 Types of gene mutations with clinical examples (Lania et al. 2001; Vassart and Costagliola 2011; Lin et al. 2007; Bashamboo et al. 2016; Birla et al. 2014; Bøe Wolff et al. 2008; Gagliardi et al. 2014; Tonelli et al. 2014; Yamaguchi et al. 2013; Baculescu 2013)

GENE MUTATION	CLINICAL EXAMPLE
Point—a change in one nucleotide at a single location in a DNA sequence	Loss-of-function germline point mutations in the *GNAS* gene at 20q13.32 can cause pseudohypoparathyroidism type Ia with or without testitoxicosis, while gain-of-function somatic point mutations in the same gene have been linked to McCune-Albright syndrome.
Missense—the change of a single base pair causes the substitution of a different amino acid in the resulting protein	46,XY gonadal dysgenesis with impaired androgen biosynthesis (external female genitalia with palpable bilateral labial testes) was reported in an infant with a heterozygous missense de novo germline mutation.
Nonsense—a change in a single base pair creates a premature stop codon that signals the cell to stop building a protein too soon	A nonsense mutation has been associated with pituitary stalk interruption syndrome resulting in neonatal hypoglycemia, and GH, TSH, and ACTH deficiencies.
Insertion—the addition of genetic material ranging from a single extra DNA base pair to a piece of a chromosome	An insertion mutation was associated with acromegaly and left atrial myxoma in Carney's complex.
Deletion—the removal of genetic material ranging from one DNA base pair within a gene to entire genes	Partial gene deletions contribute to autoimmune polyendocrine syndromes.
Duplication—a piece of DNA is abnormally copied one or more times	A duplication in the aromatase gene results in aromatase deficiency, a rare autosomal recessive disorder that prevents the conversion of androgens to estrogens.
Frameshift—addition or deletion of a nucleotide pair shifts the reading frame of the gene sequence during translation so that all the amino acids after the mutation are altered. Insertions, deletions, and duplications can all be frameshift mutations	A germline heterozygous frameshift mutation of the *CDKN1B* gene has been reported to cause recurrent hyperparathyroidism in the autosomal dominant disorder multiple endocrine neoplasia type 4 (MEN4).
Substitution—one base pair is replaced by a different base pair	A homozygous substitution mutation caused the autosomal recessive disorder familial glucocorticoid deficiency (FGD) in a patient whose parents were heterozygous for the same mutation.
Repeat expansions—a mutation that increases the number of times short nucleotide sequences are repeated in a row	A shorter CAG repeat polymorphism mediates androgen receptor activity contributing to the pathogenesis of polycystic ovarian syndrome (PCOS).

7.13 Chromosomal Abnormalities

Chromosomal abnormalities can be either structural or numerical.

7.13.1 Chromosomal Structural Abnormalities

Abnormal changes in chromosome structure can be inherited or occur randomly during gamete formation or early fetal development (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). Types of chromosomal structural abnormalities with associated clinical examples and methods for diagnostic testing are provided in Table 7.2 (Akbas et al. 2012; Choi et al. 2013; Stagi et al. 2014; Antonacci et al. 2009; Cetin et al. 2011; Sireteanu et al. 2013; Bellfield et al. 2016).

Table 7.2 Chromosomal structural abnormalities with clinical examples (Akbas et al. 2012; Choi et al. 2013; Stagi et al. 2014; Antonacci et al. 2009; Cetin et al. 2011; Sireteanu et al. 2013; Bellfield et al. 2016)

STRUCTURAL ABNORMALITY	DIAGNOSTIC TESTING	CLINICAL EXAMPLES
Translocations—a broken piece of one chromosome attaches to a non-homologous chromosome	Cytogenetic karyotype analysis	A familial balanced reciprocal translocation 46,XY,t(16;22)(p11;q13) was found in a patient with constitutional short stature. A variety of phenotypes including hypogonadotrophic hypogonadism, precocious puberty, growth hormone deficiency, and idiopathic short stature were identified in patients with 45,XY,t(13;14)(q10;q10) and 45,XX,t(13;14)(q10;q10).
Deletions—a piece of a chromosome breaks off and is lost	Standard karyotype does not detect deletion; requires FISH analysis or other molecular analysis	DiGeorge syndrome results from an autosomal dominant or de novo germline mutation causing deletion of genes on 22q11.2.
Duplications—part of a chromosome is copied too many times resulting in extra copies of genetic material from the duplicated segment	Molecular arrayCGH analysis	Growth hormone deficiency has been associated with *SOX3* gene duplication on chromosome Xq26.3-27.3.
Inversions—a chromosome breaks in two places and the resulting piece reattaches itself into the chromosome in reverse order	Molecular sequence analysis and arrayCGH analysis of inversion breakpoints and FISH analysis of inversions	Renal cysts and diabetes syndrome (RCAD) or maturity-onset diabetes of the young, type 5 (MODY5) is associated with an inversion at chromosome 17q12.
Isochromosome—a chromosome with two identical arms, formed by transverse rather than longitudinal separation of a replicating chromosome, which causes duplication of one arm and loss of the other, with associated gain or loss in copies of the genes on those arms	Cytogenetic karyotype analysis followed by multiple FISH analyses with chromosomes 4, 16, X and centromeric probes	A patient with Turner syndrome was found to have a complex karyotype including both mosaicism of an isochromosome Xq10 and a maternally inherited familial reciprocal translocation between chromosomes 4 and 16 t(4;16)(p15.2;p13.1).
Dicentric chromosomes—a chromosome with two centromeres resulting from the abnormal fusion of two chromosome pieces, each containing a centromere. Some genetic material is usually lost	Cytogenetic karyotype analysis followed by molecular SNP chromosome microarray analysis	A dicentric chromosome 14;18 was found in female with microform holoprosencephaly and Turner-like stigmata.
Ring chromosome—a chromosome that has broken in two places and the ends of the arms fuse to form a circular structure (genetic material at the tip of each arm is usually lost)	Cytogenetic karyotype analysis followed by molecular SNP chromosome microarray analysis	Ring chromosome 18p deletion is associated with anterior pituitary aplasia.

7.13.2 Chromosomal Copy Number Abnormalities

Ploidy refers to the number of sets of chromosomes in the nucleus of a cell. As described earlier in the chapter, diploid somatic cells have two copies of a set of chromosomes (2n), while haploid reproductive cells (germ cells or gametes) have one copy (n). Disorders caused by the presence of an abnormal number of chromosomes are called aneuploidies. Aneuploidies are not mutations, but like de novo germline mutations and acquired somatic mutations, these disorders are not usually inherited. They are present in an offspring but usually absent from both parents (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Disjunction refers to normal homologous chromosome or sister chromatid separation during mitotic or meiotic cell division. Aneuploidies are the result of meiotic or mitotic nondisjunction. Nondisjunction occurs when a pair of chromosomes or chromatids fail to separate during cell division. Endocrine examples include Turner and Klinefelter syndromes (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Meiotic nondisjunction usually occurs randomly during the formation of gametes in a parent resulting in an egg or sperm cell gaining one or more extra chromosome copies (Klinefelter syndrome) or losing a chromosome copy (Turner syndrome). If an abnormal egg or sperm cell is one of the gametes that forms the zygote, the aneuploidy (abnormal chromosome copy number) will be present in every cell of the offspring's body (as is seen in de novo germline mutations). In our example, a 24,XY sperm fertilizes a 23,X egg or a 23,X sperm fertilizes a 24,XX egg resulting in Klinefelter syndrome (47,XXY), or a 23,X sperm fertilizes a 22 egg or a 22 sperm fertilizes a 23,X egg resulting in Turner syndrome (45,X) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Mitotic nondisjunction occurs as a random event after conception during cell division early in fetal development and leads to mosaicism. Mosaicism means that the aneuploidy (abnormal chromosome copy number) is present only in some of the cells in the offspring's body, while other cells have the normal chromosome copy number. Following the previous examples, an individual with mosaic Klinefelter syndrome (46,XY/47,XXY) would have one X chromosome and one Y chromosome is some body cells, and an extra copy of the X chromosome in other cells. An individual with mosaic Turner syndrome (46,XX/45X) would have two X chromosomes in some body cells, and only one X chromosome in other cells. Other examples of mosaicism resulting from mitotic nondisjunction in early embryonic development include Down syndrome 46,XY/47,XY,+21, Edward syndrome 46,XX/47,XX,+18, and Patua syndrome 46,XY/47,XY,+13 (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.14 Interpreting Genetic Test Results

There are two basic types of genetic testing, cytogenetic and molecular. Cytogenetic testing examines chromosomal number and structure using microscopic analysis, whereas molecular genetic testing examines genes and chromosomes at the level of the DNA or RNA molecule using a variety of specialized molecular techniques (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). The current section will cover basic chromosomal anatomy used to interpret cytogenetic testing, give a detailed explanation of cytogenetic testing methods, and provide an overview of molecular genetic technologies. (Detailed chromosome

structural morphology including chromatin, histones, and DNA sequence was covered previously in the chapter section on gene expression and will not be duplicated here.)

The most common cytogenic test result seen in endocrine clinic is the karyotype, while molecular genetic testing results may be from molecular array analyses (SNP-arrays, microarrays, array comparative genomic hybridization), genome-wide or specific gene sequencing, and other molecular methods of mutation detection. Although cytogenetic test interpretation requires knowledge of basic chromosomal anatomy, molecular genetic test interpretation requires additional recollection of concepts such as exons, introns, promoters, and SNPs covered in prior sections of this chapter.

7.14.1 Chromosome Anatomy

Chromosomes can be viewed using a light microscope following treatment with special stains. Stained chromosomes are more easily seen during the phase of mitotic cell division when the chromosomes have replicated and are condensed. Each chromosome has a constriction, called a centromere, which divides the chromosome into short (p) and long (q) arms, and orients the chromosomes during the phases of cell division. The tip of each end is called a telomere (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

7.14.2 Cytogenic Testing

7.14.2.1 Karyotyping

A karyotype is a pictorial display of metaphase (standard) or prophase/prometaphase (high resolution) chromosomes from a mitotic cell. Karyotyping can identify abnormalities in chromosome numbers and structure. Standard karyotyping is performed on cells in metaphase when the chromosomes are most condensed, while high resolution karyotyping is performed on cells in prophase or prometaphase when the chromosomes are slightly more elongated (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The process of obtaining a karyotype involves:

- growing colonies of cells in culture medium until there is sufficient quantity for analysis
- treating the cells with a hypotonic solution to make them swell so that the chromosomes spread out and separate from one another
- arresting mitotic cell division with colchicine in prophase/prometaphase or metaphase
- using special chemicals to digest and remove all chromosomal proteins (such as histones)
- staining the condensed chromosomes with standard dyes (G, C, T, and R banding) or fluorescence (spectral banding)
- and finally, photographing the chromosomes and digitally rearranging them in pairs distinguished by length, size and shape, and unique banding patterns (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017)

Chromosomes are displayed in a karyotype with the autosomes first, arranged by longest (chromosome 1) to shortest (chromosome 22), followed by the sex chromosomes. The unique shape of each chromosome in a karyotype is determined by the location of its centromere. The shape can be described as metacentric (chromosomes 1, 3, 16, 19-20), submetacentric (chromosomes 2, 4-12, 17-18, X), acrocentric (chromosomes 13-15, 21-22, Y), or telocentric (does not exist in humans) (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

The lightness or darkness in the banding patterns is determined by the density of the DNA in that region. Darker bands are produced in adenine-thymine-rich areas in G banding, guanine–cyto-

sine-rich areas in R banding, on centromeres in C banding, and on telomeres in T banding. Chromosomes in traditional banding karyotypes appear in black and white. Spectral banding uses multiple fluorescent probes with varying amounts of fluorescent dyes that bind to specific regions of chromosomes resulting in unique spectral characteristics for each chromosome that are detected by computer software that creates a full color digital image of the chromosomes (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Karyotypes can be made at standard or high resolution. Standard metaphase karyotyping can identify 300–600 bands per chromosome, while high resolution prophase/prometaphase karyotyping can identify 700–1200 bands. Just as you were able to see greater detail at higher power magnification when you viewed a slide under a microscope in your high school biology class, higher resolution banding karyotypes can sometimes find chromosomal abnormalities not detected under standard resolution, and spectral karyotypes can sometimes detect translocations not recognizable through standard banding analysis (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Each arm of the chromosome (p and q) is divided into regions numbered sequentially from the centromere to the telomere. The bands within each region are also numbered sequentially in the same manner, and these bands are further refined by additional levels of sub-band numbering (Fig. 7.4).

A common misperception is that bands represent single genes, but in fact the thinnest bands contain over a million base pairs and potentially hundreds of genes. Gene locations on a chromosome are often shown on a cytogenetic map, which is a diagram displaying the specific banding pattern for that chromosome, with the gene location indicated at a specific distance from the centromere or telomere (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

For example, the gene responsible for Kallman syndrome is located at Xp22.3, meaning that it is located within the 3rd sub-band of the 2nd band

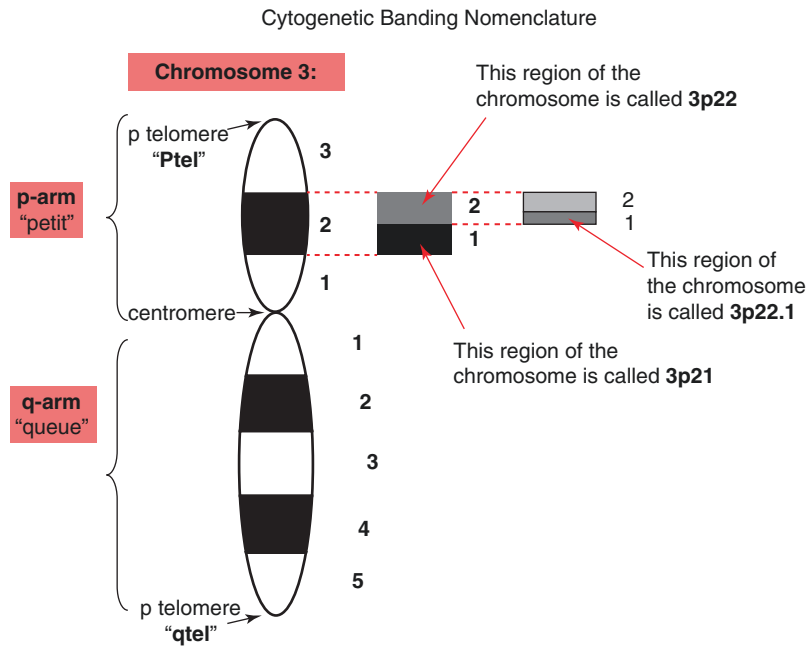


Fig. 7.4 Chromosome anatomy and banding designations (Reproduced from http://cdn.biologydiscussion.com/wp-content/uploads/2015/11/clip_image0222.jpg)

in region 2 of the short arm of the X chromosome. Another example is the area of gene deletion found in patients with Prader-Willi and Angelman syndromes, which is defined as 15q11 to 15q13, meaning that the genetic region is located between the 1st and 3rd bands within the 1st region on the long arm of chromosome 15.

Reading a karyotype report requires an understanding of the terminology used in the description of the analysis. Cells or colonies refer to the number of cells in which the chromosomes were counted, while cultures refer to the number of cell colonies examined to reduce or eliminate the chance of lab error. Cells or metaphases analyzed means the number of cells in which the chromosomes were examined in detail for length, shape, and banding pattern. Images or karyotypes refer to the number of pictures taken, or digital files generated for the report (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Three letter codes are used to describe specific banding techniques. The first letter denotes the type of banding (G, R, C, or T); the second letter indicates the general technique used to remove the chromosomal proteins to permit staining (barium hydroxide, acetic acid, trypsin, BrdU, or heating); and the third letter gives the type of stain used (Giemsa, Wright's). For example, GTG means G banding by trypsin using Giemsa; GTW means G banding by trypsin using Wright's; CBG means C banding by barium hydroxide using Giemsa; RHG means R bands by heating using Giemsa; and RBG means R bands by BrdU using Geimsa (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017).

Karyotype reports use abbreviations to indicate chromosomal abnormalities such as der (derivative chromosome, which is a structurally rearranged chromosome), inv (inversion), ins (insertion), del (deletion), t (translocation), and others (National Human Genome Research Institute 2015; National Institute of General Medical Sciences 2016; U.S. National Library of Medicine, National Institutes of Health 2017). For example, in a patient with Wittwer syndrome believed to be a variant of Wolf-Hirschhorn syndrome, a karyotype of 46,XY,der(4)t(4;17)(p16.1;q25.3) refers to a derivative chromosome 4 resulting from a translocation between the short arm of chromosome 4 at region 1, band 6, sub-band 1, and the long arm of chromosome 17 at region 2, band 5, sub-band 3 (Wieland et al. 2014). In a patient with Silver-Russell syndrome, a karyotype of 46,XX,der(16)t(11;16)(p15.3;q24.3)mat showed a derivative chromosome 16 resulting from a translocation between the short arm of chromosome 11 at region 1, band 5, sub-band 3, and the long arm of chromosome 16 at region 2, band 4, sub-band 3. The "mat" notation means that further molecular analyses revealed duplications (extra copies) of maternally derived chromosome 11p15 in this patient (Nakashima et al. 2015).

7.14.2.2 Fluorescent In Situ Hybridization

Fluorescent in situ hybridization (FISH) is a cytogenetic technique where a probe is used to locate a specific area of concern on a chromosome. Because FISH targets a specific chromosome region, the test is ordered when clinical findings suggest a specific disorder that isn't confirmed by high resolution karyotyping alone (Anderson 2016). A probe is a manufactured nucleic acid segment (a specific part of a strand of DNA) that seeks out the complementary strand of DNA in the sample and binds to it. The process of binding one complementary strand to another is hybridization. The probe is labelled with fluorescent dye or a radioactive tag for identification when it finds it target. FISH is generally used to detect microdeletions. Laboratory reports for FISH analysis use the abbreviation "ish" followed by the name of the specific probe utilized in the procedure.

7.14.2.3 Cytogenetic Testing Clinical Examples

Table 7.3 contains actual de-identified patient results for cytogenetic testing from an endocrine clinic with author comments added that allow the

Table 7.3 Cytogenetic testing clinical examples

CYTOGENETIC TESTING	
Patient test result	**Author comments**
Case 1 **Cytogenetic Report and Consultation** Quest Diagnostics Age: 7 Sex: Male Specimen Type: Peripheral blood Indication: FISH evaluation for DiGeorge/Velocardiofacial Syndrome [Chromosome analysis (HRO138293) in progress] Summary of Analysis Method: FISH Total Cells: 30 Images: 2 Results ish 22q11.2(TUPLE1x2) Interpretation Negative for DiGeorge/Velocardiofacial syndrome. A fluorescence in situ hybridization (FISH) study, using the probe TUPLE1 (Vysis, Inc.), which hybridizes within band 22q11.2, showed a normal pattern of hybridization. Therefore, the deletion associated with the majority of cases of DiGeorge and Velocardiofacial syndromes is not present in this patient. Deletions contiguous to or smaller than this probe, point mutations and diseases with other genetic etiologies will not be detected by this method.	This patient presented with short stature associated with a heart murmur, low-set ears, and hypotonia. Two tests were subsequently performed for suspicion of DiGeorge/Velocardiofacial syndrome, a FISH evaluation and a chromosome analysis. The result shown here is for the FISH evaluation. DiGeorge/Velocardiofacial syndrome is also referred to as 22q11.2 deletion syndrome. Note the limitations of this type of testing listed in the interpretation section of the results.
Case 2 **Cytogenetic Report and Consultation** Quest Diagnostics Age: 7 y Sex: Male Specimen Type: Peripheral blood Indication: Rule out chromosome abnormality [FISH for DiGeorge/Velocardiofacial Syndrome (F01 38294) negative] Summary of Analysis Method: GTG Band Level: 550 Total Cells/Colonies: 20 Cells Analyzed: 5 Images/Karyotypes: 3/2 Results 46,XY, normal male karyotype Interpretation The banding level required for high resolution analysis (at least 550 bands per haploid karyotype) was achieved in this study as requested. The following possibilities, although rare, cannot be ruled out: (a) low level mosaicism, (b) very subtle rearrangements, and (c) genetic disorders that cannot be detected by cytogenetic methods.	This result is for the chromosome analysis performed on the same patient as the FISH evaluation. Higher band levels allow greater resolution and increase the ability to identify subtler chromosomal abnormalities. Note the limitations of this type of testing listed in the interpretation section. Molecular genetics tests now available for diagnosing 22q11.2 abnormalities include: • Deletion/duplication analysis • Sequence analysis of the entire coding region • Targeted variant analysis • Detection of homozygosity.

(continued)

Table 7.3 (continued)

CYTOGENETIC TESTING	
Patient test result	**Author comments**
Case 3 **Chromosome Analysis** Genzyme Genetics Specimen Type: Peripheral Blood Indications for Study: History of presumed Cornelia de Lange Metaphases Counted: 23 Banding Technique: GTW Metaphases Analyzed: 7 Number of Cultures: 2 Metaphases Karyotyped: 3 Banding Resolution: 500 Results 47,XXY Abnormal karyotype, male Interpretation Cytogenetic analysis shows 47,XXY in each metaphase cell examined, consistent with the clinical diagnosis of Klinefelter Syndrome. The clinical manifestations are highly variable, but usually include tall stature, infertility, and a risk for gynecomastia. Mental retardation is unlikely. There is a risk for developmental delays in speech, neuromotor skills, and learning abilities (Robinson, A. et al., Prenatal Diagnosis of Sex Chromosome Abnormalities. In Milunsky, A., ed., Genetic Disorders and the Fetus, 4th edition. Baltimore: The Johns Hopkins University Press, 1998. pp. 249–85). No other chromosome abnormalities are observed. The standard cytogenetic methodology utilized in this analysis does not routinely detect small rearrangements and low-level mosaicism and cannot detect microdeletions. Genetic counseling is recommended for this family.	This patient presented with tall stature and hypothalamic hypogonadism prompting testing for Klinefelter syndrome. The test result provides an example of meiotic nondisjunction resulting in aneuploidy. Note the limitations of this type of testing listed in the interpretation section.
Case 4 **Chromosome Analysis Report** Medgenetics Diagnostic Laboratories, Inc. Age: 8 y Sex: M Requesting Diagnosis: Dysmorphic features Specimen: Peripheral blood Banding Method: G-banding (GTG) No. Metaphases Analyzed: 20 No. Karyotyped: 2 Cytogenetic Diagnosis 46,XY,del(15)?(q11orq1lq12) Interpretation Deletion of proximal long arm material from one chromosome #15 is apparent in this patient. The question arises as to whether the deletion simply involves part of q11 (generally considered to be benign) or instead encompasses q11 and q12 (associated with the manifestation of Prader-Willi/Angelman syndromes). Materiel on hand is of insufficient quality to discriminate between these two alternatives. Recommendations Please repeat for high resolution analysis. Clinical correlation requested.	This patient presented with short stature, dysmorphic facial features, obesity, hypotonia, and mild intellectual disability prompting testing for Prader-Willi syndrome. Follow-up tests that could confirm the diagnosis of Prader-Willi syndrome are listed below. Cytogenetics Tests • Fluorescence in situ hybridization (FISH) Molecular Genetics Tests • Deletion/duplication analysis • Sequence analysis of the entire coding region • Uniparental disomy study (UPD) • Targeted variant analysis • Methylation analysis • Detection of homozygosity Prader-Willi and Angelman syndromes involve imprinted genes in sections of chromosome 15. Only the paternal or maternal allele is functional in imprinted genes, while the other allele is inactivated. If both alleles are inherited from one parent instead of one allele from each parent (uniparental disomy), the functional imprinted gene may be missing (the paternal allele in Prader-Willi syndrome and the maternal allele in Angelman syndrome).

(continued)

Table 7.3 (continued)

CYTOGENETIC TESTING	
Patient test result	**Author comments**
Case 5 **Cytogenetic Report and Consultation** Quest Diagnostics Age: 8 Months Sex: Female Indication: FISH evaluation for Prader-Willi-Angelman Syndromes Specimen Type: Peripheral blood Summary of Analysis Method: FISH Total Cells: 20 Images: 2 Results ish 15q12(SNRPNx2) Interpretation Negative for Prader-Willi-Angelman syndromes. A fluorescence in situ hybridization (FISH) study, using the probe SNRPN (Vysis, Inc.), which hybridizes within band 15q12, showed a normal pattern of hybridization, no deletion nor duplication was observed in this patient. Uniparental disomy, mutations affecting imprinting, deletions contiguous to or smaller than this probe, point mutations and diseases with other genetic etiologies will not be detected by this method Genetic counseling is recommended.	This infant presented with failure to thrive, developmental delay, hypotonia, and dysmorphic facial features suspicious for Prader-Willi syndrome. Note the limitations of this type of testing listed in the interpretation section. Recommendations for additional molecular genetic tests noted in previous patient case would also apply to this case. DNA methylation analysis can detect up to 99% of cases and is now the recommended first line test for Prader-Willi syndrome. The FISH test only detects deletions, not methylation defects, imprinting defects, or uniparental disomy.
Case 6 **Cytogenetic Report and Consultation** Quest Diagnostics Age: 11 Sex: Female Indication: Rule out Turner's or Mosaic Turner's Specimen Type: Peripheral blood Summary of Analysis Method: GTG Total Cells/Colonies: 20 Band Level: 400–550 Cells Analyzed: 5 Images/Karyotypes: 3/2 Results 45,X Interpretation An abnormal female karyotype with a single X chromosome, consistent with the clinical diagnosis of Turner syndrome was noted in all metaphases. Genetic counseling is recommended. The following possibilities, although rare, cannot be ruled out: (a) low level mosaicism, (b) very subtle rearrangements, and (c) genetic disorders that cannot be detected by standard cytogenetic methods.	This patient presented with severe short stature, hypothyroidism, and features suggestive of Turner syndrome. The test result provides an example of meiotic nondisjunction, the failure of homologous chromosomes to separate during the first meiotic cell division, resulting in germline aneuploidy. Note the limitations of this type of testing listed in the interpretation section. FISH analysis using X and Y probes can identify low-level sex chromosome mosaicism for cryptic Y chromosome material.

(continued)

Table 7.3 (continued)

CYTOGENETIC TESTING	
Patient test result	**Author comments**
Case 7 **Chromosome Analysis** Specimen Type: Peripheral Blood Indication: Pituitary dwarfism Metaphases Counted: 30 Banding Technique: GTW Metaphases Analyzed: 7 Number of Cultures: 2 Metaphases Karyotyped: 3 Banding Resolution: 500 Results 45,X[17]/46,XX[13] Abnormal karyotype, female Interpretation Cytogenetic analysis shows two cell lines: Seventeen (17) of 30 metaphase cells examined show a 45,X Karyotype. A 46,XX karyotype was observed in each of the remaining cells. A 45,X cell line is characteristically associated with Turner syndrome. Patients with 45,X145,XX mosaicism can express a range of clinical features, varying from normal female maturation to full expression of Turner syndrome phenotype (Robinson, A. et al. In Milunsky, A., ed. Genetic Disorders and the Fetus, 4th edition. Baltimore: The Johns Hopkins University Press, 1998. P. 256; and Hsu, L.Y.F. In Milunsky, A., ed. pp. 219–20). No other chromosome abnormalities are observed. The standard cytogenetic methodology utilized in this analysis does not routinely detect small rearrangements and low-level mosaicism and cannot detect microdeletions. Genetic counseling is recommended for this patient/family.	This patient presented with short stature as her chief complaint. The clinic protocol was to test any female presenting with short stature for Turner syndrome. The test result provides an example of mitotic nondisjunction, the failure of sister chromatids to separate during mitosis in early embryonic development, leading to mosaicism of the aneuploidy.

reader to apply concepts covered in this chapter to clinical scenarios. Refer to key terms found at the beginning of this chapter for terminology definitions.

7.14.3 Molecular Genetic Testing

Molecular testing differs from cytogenetic testing in that it looks at changes in DNA sequence or epigenomic modifications to the DNA rather than at chromosomal number and structure within a cell. Three types of molecular genetic testing will be presented here: Microarrays, direct sequencing analysis, and methylation analysis.

7.14.3.1 Microarrays

Microarray technologies fall into two categories: array comparative genomic hybridization (aCGH) and single nucleotide polymorphism array (SNP-array or HDSNP-array). Both aCGH and SNP-array look for copy number variations (CNV) in the DNA sequence, but aCGH does so by comparing the patient's DNA to reference DNA, while SNP-arrays find CNV directly without the need for reference DNA. Microarrays have a growing number of applications including molecular karyotyping (DNA microarrays) and gene expression studies (RNA microarrays) (Bochud 2012).

Molecular karyotyping via aCGH is able to detect chromosome microdeletions and microduplications not detectable through cytogenetic methods because of its significantly higher resolution (Kirmani 2014). This means that it is able to detect CNV in regions too small to be seen microscopically, and unlike FISH, does not require clinical suspicion of an abnormality in a specific chromosomal location (Anderson 2016). It aCGH is like performing thousands of FISH tests all at one time because it detects missing regions of chromosomes (deletions) or extra segments of chromosomes (duplications) by simultaneously hybridizing the patient's DNA to

thousands of reference DNA probes. The probes are unique short DNA segments of every chromosome arranged in a grid attached to a type of glass slide called a gene chip. Because DNA probes are often called oligonucleotides, aCGH is sometimes referred to as oligonucleotide-based array comparative genomic hybridization (oligonucleotide aCGH) (Bochud 2012). The reference DNA is sometimes referred to as the control DNA because it is from individuals with no genetic abnormalities. The genetic regions of the genome represented on the array chip depends on the number of probes in the array (Anderson 2016). The patient's DNA, along with reference DNA, are broken up into fragments and labeled with fluorescent dye (usually green and red) and applied to the chip where the fragments hybridize with matching probes on the array. A microarray scanner machine then analyzes the hybridization patterns. An imbalance in green or red in the analysis indicates duplications or deletions are present (Anderson 2016).

Because there are many different proprietary chip technologies available, aCGH results will look different depending on the specific technology used in the laboratory performing the analysis (Bochud 2012). However, most provide the copy numbers of each chromosome as well as the location and number of deletions (dn) or duplications (dp). Deletions and duplications may be measured in base pairs (bp), kilobase pairs (1000 base pairs per kb), or megabase pairs (one million base pairs per Mb). Here are three examples:

- arr(1-22)x2, (XY)x1 means that the microarray found two copies of chromosomes 1-22 and one copy each of chromosomes X and Y, for a normal male karyotype (Anderson 2016).
- arr(1-22,X)x2 means the array found two copies of chromosomes 1–22 and two copies of chromosome X, for a normal female karyotype (Anderson 2016).
- 46,XY.arr12q24.31(121,332,698-122,486,277)x1dn means that the analysis found the normal number of chromosomes for a male (46,XY), but that on one copy of chromosome 12 at band position 24.31 of the long arm, there was a deletion (dn) from nucleotide #121,332,698 through nucleotide #122,486,277 (Anderson 2016).

Results may also include a picture of the aCGH analysis and diagrams of the deletions or duplications.

Endocrine examples of disorders detected through microarray technology include Williams syndrome (deletions and duplications) (Henderson et al. 2014), DiGeorge syndrome (deletion) (Henderson et al. 2014), and complex mosaic Turner syndrome (Sdano et al. 2014). Because aCGH technologies are designed to find copy number variations, aCGH analysis does not detect balanced chromosomal abnormalities that do not affect copy number, such as reciprocal translocations, inversions, ring chromosomes, low-level mosaicism, or point mutations (Anderson 2016).

7.14.3.2 Gene Expression Analysis

A detailed description of gene expression analysis or mRNA expression profiling is beyond the scope of this chapter, but an overview as it relates to microarrays is provided here. Gene expression analysis detects the protein product resulting from a gene's activity by analyzing the RNA transcript (message) of DNA rather than a specific DNA sequence. Gene expression analysis is sometimes called functional gene testing because results of gene expression analysis show that a normally functioning gene is making normal protein or that a mutated gene is actively making an abnormal protein or no protein at all. Although there are numerous methods available for measuring mRNA or protein, gene expression microarrays (GEM) using complementary DNA (cDNA) microarray technology make it possible to measure the expression of thousands of genes simultaneously under a variety of conditions (Radha and Rajendiran 2012). Clinical research is now able to predict outcomes by showing gene expression patterns during different developmental and physiological states and in response to experimental interventions (Radha and Rajendiran 2012). The technical process is like aCGH except that RNA is extracted rather than

DNA, and reverse transcription is used to generate cDNA prior to labelling, hybridization, and analysis.

Gene expression analysis research in endocrinology has identified differences in patterns X chromosome gene expression that are associated with the clinical phenotype in Klinefelter syndrome and are responsible for a number of the metabolic abnormalities observed in these patients (Zitzmann et al. 2015).

7.14.3.3 Direct Sequencing

Direct DNA sequencing is the primary molecular method used to detect mutations. Next-generation sequencing (NGS), sometimes referred to as high-throughput sequencing or sequence analysis, determines the order of nucleotide bases in a sample of DNA. NGS technology can be used to sequence a specific gene, whole exomes (all coding regions in the genome), or whole genomes (both coding and non-coding regions of the genome).

NGS is most frequently used to identify a specific mutation at a specific position in a gene when a family member is already affected by a disorder, or when a disorder is suspected for which only a few select mutations are known to be responsible (Kirmani 2014). In these instances, targeted mutation analysis and mutation scanning involves NGS of the exons and introns within one specific gene and can detect mutations scattered throughout the gene (Kirmani 2014).

Whole-exome sequencing (WES) is used when mutations in multiple genes may be involved, whereas whole-genome sequencing (WGS) is used when the genes responsible for the disorder are unknown (Kirmani 2014). Genome sequencing is also used in pharmacogenomic testing to predict an individual's genotype-specific drug responses for commonly used drugs (Harper and Topol 2012).

There are a variety of sequencing technologies available, but the basic process involves preparing a library of DNA, amplifying the DNA segment by polymerase chain reaction (PCR), breaking the amplified DNA into fragments, then sequencing it on a sequencer machine (Buermans and den Dunnen 2014).

Examples of using gene sequencing to diagnose endocrine disorders include *PTPN11* and *SOS1* gene sequencing for Noonan syndrome and *FGFR3* mutational analysis for achondroplasia/hypochondroplasia (Dauber et al. 2013), as well as the identification of numerous gene mutations responsible for idiopathic short stature (Hattori et al. 2017). Clinical investigators have also used whole-exome sequencing to diagnose 3-M syndrome in a patient with a growth disorder previously of unknown origin, as well as finding a new mutation associated with hypergonadotrophic hypogonadism in the same patient (Dauber et al. 2013). For some disorders, a combination of molecular methodologies is required for accurate diagnosis. For example, both deletion/duplication microarray analysis and sequencing of the *VHL* gene is recommended for suspected Von Hippel-Lindau disease (Kirmani 2014).

7.14.3.4 Methylation Analysis

Molecular genetic testing that examines chemical or structural modifications to the DNA affecting gene regulation rather than the DNA sequence itself falls under the umbrella of epigenomic analyses. Much investigation into epigenomic processes such as messenger RNA (mRNA) silencing through microRNAs (miRNAs), chromatin remodelling, and histone modifications is currently confined to research environments (Tapia-Orozco et al. 2017). DNA methylation analysis, however, has moved into the clinical arena in investigations of imprinting disorders, endocrine disrupting chemicals, and cancer screening (Tapia-Orozco et al. 2017; Schenkel et al. 2016). DNA methylation assays require complex DNA pre-treatment steps involving restriction enzymes (REs), bisulfite conversion, and affinity enrichment followed by analysis via microarrays or sequencing (Tapia-Orozco et al. 2017). Of importance are the cytosine-rich areas such as CpG islands where methylation is more likely to occur (see Sect. 7.11 of this chapter).

Researchers have applied methylation analysis to demonstrate the existence of multi-locus methylation defects in imprinted genes in patients

with pseudohypoparathyroidism (Rochtus et al. 2016). Others have used a combination of methylation analysis and gene expression analysis to investigate the epigenetic determinants that contribute to the pathogenesis of autoimmune endocrine disorders such as Graves' disease (Cai et al. 2015). An endocrine example of a disorder where methylation analysis has been used as a first-line molecular diagnostic tool is Beckwith–Wiedemann syndrome (BWS) (Lin et al. 2016).

7.14.3.5 Molecular Testing Clinical Examples

Figures 7.5 and 7.6 contain actual de-identified patient results for molecular genetic testing from an endocrine clinic. Author introductory comments precede each figure and allow the reader to apply concepts covered in this chapter to clinical scenarios. Refer to the glossary found at the beginning of this chapter for terminology definitions.

Case 1 The patient result in Figure 7.5 is from a child presenting with severe idiopathic short stature for whom *SHOX* deficiency was part of the differential diagnosis.

The shaded boxes connected by horizontal lines on the report represent the exons in the coding region of the SHOX gene located in the pseudoautosomal region (distal tip) of Xp and Yp.

SHOX is the short stature homeobox gene, a haploinsufficient gene, meaning that normal maternal and paternal alleles must both be present for normal gene expression to occur. Unlike haplosufficient genes, the presence of only one copy of this gene is insufficient for normal gene expression, and deficiency can result in severe short stature and mesomelic bone abnormalities.

Note the limitations of the test listed under the comments section of the report.

A type of molecular test that might address these limitations is called a resequencing array. This is a chip-based sequencing method that looks for point mutations, and small deletions or insertions in the gene. Array-based sequencing may include the entire coding region, gene promoters, and known intronic mutations.

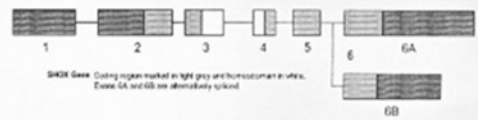
SHOXDNA^{Dx}

Molecular Genetic Assessment for SHOX Deficiency Using Mutation Detection and SNP-Based Detection of Whole Gene Deletions by DHPLC

Genomic DNA is extracted and PCR is used to amplify the SHOX coding exons and selected intragenic markers, SNPs, using custom-designed primers. Heteroduplexes are formed by heating and cooling the PCR-products. These products are then subjected to DHPLC. DHPLC chromatograms from heterozygous mutations, small deletions and small insertions are identified and then confirmed by DNA sequencing (Note that exon 6B is evaluated only by direct DNA sequencing).

Results:

Normal



Interpretation:

No SHOX deficiency was detected.

Comments:

SHOX-DNA-Dx detects small mutations and whole gene deletions. SHOX-DNA-Dx does not identify partial SHOX gene deletions or defects in the regulatory elements of the SHOX gene. SHOX-DNA-Dx is also not designed to detect mosaicism of the SHOX gene. If you have any questions concerning SHOX-DNA-Dx or your patient's results, please call the laboratory.

Fig. 7.5 *SHOX* molecular genetic assessment patient result

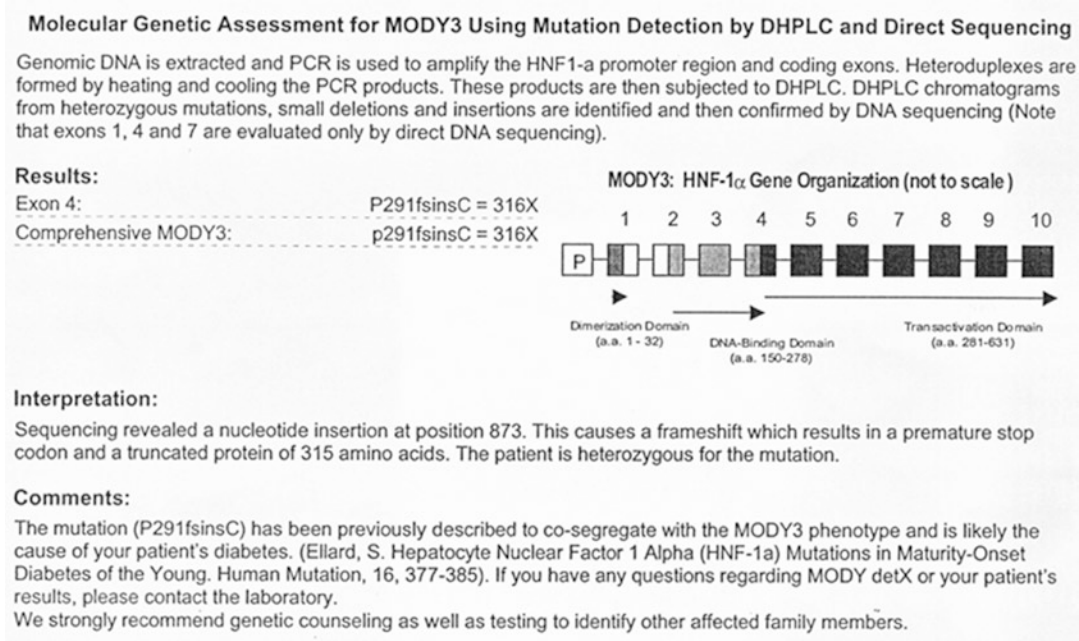


Fig. 7.6 MODY3 molecular genetic assessment patient result

Case 2 The patient result in Figure 7.6 is from a an 18 year old presenting with new onset hyperglycemia, polydipsia, polyuria, absence of ketoacidosis, negative antibody testing, and persistently detectable c-peptide.

MODY is maturity-onset diabetes of the young and is inherited through autosomal dominant transmission.

The shaded boxes connected by horizontal lines on the report represent the promotor region and exons of the HNF-1alpha gene on chromosome 12.

7.15 Family History

The family history provides critical data for evaluating an individual's genetic risk for Mendelian or multifactorial disorders. Knowledge of genetic risk promotes frank discussions regarding testing, preventative measures, monitoring, and treatment options if needed (Levy 2013; Owens et al. 2011). Ideally, the family history should include both personal and environmental information for at least 3–4 generations. Personal information refers to gender, current age if living, age and cause of death if deceased, ancestral origin, and all known diagnoses with age at onset. Environmental information refers to the presence or absence of exposure to tobacco, alcohol, recreational drugs, UV or other radiation, toxic chemicals (e.g., lead, asbestos, mercury), or pollutants in the water, air, or soil (e.g., insecticides, radon, smog). Clinicians should encourage patients to discuss their family history with their relatives to increase the accuracy completeness of the data (Levy 2013).

The process of taking a patient's family history is an economically inexpensive diagnostic tool that is often abbreviated in busy clinical settings. There are many templates available to enhance collecting family history data both manually and through an electronic health records (EHR) system. Clinicians with existing EHR systems that do not contain templates or tools for collecting and displaying genetic, personal, and environmental family history data should consult their EHR vendor regarding developing the software changes necessary to provide this resource. The EHR system should be able to organize the family history data into tables and represent it graphically in pedigrees and genograms to enhance patient education (Levy 2013).

An easily accessible publicly available online tool for obtaining a family history is the Surgeon

General's "My Family Health Portrait" (MFHP). Participants in a study evaluating the clinical utility of this tool took an average of 15 min to complete a history, with the longest entry time being 45 min (Owens et al. 2011). Health care providers can use the tool directly within the clinical setting or can instruct patients to complete the tool at home and bring the information with them to clinic. (See Sect. 7.20 at the end of this chapter for the website URL.) Individuals simply go the tool website, click on "create a family history," enter the information, then click "view diagram and chart" (Owens et al. 2011). Once completed, the information can be viewed in a table or as a pedigree.

A pedigree or genogram is like a photographic snapshot of an individual's family health history and genetic relationships expressed graphically through lines and symbols. Using a common set of pedigree lines, symbols, abbreviations, and definitions (a nomenclature) is important so that clinicians can communicate without confusion or inadvertent misinterpretation. The pedigree nomenclature of the National Society of Genetic Counselors is recognized as the international standard for family health histories (Bennett et al. 2008). See Figs. 7.7 and 7.8 for an explanation of pedigree symbols and lines, respectively. An additional set of symbols exist for assisted reproductive technology (Bennett et al. 2008).

Both written family histories and pedigrees can be HIPAA compliant by using initials or first names instead of full names, birth year or age instead of birth date, and year of or age at death instead of date of death (Bennett et al. 2008). Information from family health histories and pedigrees can be used for risk assessment, patient education, treatment planning, health promotion or surveillance, communication between health care professionals, and to enhance communication between patients and their relatives (Bennett et al. 2008). Presymptomatic and susceptibility genetic testing (if indicated by family health history) provide information about increased or decreased disease risk status for the patient, and potential genetic risks for the relatives of that individual (Bennett et al. 2008). Testing options to consider may include expanded genetic panels, full sequencing, or testing for a specific known mutation (Bennett et al. 2008). In addition, genetic testing information and personal/environmental data from family health histories can be entered in evidenced-based algorithms to help guide clinical decisions (Levy 2013).

7.16 Legal/Ethical Issues

Legal and ethical issues related to genetics such as the Genetic Information Non-discrimination Act of 2008 (GINA), patient genetic information stored in electronic medical records, and disclosure of genetic diagnoses are covered elsewhere in this textbook, but additional resources on this topic are listed at the end of this chapter under "Key Reading".

7.17 Nursing Implications

7.17.1 Attitude

Nursing professionals must demonstrate a nonjudgmental attitude toward requests for genetic testing. It is critical that nurses at all levels of practice do not inadvertently impose onto families what they might do in similar circumstances. Rather, nurses can impart empathy and compassion by understanding the patient's or parent's point of view.

7.17.2 Disclosure

Genetic testing results should always be given confidentially and in person, never over the telephone or in an impersonal electronic communication. Respect parental wishes regarding disclosure of a genetic diagnosis to a minor child, while encouraging parents to communicate this information to the child at developmentally appropriate levels as the child is growing up. Do not overwhelm families with more information than they can handle at a given time. Provide patient, simple explanations, and never rush, allowing families to digest one concept before moving on to the next. Use analogies to translate complex information and increase comprehension. Educate families to make sure all potential caregivers are present when a diagnosis is discussed so that information isn't passed along 2nd and 3rd hand.

Instructions:
— Key should contain all information relevant to interpretation of pedigree (e.g. define fill/ shading)
— For clinical (non-published) pedigrees include:
a) name of proband/consultand
b) family name/initials of relatives for identifications, as appropriate
c) name and title of person recording pedigree
d) historian (person relaying familyhistory information)
e) date of intake/update
f) reason for taking pedigrere (e.g., abnormal ultrasound, familiar cancer, develomental delay, etc.)
g) ancestry of both sides of family
— Recommended order of information placed below symbol (or to lower right)
a) age: can note year of brth (e.g., b. 1978) and/or death (e.g.,d.2007)
b) evaluation (see Figure 4)
c) pedigree number (e.g., 1-1,1-2,1-3)
— Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	b. 1925	30y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
				With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped).
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	d. 35	d. 4mo	d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/ testing.
7. Proband	P	P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP-7/1/2007 47,XY,+21	P 20 wk 46,XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	17 wks female cystic hygroma	< 10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	18 wks 47,XY,+18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	ECT		Write ECT below symbol.

Fig. 7.7 Pedigree symbols (Reproduced from https://link.springer.com/content/pdf/10.1007%2Fs10897-008-9169-9.pdf)

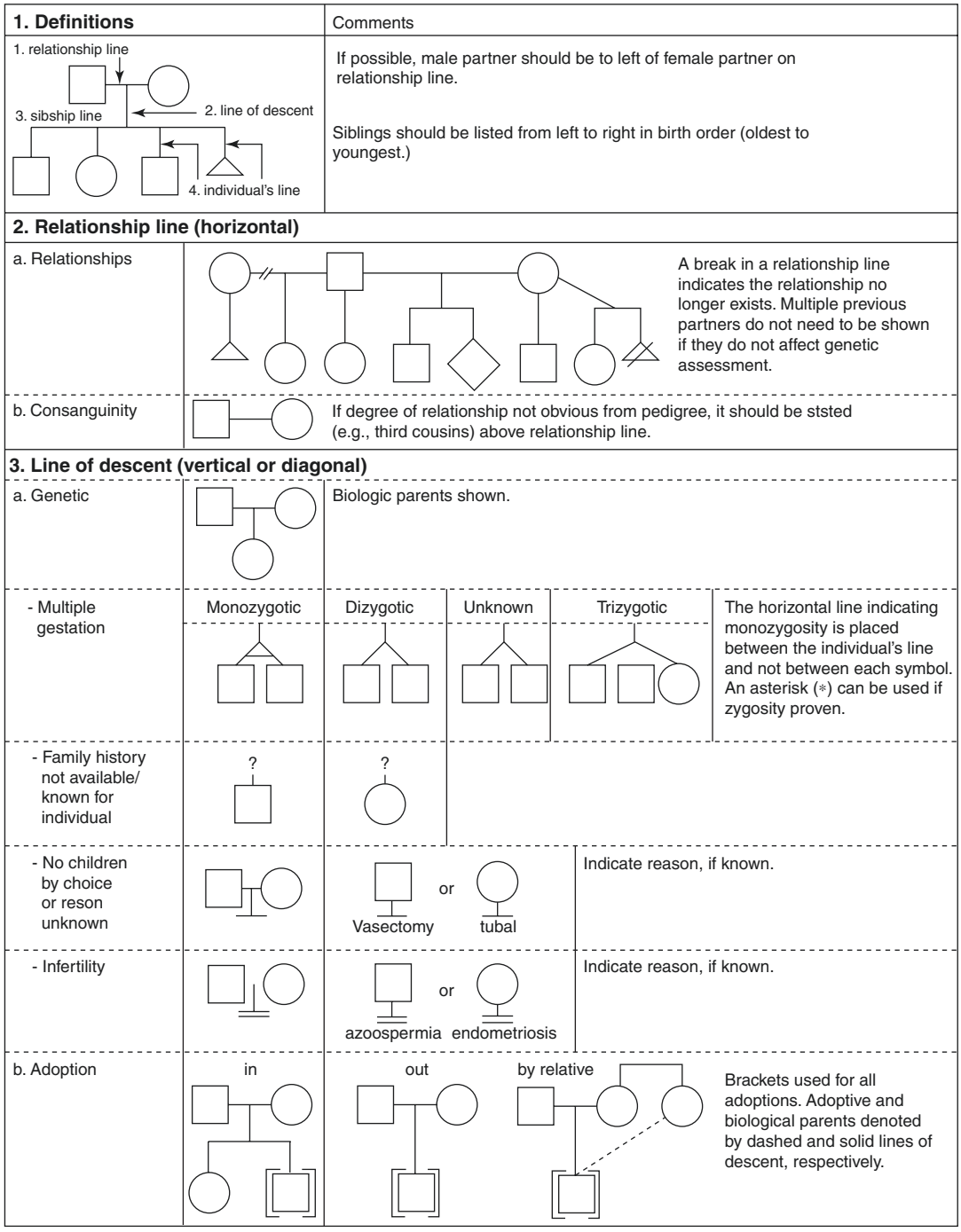


Fig. 7.8 Pedigree line definitions (Reproduced from https://link.springer.com/content/pdf/10.1007%2Fs10897-008-9169-9.pdf)

7.17.3 Care Coordination

Provide anticipatory guidance for comorbidities, and referrals to other specialists as needed, including genetic counselling. Make certain that follow-up appointments are scheduled consistently and kept. Provide information regarding support groups and organizations for families to access as needed. Gently remind families of these resources at successive appointments, realizing that they may not be ready or willing to reach out for help from strangers immediately. Encourage your institution to invest in multidisciplinary clinics that pair endocrinology with other sub-specialists and genetic counsellors. Plan for and initiate pediatric transition to adult care well before it becomes forced at age 18 years. Make sure that transitioning young adults are aware of clinical guidelines for care throughout the lifespan for their disorders, and that they can communicate these to their adult care providers.

7.18 The Future

Evolving issues in genomics affecting endocrinology are not limited to the rapid technological advances in molecular genetics diagnostic testing. Advances in gene therapy research are making the possibility of treating pituitary tumors (Rodriguez et al. 2009) and type I diabetes mellitus (Calne et al. 2010) without surgical or pharmacologic intervention closer to becoming reality. Other endocrine disorders for which gene therapy may become an option include GH deficiency (Racz et al. 2015), hypothalamic diabetes insipidus, and even multifactorial diseases such as type 2 diabetes mellitus and obesity (Yue et al. 2017). Gene therapy is essentially the transfer of genetic material to specific target cells of an individual to prevent or alter a specific disease state. Gene therapy involves the delivery of transgenes through recombinant viral and non-viral vectors. The Key Reading section at the end of the chapter lists additional sources of detailed information regarding viral and non-viral gene therapies.

7.19 Conclusions

While genetics and endocrinology may have begun as unique and separate specialties, they have become intricately interconnected, especially since the turn of the twenty-first century. Advances in molecular genetics laboratory technology have made possible the diagnosis of endocrine disorders resulting from defects in DNA sequence, expression, or regulation. Gene therapy to cure chronic endocrine disorders may become a reality within the next generation. Endocrine nurses at all levels of practice now need to meet competency guidelines in genetics to serve the evolving needs of their patients. Nurses without advanced practice training and qualifications must, at a minimum, be able to provide basic genetics education to patients and their families as related to endocrine diagnoses of genetic origin and their subsequent treatment. Advanced practice nurses must also have enough of an understanding of molecular genetics to order and explain newly available diagnostic testing. Endocrine nurses also need to be aware of ethical and legal issues that may now arise in their practice because of the interconnection of genetics and endocrinology. Such issues include the timing of diagnostic disclosure to minor patients or to individuals outside the immediate family, privacy regulations regarding genetic information contained in electronic health records, and the effects of genetic diagnoses on insurability and employment. Finally, endocrine nurses in the future may become more involved in multidisciplinary clinics where genetics counsellors and clinical geneticists work side by side with endocrine providers to deliver more comprehensive care to endocrine patients.

7.20 Additional Resources

Santos JM, Santos BS, Teixeira L. Interactive clinical pedigree visualization using an open source pedigree drawing engine. In: Kurosu M, editors. Human-computer interaction: eDesign and valuation. HCI 2015, vol. 9169, Lecture notes in computer science. Springer; 2015. https://doi.org/10.1007/978-3-319-20901-2_38. Access can be requested through https://www.

researchgate.net/publication/280446358_Interactive_Clinical_Pedigree_Visualization_Using_an_Open_Source_Pedigree_Drawing_Engine.

7.20.1 Online Software Applications and Tools

1. *List of Medical Analogies*
   www.altoonafp.org/analogies
2. *My Family Health Portrait (MFHP) Tool*
   https://familyhistory.hhs.gov/FHH/html/index.html
3. *American Medical Association Family History Tools*
   https://www.ama-assn.org/delivering-care/collecting-family-history
4. *Cyrillic pedigree drawing software for purchase for professional use*
   http://www.apbenson.com/cyrillic-downloads/
5. *Genealogy and pedigree drawing software for Macintosh*
   http://www.pedigree-draw.com/products.html
6. *CGEN—A clinical GENetics software application*
   http://onlinelibrary.wiley.com/doi/10.1002/humu.21452/full
7. *Create a pedigree*
   http://www.pedigree.varphi.com/cgi-bin/pedigree.cgi
8. *Genogram maker with genogram templates*
   https://www.smartdraw.com/genogram/genogram-maker.htm?id=107977
9. *GenPro Medical Genogram*
   https://www.genopro.com/professions/health-professionals/
10. *f-treeGC*
    A questionnaire-based family tree-creation software for genetic counseling and genome cohort studies
    https://bmcmedgenet.biomedcentral.com/articles/10.1186/s12881-017-0433-4
11. *Progeny Genetics*
    Family history, pedigree, risk assessment and EMR clinical tools
    http://www.progenygenetics.com/

7.20.2 Online Information on Genetic Concepts

The following online resources are free and publicly available.

1. *GeneEd Genetics, Education, Discovery*
   https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=17
   Provides basic education on a variety of topics including DNA, genes, chromosomes, heredity, inheritance patterns, epigenetics, inheritance and the environment, genetic conditions, and more. Provides additional links to animations, videos, articles, games, interactive tutorials, and more.
2. *Genetics Home Reference (GHR)*
   https://ghr.nlm.nih.gov/
   GHR is a guide to understanding genetic conditions, cataloguing more than 1200 health conditions, diseases, and syndrome.
3. *National Human Genome Research Institute (NHGRI)*
   https://www.genome.gov
   The website for the NHGRI, one of the institutes at the National Institutes of Health (NIH), provides current information about news, events, and developments in genomics as well as links to educational information, resources, and research on genetic disorders.
4. *The National Center for Biotechnology Information (NCBI)*
   https://www.ncbi.nlm.nih.gov/
   The NCBI website serves as a gateway to access biomedical and genomic information in scores of databases, including PubMed and all websites in this list with "ncbi" in their URL.
5. *Genes and Disease*
   https://www.ncbi.nlm.nih.gov/books/NBK22183/
   Genes and Disease is an online collection of articles that discuss genes and the diseases

that they cause. These genetic disorders are organized by the parts of the body that they affect. As some diseases affect various body systems, they appear in more than one chapter. With each genetic disorder, the underlying mutation(s) is discussed, along with clinical features and links to key websites.

6. *Genetic Testing Registry (GTR)*
   https://www.ncbi.nlm.nih.gov/gtr/
   The Genetic Testing Registry (GTR®) provides a central location for voluntary submission of genetic test information by commercial test providers. The scope of information provided includes each test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials.
7. *GeneReviews*
   https://www.ncbi.nlm.nih.gov/books/NBK1116/
   GeneReviews is an online book that serves as an international point-of-care resource for busy clinicians, providing clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling for patients and their families.
8. *MedGen*
   https://www.ncbi.nlm.nih.gov/medgen/
   MedGen is a database on human medical genetics that is searchable by a condition name, the causative gene, a clinical feature, or even an identifier from another database. MedGen also provides links to resources such as genetic tests registered in the NIH Genetic Testing Registry (GTR), information on related genes and disorders with similar clinical features, medical and research literature, practice guidelines, and consumer resources.
9. *NCBI Gene*
   https://www.ncbi.nlm.nih.gov/gene/
   Gene is a database that integrates gene-related information from a wide range of species. A record on a gene may include nomenclature, Reference Sequences (RefSeqs), maps, pathways, variations, phenotypes, and links to genome-, phenotype-, and locus-specific resources worldwide.
10. *Online Mendelian Inheritance in Man (OMIM)*
    www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
    OMIM is a comprehensive collection of concise but detailed information on human genes and genetic phenotypes that is updated daily.

7.20.3 Professional Organizations for Nurses Interested in Genetics

1. International Society of Nurses in Genetics (ISONG)
   http://www.isong.org/
2. National Society of Genetic Counselors
   https://www.nsgc.org/
3. Transnational Alliance of Genetic Counselors
   http://igce.med.sc.edu

References

Akbas H, Koksal O, Konca C, Balkan M, Budak T. Familial balanced reciprocal translocation [t(16;22)(p11;q13)mat] in a child with constitutional short stature. J Med Cases. 2012;3(2):149–52. https://doi.org/10.4021/jmc534w.

Anderson S. Chromosome microarray. Am J Matern Child Nurs. 2016;41(5):272–9. https://doi.org/10.1097/NMC.0000000000000260.

Antonacci F, Kidd JM, Marques-Bonet T, Ventura M, Siswara P, Jiang Z, et al. Characterization of six human disease-associated inversion polymorphisms. Hum Mol Genet. 2009;18(14):2555–66. https://doi.org/10.1093/hmg/ddp187.

Asa SL, Mete O. Endocrine pathology: past, present and future. Pathology. 2018;50(1):111–8. https://doi.org/10.1016/j.pathol.2017.09.003.

Baculescu N. The role of androgen receptor activity mediated by the CAG repeat polymorphism in the pathogenesis of PCOS. J Med Life. 2013;6(1):18–25.

Bashamboo A, Bignon-Topalovic J, Rouba H, McElreavey K, Brauner R. A nonsense mutation in the hedgehog receptor CDON associated with pituitary stalk interruption syndrome. J Clin Endocrinol Metab. 2016;101(1):12–5. https://doi.org/10.1210/jc.2015-2995.

Bellfield EJ, Chan J, Durrin S, Lindgren V, Shad Z, Boucher-Berry C. Anterior pituitary aplasia in an infant with ring chromosome 18p deletion. Case Rep Endocrinol. 2016;2016:2853178. https://doi.org/10.1155/2016/2853178.

Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17(5):424–33. https://doi.org/10.1007/s10897-008-9169-9.

Birla S, Aggarwal S, Sharma A, Tandon N. Rare association of acromegaly with left atrial myxoma in Carney's complex due to novel PRKAR1A mutation. Endocrinol Diabetes Metab Case Rep. 2014;2014:140023. https://doi.org/10.1530/EDM-14-0023.

Bochud M. Genetics for clinicians: from candidate genes to whole genome scans (technological advances). Best Pract Res Clin Endocrinol Metab. 2012;26(2):119–32. https://doi.org/10.1016/j.beem.2011.09.001.

Bøe Wolff A, Oftedal B, Johansson S, Bruland O, Løvas K, Meager A, et al. AIRE variations in Addison's disease and autoimmune polyendocrine syndromes (APS): partial gene deletions contribute to APS I. Genes Immun. 2008;9(2):130–6. https://doi.org/10.1038/sj.gene.6364457.

Buermans HP, den Dunnen JT. Next generation sequencing technology: advances and applications. Biochim Biophys Acta. 2014;1842(10):1932–41. https://doi.org/10.1016/j.bbadis.2014.06.015.

Cai TT, Muhali FS, Song RH, Qin Q, Wang X, Shi LF, et al. Genome-wide DNA methylation analysis in Graves' disease. Genomics. 2015;105(4):204–10. https://doi.org/10.1016/j.ygeno.2015.01.001.

Calne RY, Gan SU, Lee KO. Stem cell and gene therapies for diabetes mellitus. Nat Rev Endocrinol. 2010;6(3):173–7. https://doi.org/10.1038/nrendo.2009.276.

Cetin Z, Mendilcioglu I, Yakut S, Berker-Karauzum S, Karaman B, Luleci G. Turner syndrome with isochromosome Xq and familial reciprocal translocation t(4;16)(p15.2;p13.1). Balkan J Med Genet. 2011;14(1):57–60. https://doi.org/10.2478/v10034-011-0019-y.

Choi BH, Kim UH, Lee KS, Ko CW. Various endocrine disorders in children with t(13;14)(q10;q10) Robertsonian translocation. Ann Pediatr Endocrinol Metab. 2013;18(3):111–5. https://doi.org/10.6065/apem.2013.18.3.111.

Dauber A, Stoler J, Hechter E, Safer J, Hirschhorn JN. Whole exome sequencing reveals a novel mutation in CUL7 in a patient with an undiagnosed growth disorder. J Pediatr. 2013;162(1):202–204.e1. https://doi.org/10.1016/j.jpeds.2012.07.055.

Fisher DA. A short history of pediatric endocrinology in North America. Pediatr Res. 2004;55(4):716–26. https://doi.org/10.1203/01.PDR.0000113824.18487.9B.

Gagliardi L, Scott HS, Feng J, Torpy DJ. A case of aromatase deficiency due to a novel CYP19A1 mutation. BMC Endocr Disord. 2014;14:16. https://doi.org/10.1186/1472-6823-14-16.

Harper AR, Topol EJ. Pharmacogenomics in clinical practice and drug development. Nat Biotechnol. 2012;30(11):1117–24. https://doi.org/10.1038/nbt.2424.

Hattori A, Katoh-Fukui Y, Nakamura A, Matsubara K, Kamimaki T, Tanaka H, et al. Next generation sequencing-based mutation screening of 86 patients with idiopathic short stature. Endocr J. 2017;64(10):947–54. https://doi.org/10.1507/endocrj.EJ17-0150.

Henderson LB, Applegate CD, Wohler E, Sheridan MB, Hoover-Fong J, Batista DA. The impact of chromosomal microarray on clinical management: a retrospective analysis. Genet Med. 2014;16(9):657–64. https://doi.org/10.1038/gim.2014.18.

Kirmani S. Genetic testing in endocrinology. In: Bandeira F, Gharib H, Golbert A, Griz L, Faria M, editors. Endocrinology and diabetes. New York: Springer; 2014. p. 1–8.

Lania A, Mantovani G, Spada A. G protein mutations in endocrine diseases. Eur J Endocrinol. 2001;145(5):543–59. https://doi.org/10.1530/eje.0.1450543.

Levy HP. Genomic medicine: family history, genetic testing, and the EHR. Intern Med News. 2013;30. https://www.mdedge.com/internalmedicinenews/article/78322/pediatrics/family-history-genetic-testing-and-electronic-health. Accessed 22 Jan 2018.

Lin L, Philibert P, Ferraz-de-Souza B, Kelberman D, Homfray T, Albanese A, Molini V, Sebire NJ, Einaudi S, Conway GS, Hughes IA, Jameson JL, Sultan C, Dattani MT, Achermann JC. Heterozygous missense mutations in steroidogenic factor 1 (SF1/ Ad4BP, NR5A1) are associated with 46,XY disorders of sex development with normal adrenal function. J Clin Endocrinol Metab. 2007;92(3):991–9. https://doi.org/10.1210/jc.2006-1672.

Lin HY, Chuang CK, Tu RY, Fang YY, Su YN, Chen CP, et al. Epigenotype, genotype, and phenotype analysis of patients in Taiwan with Beckwith-Wiedemann syndrome. Mol Genet Metab. 2016;119(1-2):8–13. https://doi.org/10.1016/j.ymgme.2016.07.003.

Marty MS, Carney EW, Rowlands JC. Endocrine disruption: historical perspectives and its impact on the future of toxicology testing. Toxicol Sci. 2011;120(Suppl 1):S93–108. https://doi.org/10.1093/toxsci/kfq329.

Nakashima S, Kato F, Kosho T, Nagasaki K, Kikuchi T, Kagami M, et al. Silver-Russell syndrome without body asymmetry in three patients with duplications of maternally derived chromosome 11p15 involving CDKN1C. J Hum Genet. 2015;60(2):91–5. https://doi.org/10.1038/jhg.2014.100.

National Human Genome Research Institute. Talking glossary of genetic terms. 2014. https://www.genome.gov/glossary/. Accessed Jan 22, 2018.

National Human Genome Research Institute. A brief guide to genomics. 2015. https://www.genome.gov/18016863/a-brief-guide-to-genomics/. Accessed 22 Jan 2018.

National Institute of General Medical Sciences. The new genetics: how genes work. 2016. https://publications.nigms.nih.gov/thenewgenetics/chapter1.html. Accessed 22 Jan 2018.

Owens KM, Marvin ML, Gelehrter TD, Ruffin MT IV, Uhlmann WR. Clinical use of the surgeon gen-

eral's "My Family Health Portrait" (MFHP) tool: opinions of future health care providers. J Genet Couns. 2011;20(5):510–25. https://doi.org/10.1007/s10897-011-9381-x.

Racz GZ, Zheng C, Goldsmith CM, Baum BJ, Cawley NX. Toward gene therapy for growth hormone deficiency via salivary gland expression of growth hormone. Oral Dis. 2015;21(2):149–55. https://doi.org/10.1111/odi.12217.

Radha R, Rajendiran P. An overview on gene expression analysis. IOSR J Comput Eng. 2012;4(1):31–6. https://doi.org/10.9790/0661-0413136.

Rochtus A, Martin-Trujillo A, Izzi B, Elli F, Garin I, Linglart A, Mantovani G, Perez de Nanclares G, Thiele S, Decallonne B, Van Geet C, Monk D, Freson K. Genome-wide DNA methylation analysis of pseudohypoparathyroidism patients with GNAS imprinting defects. Clin Epigenetics. 2016;8(10). https://doi.org/10.1186/s13148-016-0175-8.

Rodriguez SS, Castro MG, Brown OA, Goya RG, Console GM. Gene therapy for the treatment of pituitary tumors. Expert Rev Endocrinol Metab. 2009;4(4):359–70. https://doi.org/10.1586/eem.09.16.

Schenkel LC, Rodenhiser DI, Ainsworth PJ, Pare G, Sadikovic B. DNA methylation analysis in constitutional disorders: clinical implications of the epigenome. Crit Rev Clin Lab Sci. 2016;53(3):147–65. https://doi.org/10.3109/10408363.2015.1113496.

Sdano MR, Vanzo RJ, Martin MM, Baldwin EE, South ST, Rope AF, Allen WP, Kearney H. Clinical utility of chromosomal microarray analysis of DNA from buccal cells: detection of mosaicism in three patients. J Genet Couns. 2014;23(6):922–7. https://doi.org/10.1007/s10897-014-9751-2.

Sireteanu A, Volosciuc M, Gramescu M, Gorduza E, Vulpoi C, Frunza I, et al. Dicentric chromosome 14;18 plus two additional CNVs in a girl with microform holoprosencephaly and Turner stigmata. Balkan J Med Genet. 2013;16(2):67–72. https://doi.org/10.2478/bjmg-2013-0034.

Stagi S, Lapi E, Pantaleo M, Traficante G, Giglio S, Seminara S, de Martino M. A SOX3 (Xq26.3-27.3) duplication in a boy with growth hormone deficiency, ocular dyspraxia, and intellectual disability: a long-term follow-up and literature review. Hormones (Athens). 2014;13(4):552–60. https://doi.org/10.14310/horm.2002.1523.

Tapia-Orozco N, Santiago-Toledo G, Barron V, Espinosa-Garcia AM, Garcia-Garcia JA, Garcia-Arrazola R. Environmental epigenomics: current approaches to assess epigenetic effects of endocrine disrupting compounds (EDC's) on human health. Environ Toxicol Pharmacol. 2017;51:94–9. https://doi.org/10.1016/j.etap.2017.02.004.

Tonelli F, Giudici F, Giusti F, Marini F, Cianferotti L, Nesi G, Brandi ML. A heterozygous frameshift mutation in exon 1 of CDKN1B gene in a patient affected by MEN4 syndrome. Eur J Endocrinol. 2014;171(2):K7–K17. https://doi.org/10.1530/EJE-14-0080.

U.S. National Library of Medicine, National Institutes of Health. DNA, genes, chromosomes-GeneEd-genetics, education, discovery. 2017. https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15. Accessed 22 Jan 2018.

Vassart G, Costagliola S. G protein-coupled receptors: mutations and endocrine diseases. Nat Rev Endocrinol. 2011;7(6):362–72. https://doi.org/10.1038/nrendo.2011.20.

Wieland I, Schanze D, Schanze I, Volleth M, Muschke P, Zenker M. A cryptic unbalanced translocation der(4) t(4;17)(p16.1;q25.3) identifies Wittwer syndrome as a variant of Wolf-Hirschhorn syndrome. Am J Med Genet Part A. 2014;164A(12):3213–4. https://doi.org/10.1002/ajmg.a.36765.

Yamaguchi R, Kato F, Hasegawa T, Katsumata N, Fukami M, Matsui T, Nagasaki K, Ogata T. A novel homozygous mutation of the nicotinamide nucleotide transhydrogenase gene in a Japanese patient with familial glucocorticoid deficiency. Endocr J. 2013;60(7):855–9. https://doi.org/10.1507/endocrj.EJ13-0024.

Yue J, Gou X, Li Y, Wicksteed B, Wu X. Engineered epidermal progenitor cells can correct diet-induced obesity and diabetes. Cell Stem Cell. 2017;21(2):256–263.e4. https://doi.org/10.1016/j.stem.2017.06.016.

Zitzmann M, Bongers R, Werler S, Bogdanova N, Wistuba J, Kliesch S, Gromoll J, Tüttelmann F. Gene expression patterns in relation to the clinical phenotype in Klinefelter syndrome. J Clin Endocrinol Metab. 2015;100(3):E518–23. https://doi.org/10.1210/jc.2014-2780.

Key Reading

1. Griffiths W, Carroll D. An introduction to genetic analysis. 11th ed. New York: W. H. Freeman; 2015.
2. Kasper CE, Schneidereith TA, Lashley FR. Lashley's essentials of clinical genetics in nursing practice. 2nd ed. New York: Springer; 2016.
3. Strachan T, Read AP. Human molecular genetics. 4th ed. New York: Garland Science; 2010.
4. Goodarzi MO. Genetics of common endocrine disease: the present and the future. J Clin Endocrinol Metab. 2016;101(3):787–94. https://doi.org/10.1210/jc.2015-3640. https://academic.oup.com/jcem/article/101/3/787/2804711.
5. American Nursing Association. Essentials of genetic and genomic nursing: competencies, curricula guidelines, and outcome indicators. 2nd ed; 2009. https://www.genome.gov/pages/careers/healthprofessionaleducation/geneticscompetency.pdf.
6. Galesic M, Garcia-Retamero R. Using analogies to communicate information about health risks. Appl Cognit Psychol. 2013;27:33–42. https://doi.org/10.1002/acp.2866. https://pdfs.semanticscholar.org/6ad5/41960ed03707c62418bd476b2e901a6b0c1b.pdf.

7. Lough ME, Seidel GD. Legal and clinical issues in genetics and genomics. Clin Nurse Spec. 2015;29(2):68–70. https://doi.org/10.1097/NUR.0000000000000101. https://www.researchgate.net/publication/272079840_Legal_and_Clinical_Issues_in_Genetics_and_Genomics.
8. de Vinck-Baroody O, Weitzman C, Vibbert M, Augustyn M. Disclosure of diagnosis: to tell or not to tell. J Dev Behav Pediatr. 2012;33(5):441–3. https://doi.org/10.1097/DBP.0b013e318258bae6. https://www.researchgate.net/publication/224949987_Disclosure_of_Diagnosis_To_Tell_or_Not_to_Tell.
9. Quigley P. Mapping the human genome: implications for practice. Nursing. 2015;45(9):26–34. https://doi.org/10.1097/01.NURSE.0000470413.71567.fd. https://www.nursingcenter.com/Handlers/articleContent.pdf?key=pdf_00152193-201509000-00008.
10. Zhang X, Ho S-M. Epigenetics meets endocrinology. J Mol Endocrinol. 2011;46(1):R11–32. https://doi.org/10.1677/JME-10-0053. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4071959/
11. Conley YP, Biesecker LG, Gonsalves S, Merkle CJ, Kirk M, Aouizerat BE. Current and emerging technology approaches in genomics. J Nurs Scholarsh. 2013;45(1):5–14. https://doi.org/10.1111/jnu.12001. http://europepmc.org/articles/PMC3773704.

Congenital Hyperinsulinism (CHI)

8

Claire Gilbert, Kate Morgan, Louise Doodson, and Khalid Hussain

Contents

8.1 Introduction 165
8.2 Clinical Presentation of CHI 166
8.3 Biochemical Basis of CHI 166
8.4 Diagnosis of CHI 167
8.5 An Example of a Hypoglycaemia Screen 168
8.6 Causes of CHI 168
8.7 Transient CHI 168
8.8 Persistent CHI 169
8.9 Management of a Patient with CHI 170
8.10 Medical Therapy 170
8.11 Case Study to Illustrate an Infant's Presentation, Diagnosis, and Treatment for CHI 171
8.12 Neurological Outcomes 174
8.13 Advances in Treatments for CHI 174
8.14 Conclusions 174
8.15 Questions to Consider 174
References 175

C. Gilbert (✉) · K. Morgan · L. Doodson
Great Ormond Street Hospital for Children NHS Trust, London, UK
e-mail: clare.gilbert@gosh.nhs.uk; Kate.morgan@gosh.nhs.uk; Louise.Doodson@gosh.nhs.uk

K. Hussain
Weill Cornell Medicine-Qatar, Ar-Rayyan, Qatar

Division of Endocrinology, Department of Paediatric Medicine, Sidra Medicine, OPC, Doha, Qatar
e-mail: khussain@sidra.org

Abstract

The aim of this chapter is to highlight a rare endocrine condition (Congenital Hyperinsulinism, CHI), which can cause low blood glucose levels leading to permanent brain injury. Many Paediatric Nurses are unfamiliar with this condition. CHI is caused by

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_8

unregulated insulin secretion from the pancreas and typically presents in the newborn period, but it can also present later in life. It is imperative for Paediatric Nurses to be knowledgeable on the subject of CHI as they are usually the first to identify the infant's low blood glucose levels, often accompanied by non-specific symptoms such as floppiness, jitteriness, fitting, lethargy, or poor feeding. It is always important to consider CHI if an infant or child presents with unexplained recurrent and persistent hypoglycaemia.

The chapter will focus on understanding how to interpret blood glucose levels, explain the biochemical basis of CHI, provide some background to the genetic causes of CHI, discuss the signs and symptoms of hypoglycaemia and finally, offer guidance for the diagnosis and management of patients with CHI. A case study will be used to illustrate the importance of early identification and prompt treatment.

Keywords
Congenital hyperinsulinism · Brain injury · Insulin · Glucose

Abbreviations

18F-DOPA	Fluorine-18-L-dihydroxyphenylalanine
A&E	Accident and Emergency
ABCC8	ATP Binding Cassette Subfamily C Member 8
ADP	Adenosine diphosphate
ATP	Mitochondrial adenosine triphosphate
b-HOB	Beta-hydroxybutyrate
CHI	Congenital hyperinsulinism
CNS	Clinical Nurse Specialist
CRP	C-reactive protein
EEG	Electroencephalogram
GA	General anaesthetic
GCK	Glu-cokinase
GH	Growth hormone
GLUD1	Glutamate dehydrogenase
G.P	General Practitioner
HADH	Hydroxyacyl-coenzyme A dehydrogenase
HNF1A	Hepatocyte nuclear factor 1A
HNF4A	Hepatocyte nuclear factor 4A
KATP	Mitochondrial adenosine triphosphate-sensitive potassium
KCNJ11	Potassium Voltage-Gated Channel Subfamily J Member 11
Kgs	Kilograms
Kir6.2	Inward rectifying potassium channel
mg/kg/day	Milligram per kilogram per day
mg/kg/min	Milligram per kilogram per minute
mL/kg	Millilitre per kilogram
mLs/kg/day	Millilitres per kilogram per day
mm	Millimetre
mmols/L	Millimoles per Litre
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
mU/L	Milliunits per Litre
NEFA	Non-esterified fatty acids
NHS	National Health Service
nmol/L	Nanomole per litre
PES	Pediatric Endocrine Society
PET	Positron emission tomography
pmol/L	Picomoles per litre
SLC16A1	Solute Carrier Family 16 Member 1
SLE	Systemic lupus erythematosus
SUR 1	Sulfonylurea receptor
µg/L	Micrograms per litre
µmol/L	Micromole per litre

Key Terms

- **Hypoglycaemia screen:** Diagnostic investigation to examine endocrine and metabolic causes of hypoglycaemia.
- **Transient hyperinsulinism:** Usually occurs for a short period post birth. Can occur with or with out associated risk factors.
- **Persistent congenital hyperinsulinism:** Ongoing hypoglycaemia often needing ongo-

ing medical or surgical treatment and can be subdivided into focal or diffuse disease.

- **Focal disease:** A specific area of the pancreas is affected. Focal lesions are usually small, measuring 2–10 mm across.
- **Diffuse disease:** Affects the entire pancreas. It can be inherited in a recessive or dominant manner or can occur sporadically.

Key Points

- If the infant has persistent hypoglycaemia, then the diagnosis of congenital hyperinsulinism (CHI) should be considered.
- Nurses at the bedside should have a low threshold for checking blood glucose level in any infants who are symptomatic of hypoglycaemia.
- Early referral to a specialist CHI centre is important to establish best medical treatment and outcomes.
- A full multidisciplinary team should be in place in order to fully support and guide the family in the treatment needed.

8.1 Introduction

Congenital hyperinsulinism (CHI) is a serious disorder, which, whilst rare, can have lifelong consequences, with severe psychomotor retardation and epilepsy being more common in patients who present in the neonatal period (Menni et al. 2001). The incidence of sporadic forms of CHI is about 1 in 40,000–50,000 with familial forms more common in communities with high consanguinity (Glaser et al. 2000).

CHI is characterized by the presence of insulin in the blood at an inappropriately high level for the concentration of blood glucose (Aynsley-Green et al. 2000). Insulin is a hormone produced by the beta-cells of the pancreas; its purpose is to lower blood glucose levels, facilitating the transport of glucose into the body's cells (Fain 2009). In CHI, the inappropriately high insulin switches off all alternative fuels for the brain to use (free fatty acids and ketone bodies), hence the risk of brain injury and even death.

There has been much debate over the definition of hypoglycaemia, especially in the neonatal population. This uncertainty has caused confusion in the past as to when to diagnose CHI and how to treat hypoglycaemia. The Pediatric Endocrine Society (PES) considered this gap in evidence-based knowledge and in 2015 convened an expert panel of Paediatric Endocrinologists and Neonatologists. Articles on transitional neonatal hypoglycaemia made recommendations for the diagnosis and management of persistent hypoglycaemia. Stanley et al. (2015) suggests that during the first 24–48 h of life, the normal neonates' blood glucose level is typically lower due to the transitional phase from intrauterine to extra uterine life. This initial period of hypoglycaemia is called transitional neonatal hypoglycaemia and should be managed according to the clinical symptoms and findings at the time. The PES recommends that the focus for the first 24–48 h of life should be on stabilization of glucose levels; however, after this initial transitional period, the physiological and biochemical mechanisms regulate the blood glucose level above 3.5 mmols/L. (Guemes et al. 2016; Thornton et al. 2015) highlights the importance of distinguishing between the normal neonates who may have transitional hypoglycaemia and the infants who have identifiable risk factors for CHI, including those normal neonates whose hypoglycaemia persists beyond 3 days. These neonates need prompt diagnosis and effective treatment to avoid the known serious consequences of hypoglycaemia including seizures and brain injury.

Nurses and midwives by the bedside have the potential to identify these infants with hypoglycaemia and to prevent possible brain injury. If there is any concern that an infant is displaying symptoms such as poor feeding, lethargy, and jitteriness, then a simple blood glucose measurement is essential to identify if the infant is

Box 8.1 Normal blood glucose values

Acceptable blood glucose range in a tertiary specialist centre (in the UK)
3.5 mmol/L—10.0 mmol/L or 63 mg/dL—180 mg/dL
(To convert mmol/L to mg/dL multiple by 18)

hypoglycaemic. Normal blood glucose values as in Box 8.1.

8.2 Clinical Presentation of CHI

Patients presenting with CHI can have persistent or recurrent hypoglycaemia despite frequent/continuous feeds or intravenous glucose (Kapoor et al. 2009a). Many neonates with CHI typically present at birth though older infants and children can show signs of hypoglycaemia when fasting. As already stated, hypoglycaemic symptoms are often non-specific, but infants are typically lethargic and hypotonic with seizures (Guemes et al. 2016). Parents often describe their infants as "not feeding well, sleepy and jittery". For the nurse by the bedside, a simple blood glucose reading at this time is a powerful tool. Unfortunately, this has been known to be overlooked. Clinical examination may also detect macrosomia, cardiomyopathy, and hepatomegaly, but the absence of these does not exclude CHI.

On taking a clinical history, there are key questions to ask when faced with an infant with CHI, which include the following:

- A thorough neonatal and birth history (looking for risk factors such as prematurity, small size for gestational age, and perinatal stress).
- Length of time for which the infant can fast (is this appropriate for age and weight?).
- Family history of diabetes mellitus (gestational or in any family member).
- Relationship between hypoglycaemic episodes to the timings of feeds or certain foods (e.g. protein or large intakes of glucose).
- In older patients, a potential relationship between hypoglycaemia and exercise. It is important to ask about this.
- Establishing if the infant/child has had any abdominal surgery, e.g. Nissens fundoplication. Again, this may be significant to the diagnosis and the treatment (Bufler et al. 2001).
- Establishing, where appropriate, if hypoglycaemia is only triggered when the infant/child is unwell with an intercurrent illness, as this could be caused by other mechanisms other than CHI**.**

8.3 Biochemical Basis of CHI

The body maintains blood glucose concentrations within a narrow range, typically 3.5–5.5 mmol/L (Kaufman 2000). In normal physiology, the pancreatic beta-cells are sensitive to the plasma glucose concentration and secrete appropriate amounts of insulin (Hussain 2005). When describing insulin secretion from the pancreatic beta-cell, it is the ATP-sensitive potassium channels (KATP channels) that are thought to play a pivotal role in glucose-stimulated insulin secretion. Figure 8.1 provides an outline of the function of the beta-cell KATP channel.

This channel consists of two proteins, SUR1 and KIR6.2 (encoded by genes *ABCC8* and *KCNJ11*), which are responsible for maintaining the electrical potential of the beta-cell membrane (Inagaki et al. 1995). The KATP channel in the beta-cell is thought to be an "on–off" switch for triggering insulin secretion (Dunne and Petersen 1991). The release of insulin is a result of glucose being metabolized in the beta-cell, and this causes an increase in the intracellular ratio of nucleotides such as ATP/ADP which closes the KATP channel. When the KATP channel is closed, the cell membrane depolarizes, which causes calcium influx via voltage-gated calcium channels, and this is thought to be the stimulus for the release of insulin (insulin exocytosis) into the bloodstream.

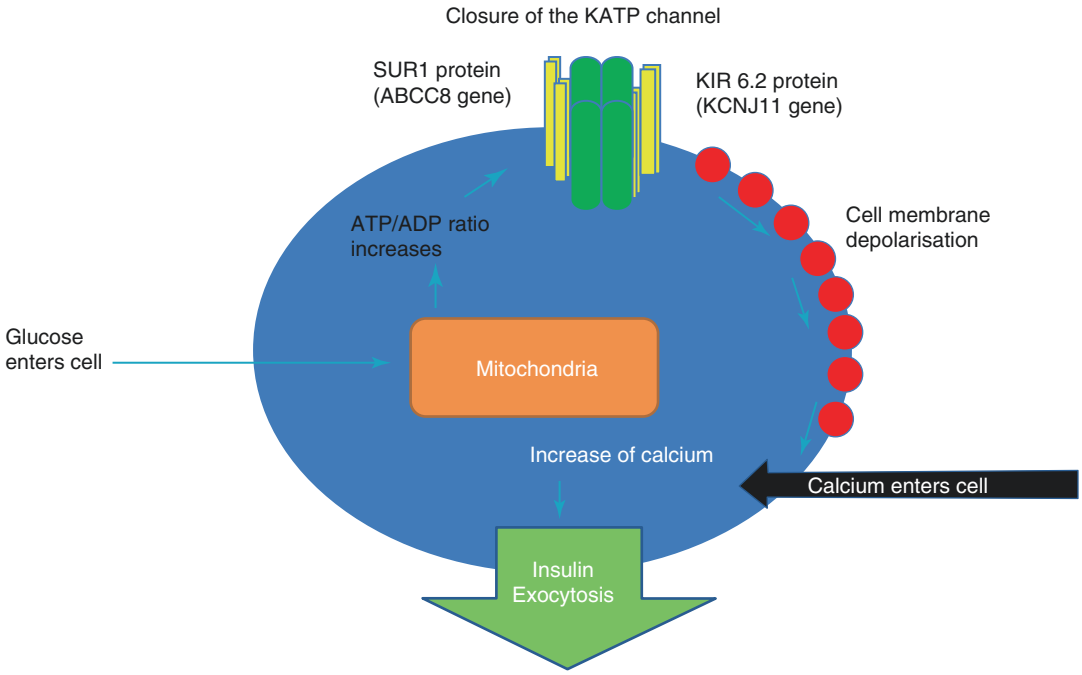


Fig. 8.1 Illustrates the mechanism of insulin secretion when glucose enters the pancreatic beta cell

In CHI, the beta-cells constantly release inappropriate amounts of insulin which is not regulated by the blood glucose level (Aynsley-Green et al. 2000). One of the major causes of this continuous inappropriate insulin production is the "on–off" KATP channel being faulty and permanently in the closed position, resulting in insulin exocytosis. This inappropriate insulin secretion has several effects: it causes glucose to be taken up by insulin-sensitive tissues (such as skeletal muscle, adipose tissue, and the liver); it reduces glucose production in the liver (via glycolysis and gluconeogenesis); and it suppresses fatty acid release and ketone body synthesis (inhibition of lipolysis and ketogenesis) (Kapoor et al. 2009b). This explains the biochemical basis of CHI being hyperinsulinaemic hypoglycaemia, with inappropriately low fatty acids and ketone body formation, hence the increased risk of brain injury (Kapoor et al. 2009b). Simply, this means that the brain is deprived of glucose plus fatty acids and ketone bodies and thus there is a risk of brain injury with this condition.

8.4 Diagnosis of CHI

Persistent hypoglycaemia and an intravenous glucose infusion rate >8 mg/kg/min (normal is 4–6 mg/kg/min) are virtually diagnostic of CHI (Kapoor et al. 2009a). However to confirm the diagnosis, critical blood samples are needed during a controlled hypoglycaemia screen (See Table 8.1) (Steinkrauss et al. 2005). A central venous access device is often the only way to safely administer high concentrations of glucose and to obtain these crucial blood samples. During this hypoglycaemia screen, there are some key factors the nurse must consider.

During the hypoglycaemia screen, the counter-regulatory hormonal response to hypoglycaemia is examined. Glucagon, growth hormone, and cortisol are all endocrine hormones that act against insulin. These hormones all act at various points of glucose metabolism to increase plasma glucose concentration; however, insulin is a glucose lowering hormone. In conclusion, if the hypoglycaemia screen shows that all other causes of hypoglycaemia are ruled out and that the

Table 8.1 Hypoglycaemia Screen

Local practice at a UK tertiary specialist centre when performing a hypoglycaemia screen
1. If the infant has had a general anaesthetic (GA) for a central venous line insertion, then it is important to wait 24 h after the GA to ensure the stress hormones are not raised, thus altering the hypoglycaemia screen results. (This is a practice based on experience in a NHS tertiary hospital.)
2. When weaning the intravenous glucose infusion rate, it is essential to do this slowly to ensure accuracy of the results.
3. All diagnostic bloods (see an example hypoglycaemia screen results) and urine should be taken when the patient is hypoglycaemic <3.0 mmols/L.
4. The laboratory glucose must be a capillary sample. At no time should a true glucose sample be taken from the intravenous line, through which glucose has been administered, as contamination can occur. From clinical experience, capillary samples are always advocated for laboratory glucose samples.
5. Based on clinical practice at an NHS tertiary hospital, the hypoglycaemia screen blood samples are taken when the blood glucose level is <3.0 mmols/L, ensuring the patient is hypoglycaemic for the shortest amount of time possible. Often this means that two nurses are required (one taking the blood samples from the central venous line and the other obtaining the capillary laboratory glucose).
6. Once all the samples are obtained, the hypoglycaemia is corrected by administering. 1 mL/kg 10% glucose bolus and intravenous fluids are recommenced. The blood glucose level is immediately rechecked and checked again after 10 min to ensure the patient is no longer hypoglycaemic.

insulin level is inappropriately raised for the blood glucose level, with corresponding low ketone bodies and fatty acids, then CHI is diagnosed (Aynsley-Green et al. 2000).

8.5 An Example of a Hypoglycaemia Screen

***Plasma glucose 2.0 mmol/L (normal range = 3.5–5.5 mmols/L).**

***Insulin 7.5 mU/L (Abnormally raised during hypoglycaemia).**

Serum cortisol 450 nmol/L.

Serum glucagon 12 (normal = <50 pmol/L).

Serum GH 1.6 μg/L (normal = 0.9–14.1 μg/L).

Serum ammonia 36 mmol/L (normal = <40 μmol/L).

Plasma lactate 1.3 mmol/L (normal = 0.7–2.1 mmol/L).

***Serum NEFA 0.07 mmol/L (Fatty acids—suppressed).**

***Serum b-HOB <0.05 mmol/L (Ketone bodies—suppressed).**

Acyl-carnitine profile reported as normal.

Urine organic acids: no abnormality.

***Glucose requirement of 20 mg/kg/min. (Normal = 4–6 mg/kg/min to maintain blood glucose levels above 3.5 mmols/L).**

***Indicates results are abnormal.**

8.6 Causes of CHI

KAPT channel defects (encoded by genes *ABCC8* and *KCNJ11)* account for the majority of causes of CHI though abnormalities in other genes account for the dysregulation of insulin secretion of approximately 10% of patients with CHI (Nessa et al. 2015). CHI is known to be caused by mutations in certain identified genes (See Table 8.2); however, there is ongoing research to explore other genetic causes.

8.7 Transient CHI

CHI can be subdivided and is distinguished by the length of treatment required and the infant's response to medical management. If CHI is evident for only a short duration and is simply treated with a small dose of diazoxide, then transient CHI is the diagnosis and is usually associated with intrauterine growth retardation, the infants of diabetic mothers, or infants with perinatal asphyxia (Mehta and Hussain 2003). Transient hyperinsulinism can, however, occur in infants with no predisposing factors. Also, some syndromes are also associated with CHI such as Beckwith-Wiedemann syndrome (Munns and Batch 2001).

Table 8.2 Genetics of CHI

Gene	Inheritance
ABCC8/KCNJ11 (Nestorowicz et al. 1996)	*Autosomal recessive* – Diffuse disease, mostly diazoxide unresponsive and often diagnosed within a few days of life *Autosomal dominant* – Often diazoxide unresponsive diffuse disease – Later presentation can be diazoxide responsive plus have family history of type 2 diabetes
GLUD1 (Stanley et al. 1998)	*Autosomal dominant* – Protein (leucine)-sensitive hypoglycaemia which is diazoxide responsive – Asymptomatic hyperammonemia
HADH (Clayton et al. 2001)	*Autosomal recessive* – Diazoxide responsive – In some patients can have abnormal levels of acylcarnitine metabolites present in plasma and urine
GCK (Davis et al. 1999)	*Autosomal dominant* – Can present at any age and variable response to diazoxide
SLC16A1 (Otonkoski et al. 2003)	*Autosomal dominant* – Exercise-induced hyperinsulinaemic hypoglycaemia
HNF4A (Pearson et al. 2007)	*Autosomal dominant* – Patients may go on to develop MODY 1
HNF1A (Stanescu et al. 2012)	*Autosomal dominant* – Diazoxide responsive – May go on to develop MODY 3

8.8 Persistent CHI

Persistent CHI is characterized by ongoing hypoglycaemia, often needing complex medical or surgical treatment**.** Histological examination of pancreatic tissue from patients who have undergone a pancreatectomy shows that there are two major histological forms of CHI, diffuse, and focal (Rahier et al. 2002). Focal lesions are characterized by beta-cell hyperplasia in a small lesion surrounded by normal pancreatic tissue (See Fig. 8.2).

These small lesions often measure only 2–10 mm and are invisible to the naked eye, though they produce excessive insulin, causing severe hypoglycaemia. Approximately 40–50% of infants with persistent CHI will have the focal form; however, this focal CHI is considered to be sporadic with very low chances of it occurring again in the same family (Ismail et al. 2011). Genetic blood results from the infant and both parents are used to lead the clinician in identifying those patients who need an 18F-DOPA-PET (positron emission tomography) scan to determine if the patient has a focal lesion, and if so, its position in the pancreas (See Fig. 8.3).

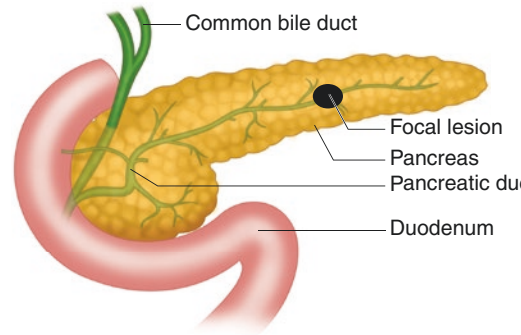


Fig. 8.2 Focal Disease

Diffuse CHI (See Fig. 8.4) affects the whole of the pancreas and is characterized by beta-cell hypertrophy and hyperplasia of the whole pancreas. Diffuse disease can be familial or sporadic and can result from recessively inherited or dominantly acting mutations (de Lonlay et al. 1997).

If located and completely surgically removed, the focal CHI can be completely cured (Barthlen et al. 2011). However with diffuse CHI, the aim

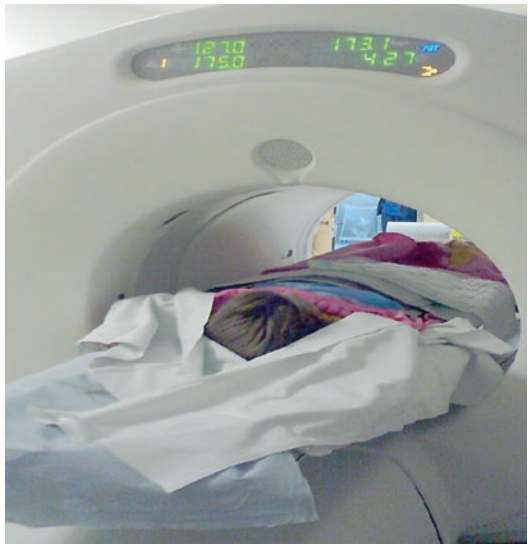


Fig. 8.3 PET scan to localize possible focal lesion

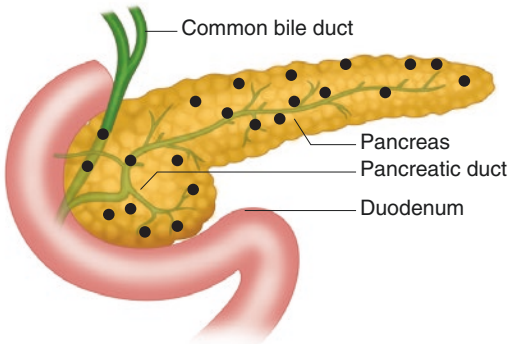


Fig. 8.4 Diffuse disease

of treatment is to medically manage the condition, avoiding surgery if possible, as this could cause the patient to develop diabetes and pancreatic enzyme deficiency in the future. If the patient is unresponsive to all medical therapy, then surgical removal of almost the entire pancreas is occasionally the only option.

8.9 Management of a Patient with CHI

In the acute management phase, high concentrations of intravenous glucose (such as 20% and 30%) are often needed to stabilize the blood glucose levels above 3.5 mmols/L. An intravenous or subcutaneous glucagon infusion is also administered as it releases glycogen stores from the liver (gluconeogenesis and glycogenolysis) (Nessa et al. 2015). A subcutaneous infusion of octreotide (a somatostatin analogue) also inhibits insulin secretion by decreasing insulin gene promoter activity and reducing insulin biosynthesis from pancreatic beta-cells. The aim of this acute treatment is to maintain a safe blood glucose level whilst allowing the infant to establish an oral feeding regimen.

8.10 Medical Therapy

Once the diagnosis of CHI has been established, medical management is trialled. The first-line medication is diazoxide, which needs an intact KATP channel in order for the channels to open and insulin secretion can be inhibited (Aynsley-Green et al. 2000). Diazoxide can cause fluid retention (especially in newborns) and so it must be used with caution, especially in patients who are receiving large volumes of intravenous fluids or oral feeds. There are also a small number of reports that diazoxide can potentially cause pulmonary hypertension and possible cardiopulmonary toxicity (Nebesio et al. 2007). It is recommended that if pulmonary hypertension is identified, then diazoxide should be stopped.

Other medical treatments include subcutaneous octreotide injections four times a day, for patients who show little or no response to oral diazoxide. Long-acting somatostatin analogues such as Lanreotide administered every 28 days are now being used, (see Table 8.3) reducing the intensity of injection therapy of octreotide from four daily subcutaneous injections to one deep subcutaneous injection four weekly.

Lastly, Sirolimus, an immunosuppressant (mTOR inhibitor), has been successfully used in a small number of patients with diffuse CHI who were unresponsive to all previous medical treatments. It is suggested that sirolimus action may affect the number of insulin receptors although the mechanism in treatment of CHI has not been fully delineated (Senniappan et al. 2014). It has been recommended

Table 8.3 Lanreotide

Lanreotide is available in a pre-filled syringe containing 60 mg Lanreotide under the brand name Somatuline® Autogel. It is a white to pale yellow semi-solid gel—a similar texture to petroleum jelly. The starting dose of Lanreotide is often 30 mg but is adjusted according to the child's response to the medicine. The injection is given every 28 days—the aim is that the daily doses of octreotide or diazoxide can be gradually cut down and then stopped.
Before starting Lanreotide injections, a child will need a series of blood tests plus an ultrasound of their liver and gall bladder. During treatment, they will then need to have blood tests along with an ultrasound scan of their gall bladder every 6 months.
Lanreotide is injected into the deep layer of subcutaneous fat under the skin, usually in the upper and outer part of the buttock as there is usually a substantial amount of subcutaneous fat in this area. This also reduces the risk of hitting the sciatic nerve with the injection. One important way to reduce the pain and irritation of injections is to rotate the administration site. Changing injection area also reduces the risk of lipohypertrophy (fatty lump) developing. Whilst this is not dangerous, it will affect how the medicine is absorbed.
It is important that a child is prepared for the injection and distraction therapy can be used whilst the injection is being administered.
Parents and/or Community Children Nurses are trained by the Clinical Nurse Specialists to administer the injection at home, once treatment has been established.

that sirolimus should only be used with caution in CHI specialized centres as adverse events have been reported (Szymanowski et al. 2016). If, after all medical treatment has been trialled, the patient remains unresponsive to medical and dietary interventions, then surgery may be deemed necessary.

8.11 Case Study to Illustrate an Infant's Presentation, Diagnosis, and Treatment for CHI

CT was born at 36 + 4 weeks gestation via a normal vaginal delivery. His birth weight was 2.73 kgs (50th centile). His mother had been treated for the first 12 weeks of pregnancy with oral steroids due to systemic lupus erythematosus (SLE). All her pregnancy scans had been reported as normal and the labour was induced due to her history of SLE. CT's parents were non-consanguineous and were of Filipino origin; he was their first child. At birth, CT was reported to be well and had normal neonatal baby checks. He was discharged after 24 h of birth, but presented in Accident and Emergency (A&E) on day 3 of life with a history of not waking and poor feeding. His mother had been trying to breast feed him but this was not well established and CT received formula top ups from day 2 of life.

On presentation, CT had reportedly had jerky movements over the previous 12–24 h as described by his parents. Seizure activity was witnessed in A&E, which included lip smacking and jerking of all limbs with evident desaturations. A blood glucose level at the time of presentation was 0.4 mmols/L and it was estimated that CT had lost 20% of his body weight since birth. His routine bloods and a blood gas sample were taken and reported as unremarkable. An initial 2 mL/kg bolus of 10% glucose was administered intravenously to correct his hypoglycaemia, which led to a clinical improvement. However, six further seizures were observed and two loading doses of phenobarbitone, one loading dose of phenytoin, and two doses of clonazepam were required to control his seizures. CT was also initially treated for sepsis but his antibiotics were ceased when his CRP was reported as normal as well as microbiologist advice. He was commenced on intravenous fluids containing glucose, though it was noted that whenever his intravenous fluids were interrupted, he would then become hypoglycaemic.

At this time, a referral was made to a tertiary specialist centre and treatment was advised. The initial hypoglycaemia screen showed evidence of CHI as the true glucose was 0.4 mmols/L with corresponding inappropriately raised insulin reported as 86 pmol/L. The protective fuels of fatty acids and ketones were both very low at the time of hypoglycaemia; hence, the diagnosis of CHI was made. All other metabolites were reported as normal. The local hospital reported that CT had abnormal tone but that he had a good suck and was alert on handling. An EEG was reported as normal though an MRI scan showed evidence of cortical necrosis and was sadly grossly abnormal.

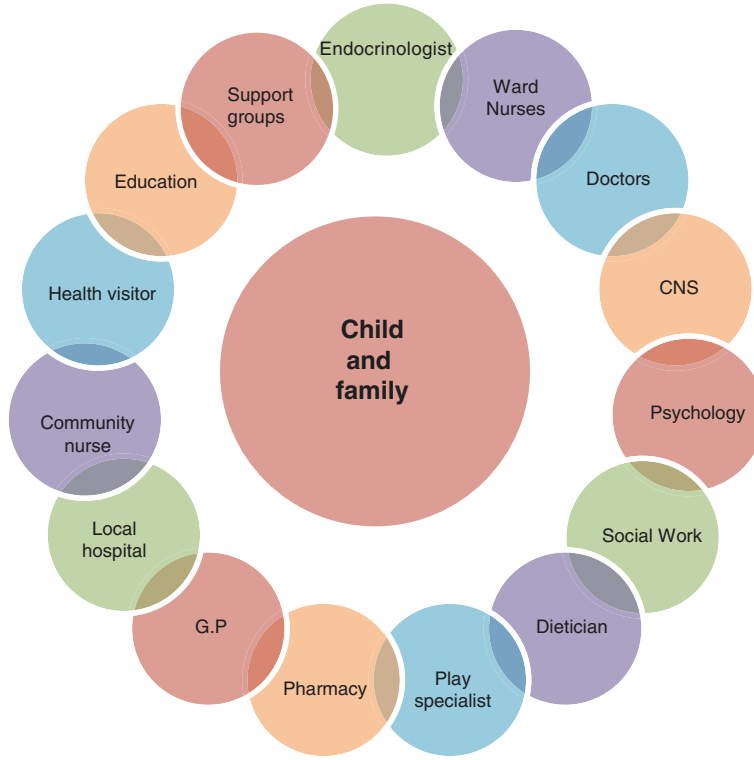


Fig. 8.5 The multidisciplinary team

CT's treatment was to fluid-restrict him to 120 mL/kg/day using a combination of high concentration glucose intravenously via central venous access device and small oral feeds of Aptamil®. On this regime, his blood glucose levels were maintained between 3.6 and 4.8 mmols/L, and his glucose requirement was calculated to be slightly raised at 10 mg/kg/min. On reducing his fluid requirement, this allowed for the safe introduction of diazoxide 5 mg/kg/day with chlorothiazide 7.5 mg/kg/day. Over the next 10 days, CT's intravenous fluids were safely titrated with his oral feeds so that he was eventually on four hourly feeds with no hypoglycaemia, as he was considered to be fully responsive to diazoxide to control his CHI. He was discharged home once his parents were competent in measuring his blood glucose levels pre-feed and in administration of his medications.

After 8 weeks, he was reviewed in the tertiary specialist centre where his dose of diazoxide was calculated to be 2.3 mg/kg/day due to his good weight gain, and there were no hypoglycaemic episodes reported by his parents. It was therefore decided to admit CT for two nights to reassess his CHI. This was done by safely stopping his medications 3 days prior to admission, then completing a 24 h glucose profile and a 6 h fast off diazoxide and chlorothiazide. The results showed that CT no longer had any hypoglycaemic episodes on his normal feeding regimen and when fasted for 6 h, his blood glucose level no longer dropped and his insulin level remained appropriately low. This means that his CHI had been transient in nature and had successfully resolved after only a short time of treatment with diazoxide. Despite the resolution of the CHI, CT's neurological developmental needed long-term follow-up. A multidisciplinary team approach is essential when caring for children with CHI (See Fig. 8.5).

This case study highlights the importance of early identification and prompt management of CHI, as untreated severe hypoglycaemia can result in severe brain injury and subsequent neurodevelopment handicap. Box 8.2 demonstrates the management pathway from diagnosis to treatment of CHI.

Box 8.2 Management pathway

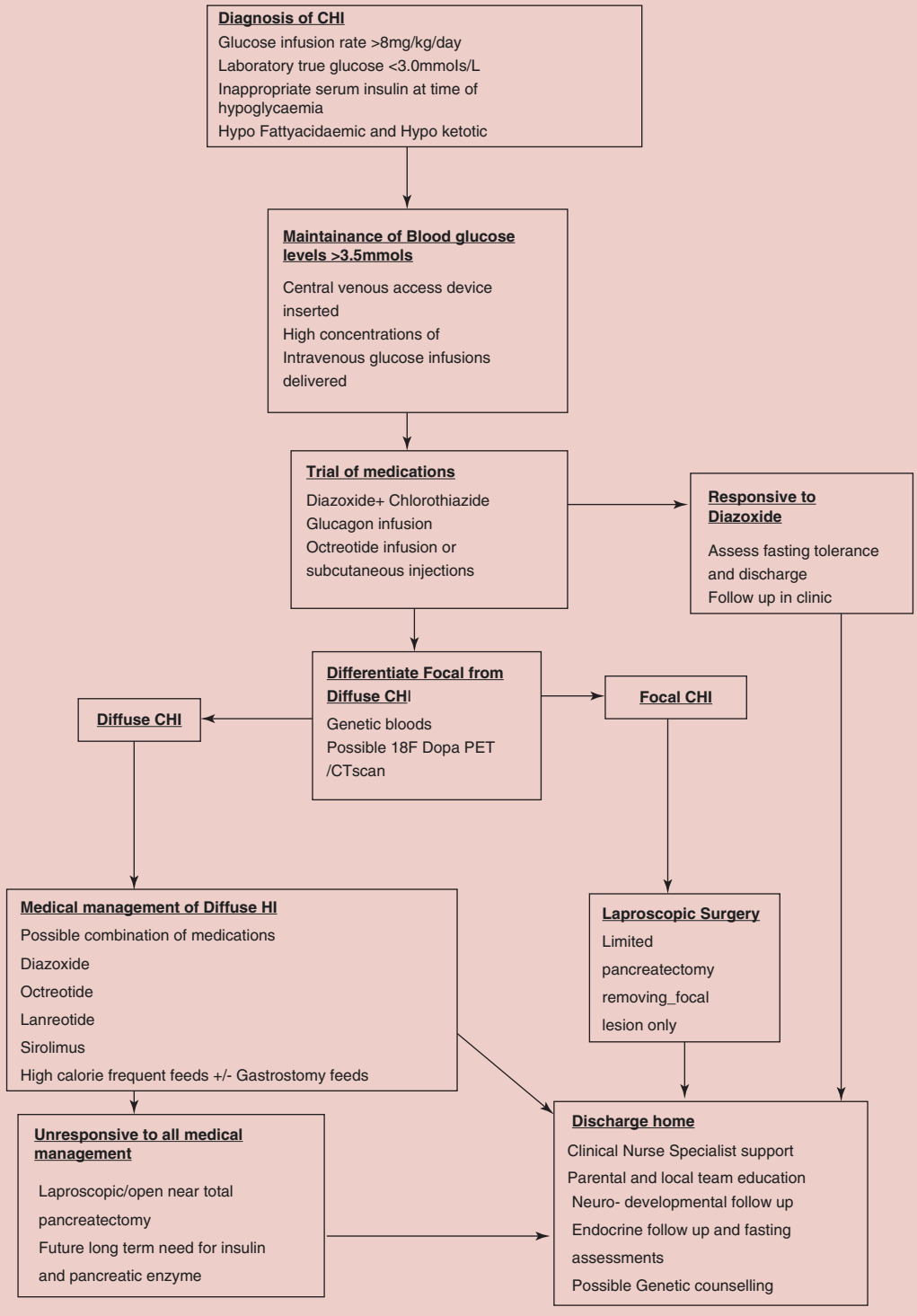


Table 8.4 Example: hypoglycaemia plan for parents

1.	If their blood glucose level is 3.5 mmols or less, re-check after 10 min on an alternative site.
2.	If their blood glucose level is still below 3.5 mmols, give one-third of a Glucogel® tube and a small feed.
3.	Re-check their blood glucose level 10 min later to ensure their blood glucose level has risen.
4.	If they have had a hypo before a feed, give the full feed.
5.	If they continue to be hypoglycaemic and do not respond to Glucogel®, please repeat step 2 and call an ambulance to take them to the nearest hospital for management. This may include insertion of an intravenous cannula and intravenous 10% glucose to stabilize their blood glucose levels especially if they are unwell and unable to tolerate feeds.
6.	If they present to hospital with a hypoglycaemic episode, they should always be admitted to have their blood glucose levels monitored and corrected with intravenous glucose.

Term infants with no risk factors are often difficult to identify due to non-specific symptoms. Parental education to recognize early symptoms of hypoglycaemia would be recommended, and education plans are drawn up and agreed with families (see Table 8.4) and prompt medical advice should be swiftly sought. Blood glucose levels measurements should be of utmost priority for babies presenting to midwives or A&E nurses with non-specific symptoms such as poor feeding and lethargy.

8.12 Neurological Outcomes

In neonates, the treatment of CHI must be diligently and intensively performed to prevent irreversible brain damage (Hussain et al. 2007). Avatapalle et al. (2013) stated that one-third of patients with CHI developed some form of developmental delay. The degree of brain injury can be variable, with some infants developing seizures and global developmental delay, although some may have very subtle problems with memory, which often manifests itself when the children are of school age. Further studies into the long-term neurological consequence of CHI are needed. The importance of the nursing role in identifying these patients with CHI—leading to a swift diagnosis and implementation of a safe management plan—cannot be over emphasized. Ultimately, by preventing hypoglycaemia, possible brain injury is also prevented.

8.13 Advances in Treatments for CHI

Research into the causes and treatment of CHI has recently exploded with advances in molecular genetics and medical therapies, including the recent use of Lanreotide and Sirolimus as treatments. The 18F-DOPA-PET imaging technique has revolutionized the diagnostic approach and accuracy of localizing focal CHI, with research continuing to make great advances in this area. The surgical approach to CHI has now advanced to being predominately laparoscopic. With this continuing research and advancement of knowledge, the aim is always to achieve more favourable outcomes for patients with this condition. The far-reaching objective is always to prevent brain injury for this patient group.

8.14 Conclusions

The purpose of this chapter was to briefly illustrate to Paediatric Nurses the importance of monitoring and managing blood glucose levels. Although CHI is a complex endocrine disorder, the outcome for this patient group is continuously improving with evidence-based knowledge and research. The key message is: early detection and treatment is crucial. Nurses at the bedside play a pivotal role in early identification of infants with CHI, and it is vital for them to have a low threshold for checking blood glucose levels in any infant who is symptomatic. If the infant has persistent hypoglycaemia, then the diagnosis of CHI should be considered (Kapoor et al. 2009b).

8.15 Questions to Consider

1. If the bedside blood glucose monitor indicated hypoglycaemia and the hyposcreen results suggested a diagnosis of CHI but the laboratory

glucose was elevated (7.8 mmols), what could this imply?

- Answer—The laboratory glucose is possibly inaccurate as it may have been taken from the intravenous line and contaminated with glucose.
- *Take home message—always take laboratory glucose from a capillary sample, preventing any risk of contamination*.

2. A student nurse has forgotten to inform you that her patient's intravenous glucose infusion is running out and needs changing. What would your actions be?

- Answer—(1) To check blood glucose level, work out how much time you have left before the infusion runs out. (2) Ensure you have an intravenous correction bolus of 1 mL/kg 10% glucose prescribed along with a new bag of fluids. (3) Urgently discuss with medical team appropriate intravenous fluids for the short term as this is an emergency. (4) Do not leave the patient without intravenous glucose and monitor blood glucose levels very closely to prevent hypoglycaemia.

3. What would you do if your central venous access device was to become dislodged and your intravenous glucose infusion was unable to be delivered?
    - Check blood glucose levels every 5–10 min.
    - Give glucogel in the oral mucosa and assess response.
    - Examine the patient and line. If the infant has a central venous device, try to bleed back on this line using Aseptic Non-Touch Technique and flush to check if the line is patent. If the intravenous line is patent, a 1 mL/kg bolus of 10% glucose should be administered. (An emergency prescription of 1 mL/kg 10% glucose should always be written for an infant at risk of hypoglycaemia). A rise in blood glucose level should be seen within 10 min. Always follow the hypo plan in the patient's notes.
    - If intravenous access is lost, please have two attempts of peripheral cannulation only. If successful, give 1 mL/kg bolus of 10% glucose to correct hypoglycaemia. Then administer infusion of 10% glucose maintenance fluids to prevent rebound hypoglycaemia. (Only 10% glucose can be administered safely via a peripheral cannula. For higher concentrations, central access is required).
    - In the event cannulation is not promptly obtained, then prescribe and give IM glucagon 1 mg stat dose. This will raise the blood glucose level within 10 min releasing the infants own glycogen stores. However, intravenous access must now be obtained as the infant will become hypoglycaemic once the stores of glycogen are utilized. An anaesthetist should be called to aid in cannulation or for reinsertion of a central line as this is now a clinical emergency.

Acknowledgements *Beki Moult - Health Information & Language Manager*, Great Ormond Street for Children Hospital, Foundation Trust, London, UK. *Dr Maria Guemes—Clinical Fellow—Hyperinsulinism*, Great Ormond Street for Children Hospital, Foundation Trust, London, UK. *Nabilah Begum—Hyperinsulinism Service Coordinator*, Great Ormond Street for Children hospital, Foundation Trust, London UK. *Dr Pratik Shah—Locum Consultant in Paediatric Endocrinology and Honorary Clinical Lecturer*, Great Ormond Street Hospital for Children and UCL Great Ormond Street Institute of Child Health, London. *Dr Ved Bhushan Arya MD PhD—Endocrine Registrar*, Great Ormond Street for Children Hospital, Foundation Trust, London, UK.

References

Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L, Caine L, Didi M, Skae M, Ehtisham S, Patel L, Padidela R, Cosgrove KE, Dunne MJ, Clayton PE. Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. Front Endocrinol. 2013;4(60):1–6.

Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fekete C, De Lonlay-Debeney P, Brunelle F, Otonkoski T, Thornton P, Lindley KJ. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed. 2000;82:98–107.

Barthlen W, Mohnike W, Mohnike K. Techniques in pediatric surgery: congenital hyperinsulinism. Horm Res Paediatr. 2011;75:304–10.

Bufler P, Ehringhaus C, Koletzko S. Dumping syndrome: a common problem following Nissen fundoplication in young children. Pediatr Surg Int. 2001;7(5):351–5.

Clayton PT, Eaton S, Aynsley-Green A, Edginton M, Hussain K, Krywawych S, Datta V, Malingre HE, Berger R, van den Berg IE. Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of beta-oxidation in insulin secretion. J Clin Invest. 2001;108(3):457–65.

Davis EA, Cuesta-Muñoz A, Raoul M, Buettger C, Sweet I, Moates M, Magnuson MA, Matschinsky FM. Mutants of glucokinase cause hypoglycaemia- and hyperglycaemia syndromes and their analysis illuminates fundamental quantitative concepts of glucose homeostasis. Diabetologia. 1999;42(10):1175–86.

de Lonlay P, Fournet JC, Rahier J, Gross-Morand MS, Poggi-Travert F, Foussier V, Bonnefont JP, Brusset MC, Brunelle F, Robert JJ, Nihoul Fékété C, Saudubray JM, Junien C. Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. J Clin Invest. 1997;100(4):802–7.

Dunne MJ, Petersen OH. Potassium selective ion channels in insulin-secreting cells: physiology, pharmacology and their role in stimulus-secretion coupling. Biochim Biophys Acta. 1991;1071(1):67–82.

Fain JA. Understanding diabetes mellitus and kidney disease. Nephrol Nurs J. 2009;36(5):465–9.

Glaser B, Thornton P, Otonkoski T, Junien C. Genetics of neonatal hyperinsulinism. Arch Dis Child Fetal Neonatal Ed. 2000;82:79–86.

Guemes M, Rahman SA, Hussain K. What is a normal blood glucose? Arch Dis Child. 2016;101(6):569–74.

Hussain K. Congenital hyperinsulinism. Semin Fetal Neonatal Med. 2005;10(4):369–76.

Hussain K, Blankenstein O, de Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management. Arch Dis Child. 2007;92:568–70.

Inagaki N, Gonoi T, Clement JP, Namba N, Inazawa J, Gonzalez G, Aguilar-Bryan L, Seino S, Bryan J. Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor. Science. 1995;270(5239):1166–70.

Ismail D, Smith VV, de Lonlay P, Ribeiro MJ, Rahier J, Blankenstein O, Flanagan SE, Bellanne-Chantelot C, Verkarre V, Aigrain Y, Pierro A, Ellard S, Hussain K. Familial focal congenital hyperinsulinism. J Clin Endocrinol Metab. 2011;96(1):24–8.

Kapoor R, James C, Hussain K. Advances in the diagnosis and management of hyperinsulinemic hypoglycaemia. Nat Clin Pract Endocrinol Metab. 2009a;5(2):101–12.

Kapoor R, Flanagan SE, James C, Shield J, Ellard S, Hussain K. Hyperinsulinaemic hypoglycaemia. Arch Dis Child. 2009b;94:450–7.

Kaufman FR. Role of the continuous glucose monitoring system in pediatric patients. Diabetes Technol Ther. 2000;2(Suppl 1):49–52.

Mehta A, Hussain K. Transient hyperinsulinism associated with macrosomia, hypertrophic obstructive cardiomyopathy, hepatomegaly and nephromegaly. Arch Dis Child. 2003;88(9):822–4.

Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycaemia. Pediatrics. 2001;107:476–9.

Munns C, Batch J. Hyperinsulinism and Beckwith-Wiedemann syndrome. Arch Dis Child Fetal Neonatal Ed. 2001;84(1):67–9.

Nebesio TD, Hoover WC, Caldwell RL, Nitu ME, Eugster EA. Development of pulmonary hypertension in an infant treated with diazoxide. J Pediatr Endocrinol Metab. 2007;20(8):939–44.

Nessa A, Asim Rahman S, Hussain K. Molecular mechanisms of congenital hyperinsulinism and prospective therapeutic targets. Expert Opin Orphan Drugs. 2015;3(8):1–11.

Nestorowicz A, Wilson BA, Schoor KP, Inoue H, Glaser B, Landau H, Stanley CA, Thornton PS, Clement JP IV, Bryan J, Aguilar-Bryan L, Permutt MA. Mutations in the sulonylurea receptor gene are associated with familial hyperinsulinism in Ashkenazi Jews. Hum Mol Genet. 1996;5(11):1813–22.

Otonkoski T, Kaminen N, Ustinov J, Lapatto R, Meissner T, Mayatepek E, Kere J, Sipilä I. Physical exercise-induced hyperinsulinemic hypoglycemia is an autosomal-dominant trait characterized by abnormal pyruvate-induced insulin release. Diabetes. 2003;52(1):199–204.

Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, Ellard S, Ferrer J, Hattersley AT. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the *HNF4A* gene. PLoS Med. 2007;4(4):0760–9.

Rahier J, Guiot Y, Sempoux C. Persistent hyperinsulinaemic hypoglycaemia of infancy: a heterogeneous syndrome unrelated to nesidioblastosis. Arch Dis Child Fetal Neonatal Ed. 2002;82(2):F108–12.

Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, Ellard S, Rampling D, Ashworth M, Brown RE, Hussain K. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycaemia. N Engl J Med. 2014;370(12):1131–7.

Stanescu DE, Hughes N, Kaplan B, De León DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. J Clin Endocrinol Metab. 2012;97(10):E2026–30.

Stanley CA, Lieu YK, Hsu BY, Burlina AB, Greenberg CR, Hopwood NJ, Perlman K, Rich BH, Zammarchi E, Poncz M. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. N Engl J Med. 1998;338(19):1352–7.

Stanley CA, Rozance PJ, Thornton PS, De Leon DD, Harris D, Haymond MW, Hussain K, Levitsky LL, Murad MH, Simmons RA, Sperling MA, Weinstein DA, White NH, Wolfsdorf JI. Re-evaluating "transitional neonatal hypoglycemia": mechanism and implications for management. J Pediatr. 2015;166(6):1520–5.

Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. J Pediatr Nurs. 2005;20(2):109–18.

Szymanowski M, Estebanez MS, Padidela R, Han B, Mosinska K, Stevens A, Damaj L, Pihan-Le Bars F, Lascouts E, Reynaud R, Ferreira C, Bansept C, de Lonlay P, Saint-Martin C, Dunne MJ, Banerjee I, Arnoux JB. mTOR inhibitors for the treatment of severe congenital hyperinsulinism: perspectives on limited therapeutic success. J Clin Endocrinol Metab. 2016;101(12):4719–29.

Thornton P, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Levitsky LL, Murad MH, Rozance PJ, Simmons RA, Sperling MA, Weinstein DA, White NH, Wolfsdorf JI. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr. 2015;167(2):238–45.

9 Genetic Syndromes Presenting in Childhood Affecting Hypothalamic Function

Kathryn Clark

Contents

9.1 **Introduction** 181

9.2 **Prader-Willi Syndrome** 181
9.2.1 Pathophysiology 181
9.2.2 Clinical Characteristics 182
9.2.3 Clinical Management 183
9.2.4 Clinical Investigations 184
9.2.5 Nursing Assessment 185
9.2.6 Nursing Care and Management 185

9.3 **Optic Nerve Hypoplasia** 189
9.3.1 Pathophysiology 190

9.4 **Conclusions** 192

References 193

Abstract

This chapter will focus on two genetic syndromes affecting hypothalamic function that typically present in childhood, Prader-Willi syndrome, and congenital optic nerve hypoplasia.

Prader-Willi syndrome (PWS) is a complex and challenging rare disorder resulting from the absence of gene expression on the paternal chromosome 15q11.2–q13. First described in 1956 as a medical syndrome, the chromosome 15 deletion was discovered in 1981. PWS is a spectrum disorder with a complex phenotype. The universal hallmark is hypotonia with decreased foetal activity noted during pregnancy. Most neonates are born with a lack of suck and respiratory irregularities. They are sleepy and seldom cry. Hypotonia and failure to thrive in infancy evolve into rapid weight gain in early childhood often with insatiable appetite and food seeking; this will lead to profound life-threatening obesity if not well managed at home and in school. Hypothalamic impairments complicate day-to-day life—high pain tolerance, temperature dysregulation, sleepiness, and

K. Clark (✉)
Prader-Willi Syndrome Association (USA), Sarasota, FL, USA

University of Michigan Hospital, Ann Arbor, MI, USA
e-mail: kclarkscio@comcast.net

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_9

constant drive to eat. Pituitary deficiencies of growth hormone and GnRH require skilled endocrine care throughout the lifespan. Children with PWS are at risk for respiratory crises from central apnoea and hypotonia with poor ventilatory effort in infancy and aspiration from impaired swallowing motility. Intellectual abilities span a wide spectrum although many children are successful in mainstream classrooms. Unique behavioural patterns including perseveration, skin picking, anxiety, and difficulty with task switching are common. With early diagnosis and intervention, developmental progress, health, and family stress can be significantly improved. Families need diagnosis-specific interventions with specialized medical care throughout the lifespan. Researchers are expanding understanding of PWS. Children born in the past two decades enjoy improved quality of life over previous generations. Treatment remains symptom driven, with no cure for the gene deletion.

Congenital optic nerve hypoplasia is correlated with pituitary dysfunction and developmental brain abnormalities. Nystagmus in infancy should be promptly assessed in the endocrine setting as pituitary deficiencies can include life-threatening hypoglycaemia and shock. Newborn screening programmes designed for congenital hypothyroidism seldom detect thyroid stimulating hormone (TSH) deficiency leaving these babies at high risk of hypothyroidism at the most critical time. Visual impairment ranges from unilateral visual field defects to bilateral complete blindness; pituitary deficiencies can be complete deficiencies of all hormones with prenatal onset, or development of insufficiencies over time. Brain abnormalities noted on magnetic resonance imaging (MRI) have relevance in predicting developmental and intellectual challenges, which occur in a wide spectrum. Endocrine nurses have a critical role in supporting and educating these families, and in helping them understand the unique impact of visual impairment on the child's development and behaviour.

Keywords

Growth hormone · Hypothalamic dysfunction · Hypotonia · Obesity · Optic nerve hypoplasia · Prader-Willi syndrome · Septo optic dysplasia

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
APGAR	Appearance-Pulse-Grimace-Activity-Respiration
BMI	Body mass index
cm	Centimetre
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
FISH	Florence in situ hybridization
FPWR	Foundation for Prader-Willi Research
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
hCG	Human chorionic gonadotropin
IGF-1	Insulin like growth factor 1
IPWSO	International Prader-Willi Syndrome Organization
kg	Kilogram
mg	Milligram
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
ONH	Optic nerve hypoplasia
OT	Occupational therapy
PC1	Prohormone convertase
PT	Physical therapy
SOD	Septo optic dysplasia
TSH	Thyroid stimulating hormone
USA	United States of America

Key Terms

- **Uniparental disomy:** This occurs when a person receives two copies of a chromosome from one parent but no copy from the other parent.
- **Genomic imprinting:** Epigenetic phenomenon that causes genes to be expressed in a

parent-of-origin specific way; it is a process of silencing genes through DNA methylation.
- **Food security:** Condition that relates to the availability of a food supply that allows a person to meet their dietary needs in a safe and healthy way. No hope of independent access to food.
- **Oral aversion:** Refers to the avoidance, reluctance or fear/anxiety of eating, drinking, or allowing sensation in or around the mouth.

Key Points
- PWS is a genetic imprinting mutation resulting in a spectrum of diverse medical problems, cognitive effects, and behavioural challenges. Early diagnosis improves outcomes.
- Families require hope, support, and education in raising a medically fragile and complex child with unique medical problems and unusual behaviour patterns. Families with rare conditions can feel isolated and need significant support.
- Food security (no hope of independent access to food) is essential to control troublesome behaviours and preventing life-threatening obesity.
- Children with PWS are at risk in the health care setting because of high pain tolerance and unusual responses to medications including anaesthesia. Providers are often unaware of these unusual morbidities and parents must learn to advocate for their child within the health care system. Printed medical alert booklets are available from international advocacy groups which outline these findings.
- This chapter will describe the physical findings in children born with optic nerve hypoplasia and the pathophysiology associated with the syndrome known as septo optic dysplasia. The spectrum of physical and developmental challenges will be explained. Visual impairment beginning at birth results in unique learning needs which will be described. Nurses in the endocrine setting should acquire the experience and wisdom needed to help these families.
- The endocrine needs of an individual with this disorder are the same as other types of pituitary and hypothalamic insufficiencies and the reader is encouraged to review those chapters.

9.1 Introduction

This chapter will provide an overview of two genetic syndromes affecting hypothalamic function that typically present in childhood, Prader-Willi syndrome, and congenital optic nerve hypoplasia.

9.2 Prader-Willi Syndrome

9.2.1 Pathophysiology

Chromosome 15 includes a 5–6 Mb gene region in which the maternal gene is silenced and only the paternal region is expressed, one of the few patterns of imprinting in the human genome. In PWS, region 15q11.2–q13 is not active due to random loss (paternal deletion), or maternal disomy with paternal loss (uniparental disomy). An extremely rare inherited imprinting defect has also been identified (Butler et al. 2016b). There are a variety of identified genes in this region, none of which completely explains the complex phenotype. This rare disorder affects males and females equally; estimated incidence is 1:10,000–30,000 live births. Specific testing is required with all subtypes of PWS detected by deoxyribonucleic acid (DNA)-based methylation testing or chromosomal microarray. Inadequate genetic testing (e.g. fluorescence in situ hybridization (FISH)) will not detect all the subtypes and is not

the recommended initial test. Further testing for IC micro deletions are also recommended (Butler et al. 2016b). There are consensus guidelines to make this diagnosis using specific weighted clinical criteria when genetic testing is unavailable, but genetic testing is the standard of care.

The mechanisms of hunger in PWS do not follow typical hunger hormonal patterns such as blood sugar and insulin, ghrelin, and leptin. Bariatric surgery does not interrupt the hunger and satiety cycle, and it is not recommended by PWS experts. Bariatric surgery creates significant risks with anaesthesia metabolism, gut motility impairment, impaired pain sensation, and high risk of picking the surgical sites. Of greatest concern is that the individual with PWS will return to the same environment that allowed profound weight gain to occur in the first place—no food security.

9.2.2 Clinical Characteristics

At birth, profound hypotonia generally alerts the medical team to the possible diagnosis. APGAR (Appearance-Pulse-Grimace-Activity-Respiration) scores will be low. Suck and cry may be absent. The baby may not be easily stimulated to fully awaken. Few of these children would survive without a stay in the neonatal intensive care unit (NICU). Early failure to thrive is common and support is needed to ensure weight gain in a sleepy child with poor suck and no sense of hunger. Nasogastric feedings of formula or breast milk may be required to supply adequate nutrition; enrichment may be needed. Most babies progress over a few weeks to an adequate suck, with feeding specialist expertise in selecting a nipple. In some cases, hypotonia, sleepiness, or swallowing abnormalities are so profound that gastric tube feedings are needed to send the baby safely home. Swallowing is often abnormal and presents an aspiration risk.

Babies need hip examinations to look for the common dysplasia seen in PWS, related to hypotonia. Early scoliosis often responds well to bracing or serial casting. A standard back examination for scoliosis screening is inadequate in this population, due to hypotonia masking curves; a scoliosis series is recommended at age one year, and examination and X rays throughout childhood. Curves progress very quickly in this population and surgery can lead to many unique risks and challenges for those with PWS.

Strabismus is common. Eyeglasses, patching, or surgery are commonly required.

Persons with PWS also have low muscle mass, which reduces metabolic rate, even if hypotonia improves. Facial features are affected by hypotonia; babies may have a longer face, almond-shaped eyes, and a downturned mouth (Butler et al. 2016b; Irizarry et al. 2016). Hypopigmentation is typical but not universal. It is a subtle and appealing phenotype.

Gastric and intestinal motility are erratic, and constipation is very common. Infants have poor suck and swallow, and children have delayed milestones in eating skill attainment. Impairments in swallowing may not improve over time and could explain higher rates of respiratory infections (Gross et al. 2017; Tan and Urquhart 2017). Saliva tends to be thick and sticky, a challenge for swallowing and chewing and impairing dental health.

Hypothalamic impairment contributes to poor temperature control, reduced sensation of pain, reduced respiratory drive, and pituitary dysfunction. GnRH deficiency and gonadal dysfunction are common (Butler et al. 2016b; Irizarry et al. 2016). Most boys with PWS are born with undescended testes and often micro phallus. This indicates prenatal GnRH deficiency. PWS experts recommend 6–10 weeks of human chorionic gonadotropin (hCG) treatment to attempt to stimulate testicular growth and spontaneous descent prior to consider surgery. These testes are often very high in the abdomen and difficult to locate without this stimulatory boost. HCG also prompts a small boost in natural testosterone levels and can improve phallic size and muscular strength. Micro phallus may require testosterone treatment, and while this is not urgent, valuable improved muscle strength is a side benefit of testosterone injections (Angulo et al. 2015; Bakker et al. 2015; Irizarry et al. 2016). There have been no reports of fertility in men with PWS; three

births have occurred in women with the syndrome. Female puberty is often incomplete due to GnRH deficiency.

9.2.3 Clinical Management

Prompt treatment with growth hormone (GH) is highly recommended by PWS experts (Butler et al. 2016b; Deal et al. 2013a; Emerick and Vogt 2013; Irizarry et al. 2016). There are myriad studies of the impact of GH beyond physical growth—breathing strength, suck ability, social engagement, learning, and improved milestone attainment. Different protocols are used for deciding when to treat, with some babies treated while still in the NICU. Sleep and breathing issues must be explored, either prior to or shortly after beginning GH. Weight gain must be established for adequate response to GH. Sleep apnoea and tube feedings are not contraindications to beginning GH therapy. GH deficiency is common, but the use of GH is more global, with significant benefits not seen in other GH-deficient populations. Long-term treatment has a lasting impact on body mass index (BMI), strength, cognitive improvements, and energy, in addition to growth (Bakker et al. 2013; Butler et al. 2016b; Deal et al. 2013a; Dykens et al. 2017; Emerick and Vogt 2013; Irizarry et al. 2016). Optimal dosing is not well understood, but many children respond well to lower doses than typical in the GH-deficient population, often with robust IGF-1 responses (Bakker et al. 2013).

Somewhere between ages 1 and 3 years, most children with PWS will begin to become more interested in food. Weight gain increases even without an increase in caloric intake. Meals need to be well regulated, nutrient balanced with a multivitamin, and snacks should be provided on a schedule. Caloric needs are between 60 and 80% of typical children; there is a movement toward lower carbohydrate diets (Emerick and Vogt 2013). Parents need to establish food rules early—adults control the food, which is never provided upon request. This approach builds a solid framework for the future and is known to decrease anxiety in children with PWS, as well as control weight. Spontaneous treats or unexpected changes in dinnertime or what food is being served can lead to emotional breakdowns in these children. For many families, locking cupboards and the refrigerator is the best solution to food security and also diminishes anxiety about available food for the person with PWS.

Hydration can become a problem, as many persons with PWS do not like to drink water. This may be related to swallowing coordination issues (Gross et al. 2017). Constipation may occur, and daily bulking agents are often indicated. Poor sensation of the need to defecate is common.

Children with PWS have a wide variety of educational needs, with some requiring special education throughout the day and others thriving in typical classrooms. One central need is complete food security—no candy from teachers, no surprise cupcake treats for birthdays, no donut sales in the school hallway. Any food events must be well planned to avoid tantrums and behaviour problems. Many children need the assistance of an aide to ensure a smooth day, with routines that cannot always be controlled, but can be managed. During the school day, therapies such as speech, occupational or physical therapy (OT, PT) can be provided. Children with PWS benefit from daily exercise as a part of their education plan, in addition to recess or classroom gym time. As children get older and playtime is eliminated, many children with PWS should continue with a daily exercise plan to benefit both weight and behaviour.

Developmental patterns may be delayed, sometimes through poor muscle tone and the lack of experiences due to sleepiness and decreased activity. Speech may be delayed, and apraxia is not uncommon. Speech therapists are essential team members, not just for communication skills but also to assist with the transition to pureed and table foods.

A small insect bite can become a sore that does not heal for years because people with PWS have an unusual habit of picking at sores, surgical scars, and sometimes the rectum. Open wounds must be kept covered, insect bites avoided, and attention redirected.

The personality style of persons with PWS is often described as charming and loving, with an

affectionate nature and desire to please others. The need for routines and a love of repetitive behaviours is common (Whittington and Holland 2010). Tantrums of epic proportion often accompany thwarted expectations or unexpected changes in routines. Since pleasing others and appearing "good" is highly valued by persons with PWS, telling the truth is often difficult. The drive for food is variable, but most individuals will take any opportunity to rapidly eat food, which is suddenly unguarded. Choking, often during a furtive food binge, is a significant cause of early death. Stubbornness is common.

The phenotype of PWS has changed significantly over the past decades due to the action of GH on muscle development and parental empowerment to limit food and optimize development through a variety of therapies. Older individuals with PWS, without exposure to GH in childhood, have short stature, with small hands and feet, and poor muscle development. Excessive fat is often deposited on hips and thighs, even with normal BMI. If the individual has not been prevented from overeating, profound obesity will result with the expected dire medical outcomes including early death.

9.2.4 Clinical Investigations

No single gene has been shown to contain all impaired functions seen in PWS, but identifying the gene for each cluster of problems has been rapidly advancing (Angulo et al. 2015). Prohormone convertase (PC1) deficiency, linked to a critical region in the deleted gene has been identified as the likely source of the major neuroendocrine features of PWS (Burnett et al. 2017). Scientific research and treatment options for any of the many problems in PWS would have potential impact on much larger populations, especially those affecting hunger and obesity.

Given the known hypothalamic dysregulation, oxytocin replacement has promising potential, with decreased oxytocin neurons noted in adults. Preliminary trials in infants (Tauber et al. 2017) demonstrated improved sucking and swallowing and maternal-infant gaze (bonding) after a short course of intranasal oxytocin. Miller et al. (2017) found less robust effect in a 2017 study of older children.

Orexin a (hypocretin 1) is a hypothalamic neuropeptide which is an important regulator of appetite and feeding behaviour, as well wakefulness, gut motility, and pleasure seeking and may be dysfunctional in PWS (Manzardo et al. 2016).

Anxiety can become a more challenging problem than hunger. Typical psychotropic medications may be prescribed but often do not always manage the symptoms. The basis of anxiety in PWS is multifactorial, with hypothalamic factors and gene deletions known to have an impact on anxiety. Other behavioural patterns, such as psychosis risk, skin picking, and repetitive behaviours are targets for research.

Once profound obesity has occurred, survival may be in jeopardy. Caloric needs are extremely low after infancy, and normal diets and lack of food security will lead to profound obesity. Medications are in clinical trials to both decrease hunger and appetite and cause weight loss. The broad utility of these medications would benefit more people than just those with PWS. One promising trial was withdrawn by the manufacturer after two deaths occurred due to thrombotic events. Thrombotic events may be a significant cause of mortality in PWS, rather than a response to a study medication, and data is being collected to better understand this risk.

Behaviours seen in autism overlap much of the behavioural phenotype of PWS. These include repetitive behaviours, repeated questioning, and an insistence on sameness and routines. Language delays such as apraxia may mimic the communication issues seen in autism spectrum disorders (ASD). One study of 146 children found that while many children with PWS have ASD behaviours, only 12% meet diagnostic criteria for ASD. This number is much greater than the current average of 1–2% of the population (Dykens et al. 2017), but it is certainly not universal and did not follow the typical ASD gender as the PWS group were equally female and male. PWS is of interest to autism researchers because of a shared gene mutation, which has been found in some children with autism.

9.2.5 Nursing Assessment

Assess family systems and coping. Post-partum issues such as physical separation of mother and baby or maternal health challenged are immediate priorities.

Expert Quote: Greet the new family with congratulations on the birth of their beautiful child. Admire and praise the baby—this is not just a child with a rare genetic disorder, but an anticipated and beloved new family member. Provide the family with hope before providing education or a treatment plan.

Physical assessment will always focus on growth patterns, weight and length/height, BMI. There are PWS-specific growth charts for children with PWS who are on GH (Butler et al. 2016a). Rate of weight gain is important, with failure to thrive dominating in infancy and rapid fat gain beginning between age 1 and 3 years. Diet should be discussed at each encounter. Obtain specific information about supplements.

Document the genetic subtype and the results of all genetic tests. There are different health risks associated with the two most common subtypes, paternal deletion and mUPD.

Developmental assessment at each visit should include asking parents for positive changes and progression. Assess language skills, receptive and expressive.

Assess whether parents have PWS-specific emergency medical information to share with providers who are unfamiliar with the syndrome. These are available from the PWS advocacy organizations and are available online.

9.2.6 Nursing Care and Management

Children with PWS require a team of specialists for optimal care. Endocrinology, genetics, sleep, orthopaedic surgery, dietician, behaviour/developmental, ophthalmology, and gastroenterology will all be consulted in the first years of life. This is in addition to the therapists—feeding expert, physical therapist, occupational therapist, and speech therapist. Coordination of these visits relieves a travel and communication burden for families and promotes interdisciplinary care and understanding of this rare disorder.

Advocacy and education are primary roles of the nurse (Vitale 2016). Assist parents by providing the resources, which are available through national and international support groups. If the child is in the NICU, help parents obtain the booklet available at this website: www.pwsausa.org. National and international organizations maintain up-to-date educational materials for professionals and parents. Support groups can offer trained parent mentors and group meetings. Some parents may need repeated encouragement to connect with this invaluable resource.

Early therapies such as OT, feeding specialists, and PT are essential. With poor upper body strength, babies will need help with tummy time and safe positioning in car seats and carriers. Sleepy babies miss opportunities to learn, and parents need help in making choices that optimize brain development. Parents should be encouraged to stimulate development during wakeful times and not let these windows of energy be missed.

Parents must wake the baby for scheduled feedings, as hunger is generally absent for the first year of life. Careful tracking of weight gain is important. Diet management will require a dietician to stay up to date on the unique and emerging dietary approaches to PWS. In the neonatal period, weight gain is essential for brain growth. The transition to oral feedings is often slow and many infants require nasogastric feedings for 3–6 months. Oral feedings should be limited to 20 min to avoid exhausting the baby. Feedings may need to be thickened. Breast milk may require fortification to meet caloric needs.

As children transition to oral feedings, parents may fear obesity and underfeed the child. There will be a wide range of needs, as some children will have significant delays in motor skills and thus require fewer calories than a typical toddler. After age 1 year, 10 kilocalorie/cm/day is a good starting point for most children. There is emerging evidence that a very low carbohydrate diet (45%) can decrease hunger. Many children with PWS require 60% of typical calories in order to

manage weight gain. Multivitamins are needed due to the low volume of foods. There is evidence that high quantities of raw foods, such as salads, which was a common approach in the past, may lead to more digestive motility problems. Softer cooked vegetables or soups may help avoid bowel obstructions. Be aware that over the counter supplements are very popular with young parents. These include coenzyme Q10, carnitine, coconut oil, and MCT oil.

Endocrine nurses will already be familiar with GH treatment. These children are most rewarding to treat with significant changes in body composition and muscle tone along with improved growth. Parents see this therapy as life changing and issues of access to care or changes in doses or brands of GH can be significantly more stressful for them than for other patient populations. Nurses should be proactive in prescription renewals and authorizations to avoid stress on the family.

Constipation is almost universal, likely from multiple factors, including poor muscle tone, delayed motor milestones, and intestinal dysmotility. Polyethylene glycol is generally well tolerated and may be needed daily. High-fibre diets or increased raw foods are not recommended due to known risks of bowel obstruction.

When interacting with children who have PWS, thoughtful communication is key. As concrete thinkers, persons with PWS will respond poorly to teasing or figurative speech. Auditory processing is slow; so allow time to answer questions without rushing them. Avoid "thinking out loud"—they will count on the nurse to be consistent and not change the plans. Children with PWS are eager to please; give them a chance to shine. Asking questions about negative behaviours will often be met with anxiety and outright lies. For example, there is no point in asking if someone is following the correct diet if the nurse has determined that weight gain has been excessive. Speak privately with parents when complex issues need discussion.

Genetic diagnoses come with guilt, shame, and blame. Parents and grandparents will need repeated explanations over the years. While the geneticist and genetic counsellor are the experts in explaining the genetic details, families will continue to seek answers from other providers. The genetics visit may have been a time of shock, grief, and exhaustion, so prepare for further questions. Invite extended family members to clinic visits to directly educate them and to help parents by addressing difficult topics with family members.

Expert Quote: Specifically, state that PWS is not caused anything that the parents did or were exposed to, that it does not "run in families" (check first to determine whether the child has the very rare familial imprinting disorder instead of the more common paternal deletion or mUPD). Paternal deletion may be misunderstood to mean that it is the father's "fault"—specifically state that many fathers or mothers interpret the genetic terminology to mean that PWS was because of something defective on their part, but that this is not the case.

To advance the understanding of rare disorders, the National Institutes of Health (NIH) in the USA has developed sophisticated data base platforms for data collection voluntarily provided by parents through an online portal. This international registry is cross-cultural and includes historic data; it will allow researchers to seek participants for clinical trials. Encourage parents to enrol their child in the Global Registry at www.pwsregistry.org.

Connections to the local, national, and international parent support and advocacy groups are a lifeline for parents struggling with a rare diagnosis that includes a potentially frightening future. In 1975, an American parent and professional group was formed (Prader-Willi Syndrome Association (USA)) for the purpose of family support, education, and the advancement of research. The organization continues to provide new parents with peer mentors, local chapters, advocacy, and educational materials for parents and professionals. Professionals interested in the syndrome have benefitted from this and other organizations which supply funding for research. Many countries (UK, Australia) have their own independent organizations with similar websites, with extensive materials for families and professionals. Foundation for Prader-Willi Research

(FPWR) was formed with the goal of finding a cure. Their website provides information for families interesting in joining in clinical trials and reading about breakthroughs in research. International Prader-Willi Syndrome Organization (IPWSO) can help families locate PWS clinicians and parent groups around the world and includes links to the most vital written materials, translated into many languages. This organization also offers free genetic testing for PWS to those families unable to access this in their own country. Nurses should encourage connection to these groups. Internet information can also exhaust a parent who cannot filter out fears and negative thoughts, so also ask whether these groups are helpful or draining, and give permission to parents to take time off from their groups, if needed. IPWSO.org, pwsausa.org, and fpwr.org are excellent resources. These resources are also the most up-to-date source for providers and the nurse should access these as a primary source of information.

Skin picking often starts with an insect bite. Recommend skin protection when outdoors, and covering any small lesion. Distraction and redirection can be helpful; chastising them or punishment can increase the picking through anxiety and stubbornness.

Recognize the patterns of behaviour change, such as repetitive play, repeated questioning, and tantrums. Children who have these challenges benefit from behaviour plans that include understanding of the syndrome. While some families will naturally provide structure and routine, this may be very challenging for other families. Sleepiness and low energy should be addressed as these interfere with learning and social time.

Health supervision guidelines and anticipatory guidance for children with PWS are outlined in the American Academy of Paediatrics 2010 Clinical Report—Health Supervision for Children with PWS (McCandless 2011).

The following resource has specific guidelines for the endocrine specialist (Table 9.1).

Case Study: Prader-Willi Syndrome

With a primiparous mother, reports about poor foetal activity were minimized. Samuel was born at 34-week gestation with Apgar score of 2 and 4. He was admitted to the NICU for poor respiratory effort and failure to suck. He had profound hypotonia with atypical neonate positioning, arms and legs fully extended. He was on a ventilator for 3 weeks and was fed by nasogastric tube with no attempt to suck. On physical examination, he had very low muscle tone, was difficult to arouse; he was blond and pale, different from his dark-haired parents. He had bilaterally undescended testes with the right palpable in the inguinal canal. Phallic size was abnormal at 2.0 cm. Scrotum was small. NICU physicians immediately suspected PWS and sent DNA methylation studies, which confirmed the diagnosis of PWS.

When he was born, the Food and Drug Administration (FDA) in the United States of America (USA) had not yet approved GH for PWS. After contacting the national PWS organization, his parents took him to another academic institution where a pioneer in the care of PWS children assessed him and urged GH therapy. He returned to his home setting and was tested for growth hormone deficiency using standard testing. IGF-1 was low and GH peaks were less than 5 ng/dL. At age 3 months, GH was started at a very low dose, 0.1 mg daily. He was still on oxygen at night and using a nasogastric tube to complete his feedings, beginning to suck and swallow. He did not smile, but made good eye contact and was a cuddly baby, although he slept for about 16 h daily and needed to be woken for therapies and feedings. Parents pursued all early intervention therapies and he was involved in occupational therapy, speech/feeding, and physical therapy. They maintained contact with the local and national support groups for up-to-date information and shared this with his providers.

At age 5 months, he returned to the paediatric endocrine clinic. He was smiling and kicked his legs to show happiness. He had poor head control. The nasogastric tube was gone; he was feeding by mouth, and was awake for at least 10 h per day. Weight gain was excellent and he was growing well. He was no longer on oxygen.

He was given hCG 500 units intramuscular injection twice weekly for 6 weeks with resulting

Table 9.1 Endocrine management of patients with Prader-Willi syndrome (Emerick 2013)

Age	Area to address	Testing/treatment
Birth to 3 months or at diagnosis	Diagnosis	• DNA methylation analysis as initial test
		• Subsequent determination of genetic subtype
	Hypothyroidism	• TSH, FT4
		• Start treatment if hypothyroxinemic
	Growth hormone	• Initiate discussion of hGH therapy
3 months through childhood	Hyperphagia	• Provide education on: nutritional phases, need for food security, strict dietary control and routine, regular physical
		• Nutrition referral
	Cryptorchidism	• Urology referral
		• Consider trial of hCG
	Hypothyroidism	• Annual TSH and FT4 starting at age 1
	Growth hormone	• Consider starting therapy in the first few months of life, or prior to onset of obesity
		• No pre-treatment testing required
		• Starting dose: 0.5 mg/m^2/day with progressive increase to 1 mg/m^2/day
		• Aim to keep IGF-1 levels between +1 and + 2 SDS
	Growth hormone monitoring	Prior to starting therapy:
		1. Otolaryngology referral if there is a history of sleep disordered breathing, snoring, or enlarged tonsils or adenoids are present, with consideration of tonsillectomy and adenoidectomy
		2. Referral to a pulmonologist or sleep clinic
		3. Sleep oximetry in all patients, preferably polysomnographic evaluation
		4. Spine film with orthopaedic referral if significant scoliosis present
		5. Bone age film if at appropriate chronologic age
		6. Consider body composition evaluation (e.g. DXA)
		Contraindications to therapy:
		1. Untreated severe OSA
		2. Uncontrolled diabetes
		3. Severe obesity
		4. Active malignancy
		5. Active psychosis
		While on therapy:
		1. IGF-1 every 6–12 months
		2. Repeat polysomnography within the first 3–6 months of initiating hGH therapy
		3. Spine film and/or orthopaedic assessment if concerns for scoliosis progression
	Adrenal insufficiency	• Consider obtaining cortisol and ACTH levels during acute illness or other stressful situation to clarify diagnosis
		• Consider stress dose steroids for all patients with PWS during stress to include mild upper respiratory infections and the perioperative period

Table 9.1 (continued)

Age	Area to address	Testing/treatment
Puberty through adulthood	Hypogonadism	• Sex steroid therapy as needed to promote normal timing and progression of puberty in males and females
		• Adult females: sex steroid replacement if oligo/amenorrhoea or low BMD in the setting of a low oestradiol level
		• Adult males: testosterone replacement as for hypogonadal males. May be behavioural benefits from topical androgen formulations
	Growth hormone	• Adults: evaluate the GH/IGF-1 axis prior to initiating hGH
		• Adult staring dose: 0.1–0.2 mg/day
		• Aim to keep IGF-1 0 to +1 SDS
	Diabetes	• Screen prior to initiation of and annually during growth hormone therapy in patients ≥ 12 years of age
		• Screen in obese individuals as is recommended for the general population
	Obesity	Periodic monitoring of/for:
		1. Lipid profiles
		2. Hepatic steatosis

complete descent of the right testis. Phallic size increased to normal for 6 months. Strength was improved by parental report. Urology assessed him and scheduled surgery for left orchiopexy, which he tolerated well. Special attention was given to anaesthesia risks and he stayed overnight for this typically outpatient procedure.

Sam continued on growth hormone with normal growth and height throughout childhood. He always had a normal BMI and appeared slender; at times, his parents were urged to increase his calories to improve weight gain. He did not seek food or binge eat. Sam enjoyed obeying the rules and being a "good" boy; he also had a family who kept a very solid routine for Sam and his younger brother, with excellent food security at home.

Kindergarten was delayed due to speech delays and poor motor skills, but when he entered kindergarten, it was in a mainstream classroom, with OT, PT, and speech therapies at the school. He was an excellent reader but required academic support throughout his schooling. Sam developed into a charming happy child, eager to please others, energetic, and very positive—a joy to be around. By high school, he had achieved a black belt in Tae Kwon Do and he finished his Eagle Scout aware by graduation. Scoliosis developed rapidly and he had surgery for rod placement at age 15 years; he recovered easily from this, determined to be as healthy as possible. This surgery improved his height by 3 in. and his adult height is 173 cm with a weight of 60 kg.

During early adolescence, Sam became aware of his limitations and developed anxiety, which was treated with medications. This anxiety increased in high school, as he considered what his future would hold. He is now attending community college and living with his parents, considering moving to a PWS community in the future.

9.3 Optic Nerve Hypoplasia

When a child is noted to have unusual eye movements, a prompt ophthalmologic evaluation is essential. If small optic discs, consistent with optic nerve hypoplasia (ONH) are noted, an endocrine evaluation and brain magnetic resonance imaging (MRI) are required, regardless of the lack of other symptoms. These children must be promptly evaluated to rule out hypoglycaemia, thyroid deficiency, and adrenocorticotropic hormone (ACTH) or cortisol deficiency, all critically important in the neonatal period. MRI imaging is needed for assessment of the entire brain as well as special attention to the pituitary/hypothalamic/optic chiasm.

Septo optic dysplasia (SOD) is diagnosed when there are two abnormalities in this triad: pituitary/hypothalamic disorders; visual deficits

or blindness; and/or abnormalities of brain structures. For example, a child with optic nerve hypoplasia and pituitary deficiencies has SOD, as does the child who has a hypoplastic corpus callosum and optic nerve hypoplasia (ONH), without pituitary deficiencies. The impairments and life challenges in SOD are primarily related to the degree of brain abnormalities rather than the degree of pituitary hypofunction or visual loss.

Visual impairment at birth results in a unique developmental pattern. A multidisciplinary team is needed for optimal development of these children, as well as for support of the parents and family. SOD babies are often first-born children of young mothers, and experience in parenting is often limited. Endocrine care and support is not different in this population from that of other patients who have pituitary deficiencies. However, expert-nursing involvement is essential for parental confidence and competency and for best outcomes for the child with this challenging diagnosis.

9.3.1 Pathophysiology

The connection between underdevelopment of the optic nerves and pituitary function was first made in 1970 (Borchert 2012). For many years, this heterogeneous developmental condition was referred to as "De Morsier's Syndrome" and septo optic dysplasia (SOD), despite the negligible role of the septum pellucidum. SOD now is used to describe the condition when there are at least two of three abnormalities: optic nerve hypoplasia, abnormalities of midline brain structures, and hypothalamic/pituitary dysfunction. Thus, some individuals diagnosed with SOD will not have endocrine disorders, and most do not have abnormalities of the septum pellucidum.

A genetic cause of ONH is found in only a small minority of patients tested (McCabe and Dattani 2014), and it is very rare for families to have more than one child with this disorder (Borchert 2012). Genes responsible for the development of pituitary and optic nerve (Deal et al. 2013b). *HESXI* effects are variable but have been associated with pituitary dysfunction and ONH (McCabe and Dattani 2014). *Sox 2*, *Sox 3* and *Sox 3* are required for anterior pituitary development. PROP1 stimulates pituitary cell differentiation; TBX19 is involved in ACTH deficiency (McCabe and Dattani 2014).

Risk factors for SOD include young maternal age, primiparous state (Borchert 2012; Garcia-Filion and Borchert 2013),"unhealthy behaviour, and poor pre-conception health" (Garcia-Filion and Borchert 2013). However, there is a dearth of findings of risky behaviours in mothers (Garcia-Filion and Borchert 2013) and no data found on the fathers. First trimester vaginal bleeding has been noted to be more common (Ryabets-Lienhard et al. 2016).

Optic nerve hypoplasia is the second leading cause of blindness in neonates (Borchert 2012; Garcia-Filion and Borchert 2013) and the leading cause of permanent blindness in children in the western world (Ryabets-Lienhard et al. 2016). Incidence around the world has been increasing since the 1980s (Ryabets-Lienhard et al. 2016) with Sweden reporting 17.3 per 100,000 in 2014 and the United Kingdom (UK) reporting 10.9 per 100,000 (Garcia-Filion and Borchert 2013; Ryabets-Lienhard et al. 2016). Lack of central registries and schools for the blind in the USA may be explanations for the somewhat lower incidence of 9.7 per 100,000 (Ryabets-Lienhard et al. 2016).

9.3.1.1 Clinical Characteristics

Optic nerve hypoplasia is expressed with a broad range of visual function, from minor unilateral visual field impairment, to complete bilateral blindness. Actual visual ability is uncertain in infancy, and initial exams cannot predict eventual visual ability. Improvement in vision has been noted in the first years of life in some children (Ryabets-Lienhard et al. 2016).

Nearly 80% of children with bilateral optic nerve hypoplasia will have pituitary dysfunction (Garcia-Filion and Borchert 2013) and developmental delays. Those with unilateral ONS have less risk of developmental delay and pituitary problems (70%) (Borchert 2012; Garcia-Filion and Borchert 2013). Hypothalamic impairment is not uncommon in SOD and is more likely than

primary pituitary dysgenesis (Borchert 2012). Hypothalamic impairment can cause temperature dysregulation, abnormal thirst, abnormal hunger, and sleep disturbances.

Brain abnormalities may include absent or hypoplastic corpus callosum, white matter hypoplasia, schizencephaly, and arachnoid cysts. These findings carry a higher probability of impaired cognitive function.

Isolated absence of the corpus callosum is related to significant risk of developmental delay. When seen in combination with pituitary dysfunction and/or optic nerve hypoplasia (SOD), children with abnormalities of the corpus callosum generally face significant developmental challenges. Cortical (brain) abnormalities are prognostic of the greatest challenges, including seizures, motor development delay, and global cognitive impairment (Signorini et al. 2012).

Endocrine abnormalities may not all present at the time of diagnosis, so surveillance is needed during childhood. The most common abnormality in SOD is growth hormone deficiency, seen in 70%. Thyroid secreting hormone (TSH) deficiency is diagnosed in 43%, ACTH deficiency in 27%, and ADH deficiency, diabetes insipidus, 5% (Ryabets-Lienhard et al. 2016; Cemeroglu et al. 2015). Abnormalities of gonadotropin releasing hormone (GnRH) function can also occur, with micro phallus noted at birth and GnRH deficiency, and paradoxically, precocious puberty (Borchert 2012).

The initial endocrine evaluation includes the entire array of pituitary hormones, insulin like growth factor 1 (IGF-1) as proxy for growth hormone (GH), cortisol, free thyroxine and TSH, prolactin, and electrolytes. If the child presents in infancy, gonadotropins and the sex appropriate gonadal hormone (oestradiol or testosterone) should be measured, as these early levels are predictive of gonadotropin releasing hormone (GnRh) deficiency in adolescence (Borchert 2012). In infancy, the danger of hypoglycaemia from cortisol deficiency cannot be overstated. Growth hormone also plays a significant role in homeostasis although the role of GH in linear growth is not significant until the child is 6–9 months old. Treatment guidelines are the same as for any individual with multiple hormone deficiencies; for example, cortisol must be replaced before starting thyroid replacement. Treatment of micro phallus in infancy, once the child is stable, can make toilet training easier, which is not an insignificant challenge.

Sleep issues are significant in the blind population. These children often lack normal sleep patterns, and parents require significant support to handle the challenges of poor or absent sleep. Melatonin may help some children with sleep initiation, but other children and adults may not acquire a true diurnal rhythm; the assistance of a sleep specialist may be essential.

9.3.1.2 Nursing Care and Management

Early intervention for developmental delays is essential. Children with visual impairment will not proceed through the typical patterns of other children (Garcia-Filion and Borchert 2013). They may be fearful of moving, and delay creeping and walking. Motor delays are common (75% of children with SOD) (Borchert 2012). Some are very quiet and watchful babies, as they take in auditory information; they may be overwhelmed by stimulation, responding by crying or by tuning out the world. Well-meaning adults may provide too many musical toys, for example. Close work with occupational (OT) and physical therapy (PT) and vision consultants can help the parents understand their child's unique needs. These babies are especially prone to plagiocephaly, as they resist "tummy time", lacking the visual motivation to lie prone.

Blind children often develop routinized behaviours, called "blindisms", which are self-stimulatory behaviours, such as rocking, head bobbing, hand flapping, and eye tapping. A diagnosis of autism spectrum is found in 33% of children with SOD (Jutley-Neilson et al. 2013). It is more common (57%) in children with near total visual loss, and in 12.5% of those with mild to moderate visual impairment (Garcia-Filion and Borchert 2013). This is a higher rate of autism than in the general blind population (Borchert 2012).

Oral aversion is a common problem in the visually impaired child. They lack the anticipation of a bottle coming near, and do not see others

eating at the table; spoon-feeding is a mystery to them, and they may respond with distress. In addition, many of these children lack oral coordination, which can lead to unnecessary upper gastrointestinal evaluations. Instead, intensive OT and speech therapy can assist with the slower progression many of these children need on the path to competent eating. For many children with oral aversion, chronic constipation is also an issue and should be considered part of this cluster of developmental challenges.

Case Study: Optic Nerve Hypoplasia

Maria was born at 41-week gestation at 2720 g 48 cm to a gravida 1- para-1, 17-year-old woman. Prenatal care did not begin until 15-week gestation, but the pregnancy was uneventful. Maria's father was not involved or aware of the pregnancy. Maria's mother was planning to finish high school and had good support from her mother.

The baby demonstrated poor sucking and lethargy in the newborn nursery. Blood glucose level was 45 mg/dL, but she was sent home without concerns. Newborn screening for thyroid levels (TSH) was not abnormal. During the first 2 weeks of her life, mother fed her every 3 h using formula and a premature nipple. Maria was a good sleeper and had to be woken for feedings. At age 2 weeks, she had not gained any weight. She was noted to be slightly jaundiced, but no other abnormalities were noted. Mother expressed concern that Maria did not make eye contact, and that her eyes "looked funny" but this was not observed by her paediatrician.

At her 1-month visit, her yellowish skin colour had not resolved. She had periods of shakiness, and mother continued to worry about her "shaking" eyes. Weight gain and growth had been poor (3000 g, 49 cm); the paediatrician noted nystagmus and referred her to a paediatric ophthalmologist. Mother was encouraged to wake the baby more often and continue 3-h feedings around the clock.

The ophthalmologist diagnosed optic nerve hypoplasia and referred her urgently to a paediatric endocrinologist. An MRI was ordered but was delayed until the hormone evaluation was completed. At her endocrine visit, cortisol was undetectable, TSH was 0.3 miu/L, free T4 was 0.5 ng/dL, and IGF-1 less than 10 ng/mL. Non-fasting glucose was 55 mg/dL. Liver enzymes were slightly elevated, but all other labs were within normal limitations for her age. Clinical exam was consistent with panhypopituitarism, including small labial folds. Maria's mother had done a remarkable job of keeping her fed and well hydrated.

Maria was diagnosed at age 2 months with ACTH, TSH, and probable GH deficiency. Cortisol replacement began first, followed by thyroid replacement. When she was stable, an MRI of the brain revealed bilateral optic nerve hypoplasia and a thin corpus callosum. Initiation of the hormone replacement resulting in immediate improvement in her wakefulness and eating behaviour. She began to gain weight well and to grow. Glucose level normalized immediately.

The nurse provided education on the complex medications. She assured the mother and grandmother that this disorder has no known cause, and that while feelings of guilt are normal, there is not a known cause or any way to prevent this condition. The nurse followed up with frequent phone contact and made referrals for social services and early intervention services. At each visit, the nurse assessed the baby's developmental progress and pointed out progress typical of a child with a visual impairment.

9.4 Conclusions

PWS is a complex rare genetic disorder. The current generation of children has a different and more hopeful health and behavioural profile than in the past. Researchers are rapidly identifying specific gene actions, which are responsible for the phenotype and medical complications. While targeted treatments are still under investigation, the mainstay of health care for children with PWS is avoidance of obesity, proactive approaches to behaviour problems, and detection and treatment of known medical risks. Intensive early therapies, especially growth hormone treatment, have been instrumental in the development

of a very different outcome for the youngest generations with this rare disorder. Parents must learn to become advocates and to educate the providers. They will need ongoing education as new therapies and treatments emerge. Nurses caring for children with this rare disorder need to stay up to date as research is rapidly changing the focus of care and recommended practices.

In addition to the challenges of managing multiple pituitary deficiencies in childhood, children with SOD may have the additional burdens of visual impairment and brain abnormalities. There are challenges in childhood, including motor development, feeding, risk of autism and seizure disorders, sleep disturbances, and uncertainty of cognitive potential. Parents are often young and require guidance and support.

Acknowledgements With special thanks to Kathy Clark, Medical Coordinator for Prader-Willi Syndrome Association (USA), for including information about the Patient Advocacy Groups: Prader-Willi Syndrome Association (USA) (https://www.pwsausa.org), Foundation for Prader-Willi Research (FPWR) (https://www.fpwr.org), and the International Prader-Willi Syndrome Organization (IPWSO) (https://www.ipwso.org).

Web Resources for Families

http://www.onesmallvoicefoundation.org/
http://www.onhconsulting.com/
https://www.familyconnect.org/parentsitehome.aspx
https://www.magicfoundation.org
https://www.chla.org/the-vision-center-ophthalmology (United States Resource).

References

Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Investig. 2015;38(12):1249–63.

Bakker NE, Kuppens RJ, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Bindels-de Heus GC, Bocca G, Haring DA, Hoorweg-Nijman JJ, Houdijk EC, Jira PE, Lunshof L, Odink RJ, Oostdijk W, Rotteveel J, Schroor EJ, Van Alfen AA, Van Leeuwen M, Van Pinxteren-Nagler E, Van Wieringen H, Vreuls RC, Zwaveling-Soonawala N, de Ridder MA, Hokken-Koelega AC. Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects. J Clin Endocrinol Metab. 2013;98(10):4013–22.

Bakker NE, Wolffenbuttel KP, Looijenga LH, Hokken-Koelega AC. Testes in infants with Prader-Willi syndrome: human chorionic gonadotropin treatment, surgery and histology. J Urol. 2015;193(1):291–8.

Borchert M. Reappraisal of the optic nerve hypoplasia syndrome. J Neuroophthalmol. 2012;32(1):58–67. https://doi.org/10.1097/WNO.0b013e31824442b8.

Burnett LC, LeDuc CA, Sulsona CR, Paull D, Rausch R, Eddiry S, Carli JF, Morabito MV, Skowronski AA, Hubner G, Zimmer M, Wang L, Day R, Levy B, Fennoy I, Dubern B, Poitou C, Clement K, Butler MG, Rosenbaum M, Salles JP, Tauber M, Driscoll DJ, Egli D, Leibel RL. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. J Clin Invest. 2017;127(1):293–305.

Butler MG, Lee J, Cox DM, Manzardo AM, Gold JA, Miller JL, Roof E, Dykens E, Kimonis V, Driscoll DJ. Growth charts for Prader-Willi syndrome during growth hormone treatment. Clin Pediatr (Phila). 2016a;55(10):957–74.

Butler MG, Manzardo AM, Forster JL. Prader-Willi syndrome: clinical genetics and diagnostic aspects with treatment approaches. Curr Pediatr Rev. 2016b;12(2):136–66.

Cemeroglu AP, Coulas T, Kleis L. Spectrum of clinical presentations andendocrinological findings of patients with septo-optic dysplasia: a retrospective study. J Pediatr Endocrinol Metab. 2015;28(9–10):1057–63.

Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS. 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013a;98(6):E1072–87.

Deal C, Hasselmann C, Pfäffle RW, Zimmermann AG, Quigley CA, Child CJ, Shavrikova EP, Cutler GB Jr, Blum WF. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growthhormone deficiency: data from an International Observational Study. Horm Res Paediatr. 2013b;79(5):283–92.

Dykens EM, Roof E, Hunt-Hawkins H. Cognitive and adaptive advantages of growth hormone treatment in children with Prader-Willi syndrome. J Child Psychol Psychiatry. 2017;58(1):64–74.

Emerick JE, Vogt KS. Endocrine manifestations and management of Prader-Willi syndrome. Int J Pediatr Endocrinol. 2013;2013(1):14.

Garcia-Filion P, Borchert M. Optic nerve hypoplasia syndrome: a review of theepidemiology and clinical associations. Curr Treat Options Neurol. 2013;15(1):78–89.

Gross RD, Gisser R, Cherpes G, Hartman K, Maheshwary R. Subclinical dysphagia in persons with Prader-Willi syndrome. Am J Med Genet A. 2017;173(2):384–94.

Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. Adv Pediatr Infect Dis. 2016;63(1):47–77.

Jutley-Neilson J, Harris G, Kirk J. The identification and measurement ofautistic features in children with septo-optic dysplasia, optic nerve hypoplasia and isolated hypopituitarism. Res Dev Disabil. 2013;34(12):4310–8.

Manzardo AM, Johnson L, Miller JL, Driscoll DJ, Butler MG. Higher plasma orexin a levels in children with Prader-Willi syndrome compared with healthy unrelated sibling controls. Am J Med Genet A. 2016;170(9):2328–33.

McCabe MJ, Dattani MT. Genetic aspects of hypothalamic and pituitary gland development. Handb Clin Neurol. 2014;124:3–15.

McCandless SE. Committee on Genetics. Clinical report—health supervision for children with Prader-Willi syndrome. Pediatrics. 2011;127(1):195–204.

Miller JL, Tamura R, Butler MG, Kimonis V, Sulsona C, Gold JA, Driscoll DJ. Oxytocin treatment in children with Prader-Willi syndrome: a double-blind, placebo-controlled, crossover study. Am J Med Genet A. 2017;173(5):1243–50.

Ryabets-Lienhard A, Stewart C, Borchert M, Geffner ME. The optic nerve hypoplasia spectrum: review of the literature and clinical guidelines. Adv Pediatr Infect Dis. 2016;63(1):127–46.

Signorini SG, Decio A, Fedeli C, Luparia A, Antonini M, Bertone C, Misefari W, Ruberto G, Bianchi PE, Balottin U. Septo-optic dysplasia in childhood: the neurological, cognitive and neuro-ophthalmological perspective. Dev Med Child Neurol. 2012;54(11):1018–24.

Tan HL, Urquhart DS. Respiratory complications in children with Prader-Willi syndrome. Paediatr Respir Rev. 2017;22:52–9.

Tauber M, Boulanouar K, Diene G, Çabal-Berthoumieu S, Ehlinger V, Fichaux-Bourin P, Molinas C, Faye S, Valette M, Pourrinet J, Cessans C, Viaux-Sauvelon S, Bascoul C, Guedeney A, Delhanty P, Geenen V, Martens H, Muscatelli F, Cohen D, Consoli A, Payoux P, Arnaud C, Salles JP. The use of oxytocin to improve feeding and social skills in infants with Prader-Willi syndrome. Pediatrics. 2017;139(2).

Vitale SA. Parent recommendations for family functioning with Prader-Willi syndrome: a rare genetic cause of childhood obesity. J Pediatr Nurs. 2016;31(1):47–54.

Whittington J, Holland A. Neurobehavioral phenotype in Prader-Willi syndrome. Am J Med Genet C Semin Med Genet. 2010;154C(4):438–47.

Key Reading

1. Irizarry KA, Miller M, Freemark M, Haqq AM. Prader-Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. Adv Pediatr. 2016;63(1):47–77.
2. Emerick JE, Vogt KS. Endocrine manifestations and management of Prader-Willi syndrome. Int J Pediatr Endocrinol. 2013;2013(1):14.
3. McCandless SE. Committee on Genetics. Clinical report—health supervision for children with Prader-Willi syndrome. Pediatrics. 2011;127(1):195–204.
4. Borchert M. Reappraisal of the optic nerve hypoplasia syndrome. J Neuroophthalmol. 2012;32(1):58–67.
5. Garcia-Filion P, Borchert M. Optic nerve hypoplasia syndrome: a review of the epidemiology and clinical associations. Curr Treat Options Neurol. 2013;15(1):78–89.
6. Ryabets-Lienhard A, Stewart C, Borchert M, Geffner ME. The optic nerve hypoplasia spectrum: review of the literature and clinical guidelines. Adv Pediatr. 2016;63(1):127–46.

10 Genetic Syndromes Presenting in Childhood Affecting Gonadotropin Function

Sharron Close, Ana Claudia Latronico, and Marina Cunha-Silva

Contents

10.1 **Introduction** 197

10.2 **Klinefelter Syndrome** 197
10.2.1 Background of KS 198
10.2.2 Genetic Mechanism for KS 198
10.2.3 Diagnosis of KS 198
10.2.4 Case Presentation of KS 198
10.2.5 KS Physical Health and Other Health Characteristics 199
10.2.6 Endocrine Basis for Symptoms and Treatment in KS 200
10.2.7 Health Surveillance of KS 201

10.3 **Testotoxicosis** 201
10.3.1 Treatment of Testotoxicosis 203

10.4 **Nursing Role** 203
10.4.1 Complexity of Care for Patients Diagnosed with Klinefelter Syndrome or Testotoxicosis 203

10.5 **Conclusions** 204

References 205

Abstract

This chapter will focus on two genetic syndromes affecting gonadotropin function that typically present in childhood, Klinefelter syndrome, and testotoxicosis.

Klinefelter syndrome (47,XXY) is the most common sex chromosome aneuploidy with a prevalence of 1 in 450–500 male births. Unless detected by prenatal screening or prenatal diagnosis, this chromosome variation diagnosis is frequently missed in children. Physical, neurocognitive, and psychosocial phenotypes of boys with 47,XXY

S. Close (✉)
Emory School of Medicine, Emory University School of Nursing, The eXtraordinarY Clinic at Emory, Atlanta, GA, USA
e-mail: sharron.m.close@emory.edu

A. C. Latronico · M. Cunha-Silva
Unidade de Endocrinologia do Desenvolvimento de Hormônios e Genética Molecular LIM42, Disciplina de Endocrinologia e Metabologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil, São Paulo, Brazil

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_10

are extremely variable, making a typical case difficult to characterize. Health care needs of boys born with 47,XXY are complex including the need for monitoring growth, pubertal development, optimization of reproductive capacity, bone health, and acknowledgement of physical symptoms such as fatigue, hypotonic muscle strength, tremors, tics, and pain. Physical health risks associated with 47,XXY include: metabolic syndrome, Type II diabetes, cardiovascular disease, immunological issues, bone loss, and certain types of malignancies. Boys with 47,XXY frequently show executive function issues, language-based learning difficulties, problems with communication, and struggles with behavior that contribute to stressors for the boys as well as for their families. Psychosocial manifestations of these stressors include low self-esteem, increased risk for depression, difficulties maintaining personal relationships, and adverse quality of life. There is a general lack of awareness in the health care community about the complexities of care required for families who have sons with 47,XXY. Since puberty is a sentinel time for diagnosing and monitoring hypogonadism, families often depend on professionals in the specialty of endocrinology to address their many concerns. Families seeking anticipatory guidance about how 47,XXY will influence the growth and development of their sons often look to the specialty of endocrinology to help them navigate a health care environment that is confusing to them. This chapter will describe the physical, neurocognitive, and psychosocial phenotype of 47,XXY in childhood and provide suggestions for endocrine-related health surveillance for advanced practice nurses (APRN). APRNs in endocrinology practice are perfectly positioned to assess, coordinate, and provide family-centered navigation for health surveillance according to child's level of development.

Testotoxicosis or familial male-limited precocious puberty is a rare dominant form of gonadotropin-independent precocious puberty caused by constitutively activating mutations of the luteinizing hormone receptor. Affected males present premature and progressive virilization associated with accelerated growth and advanced bone age between 2 and 4 years of age. Hormonal profile is characterized by elevated testosterone levels, despite prepubertal levels of luteinizing hormone. Treatment typically consists of reducing hyperandrogenism with ketoconazole or a combination of antiandrogens and aromatase inhibitors.

Keywords
Klinefelter syndrome · 47,XXY
Sex chromosome aneuploidy · Phenotype
Androgen deficiency · Puberty · Receptor
Mutations · Virilization

Abbreviations

APN	Advanced Practice Nurse
BA	Bone age
c-AMP	cyclic adenosine monophosphate
cm	Centimeter
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
G-protein	Guanine-protein
hCG	Human chorionic gonadotropin
IU/L	International unit/Liter
kg	Kilogram
KS	Klinefelter syndrome
LH	Luteinizing hormone
LHCGR	Luteinizing hormone receptor gene
mg	Milligram
ng/dL	Nanogram/deciliter
SD	Standard deviation

Key Terms

- **Sex chromosome aneuploidy:** Chromosomal disorder characterized by the loss or gain of one or more of the sex chromosomes.
- **Hypergonadotropic hypogonadism:** Also known as primary hypogonadism, which involves an impaired response of the gonads to gonadotropins (FSH, LH) and results in

lack of sex steroid production and delayed sexual development.

- **Activating mutations:** Also known as gain-of-function mutation, which changes the gene product and results in enhanced activation and abnormal function.
- **Virilization:** Development of male secondary sex characteristics in prepubertal males and females (i.e. facial and body hair, male pattern hair growth, enlarged clitoris, enlarged penis, masculinization of urogenital tract) associated with androgen excess.

Key Points

- Boys born with an extra X chromosome have complex health care and social needs that are not easily recognized or addressed by health care providers.
- While boys with 47,XXY are known to demonstrate hypergonadotropic hypogonadism beginning in puberty, androgen deficiency alone does not account for many characteristics and symptoms associated with 47,XXY.
- Testotoxicosis is a rare cause of peripheral precocious puberty that affects boys exclusively. The pattern of inheritance is autosomal dominant in the familial form of testotoxicosis.
- The hormonal profile of testotoxicosis is characterized by elevated serum levels of testosterone, contrasting with prepubertal basal and GnRH-stimulated LH levels. Rapid and progressive virilization, growth acceleration, and skeletal maturation are typical manifestations.
- Constitutively activating mutations of the luteinizing hormone receptor gene represent the genetic basis of testotoxicosis.
- APRNs in endocrinology practice are perfectly positioned to assess, coordinate, and provide family-centered navigation for health surveillance according to child's level of development.

10.1 Introduction

This chapter will provide an overview of two genetic syndromes affecting gonadotropin function that typically present in childhood, Klinefelter Syndrome, and testotoxicosis familial male-limited precocious puberty.

10.2 Klinefelter Syndrome

Knowledge of genetics and the ability to develop an index of suspicion for the genetic basis of endocrine-based problems are important aspects of practice for APRNs (refer to Chap. 7). Sex chromosome variations are among the many genetic conditions that require endocrine management in coordination with other treatment or therapy. Several variations of sex chromosomes exist involving additional Xs or Ys that are associated with a number of physical, psychological, and medical issues that require coordinated multidisciplinary care (Tartaglia et al. 2015). The most common of these variations is the karyotype 47,XXY, also known as Klinefelter Syndrome (KS). The prevalence of KS is estimated to be about 1 in 450–600 male births (Bojesen et al. 2003; Herlihy et al. 2011). While the prevalence of KS is not rare, it is not commonly diagnosed and is often discovered incidentally when mothers undergo prenatal screening for other genetic conditions. Even with the advent prenatal screening, only 10% of affected individuals are diagnosed during childhood and almost 75% are unaware that they carry an extra X (Abramsky and Chapple 1997). Diagnosis of KS is done by chromosomal analysis, a study of the structure, and number of chromosomes that is also known as a karyotype. This section will discuss the background of KS, genetic mechanism underlying the karyotype, the physical, neurocognitive, and psychosocial phenotype, the endocrine basis for symptoms, treatment, associated health risks and issues regarding the complexities of care for patients.

10.2.1 Background of KS

The syndrome known as 47,XXY was originally described in 1942 by Dr. Harry S. Klinefelter and colleagues in a case series of 9 patients with similar physical characteristics (Klinefelter et al. 1942). These characteristics included tall stature, light or absent facial hair, small testes, low testosterone levels, and azoospermia. In 1959, using radiographic imaging of chromosomal structures, Patricia Jacobs and colleagues discovered that men with KS characteristics also had an extra X resulting in the karyotype 47,XXY (Jacobs and Strong 1959). Since the original report of physical characteristics, clinicians and scientists have expanded the physical phenotype to include descriptions of neurocognitive and psychosocial characteristics as well (Close et al. 2015; van Rijn et al. 2014a; Nieschlag 2013; Tartaglia et al. 2010; Boada et al. 2009).

10.2.2 Genetic Mechanism for KS

Klinefelter syndrome is not an inherited condition. It is not passed down from one generation to the next by autosomal dominant or autosomal recessive pattern. Rather, the genetic mechanism is the result of non-disjunction of sex chromosomes during development of gametes (sperm or eggs) or during Meiosis I or II in the embryological phase of development. During formation of gametes, cells divide to distribute one sex chromosome (and X or a Y) to each gamete. On occasion, sex chromosomes fail to divide properly thereby distributing more than one X or Y. If one gamete has more than one sex chromosome present, it combines with the other parental gamete to develop an embryo with multiple sex chromosomes. Extra Xs may come from paternal or maternal origin. Parental contribution occurs 50% of the time from the father and 50% of the time from the mother (Jacobs et al. 1988). The extra X in the XXY karyotype may have variable effects due to the processes of activation, inactivation, or partial activation of one or both X chromosomes (Zitzmann et al. 2004). Gene "dosage" is highly variable and thought to contribute the variable phenotypes observed in KS.

Non-disjunction may also occur after fertilization and this can lead to mosaicism when the developing embryo has a cell line of 46 XY as well as 47,XXY. Individuals with 46 XY/47,XXY mosaicism are reported to have milder physical and neurocognitive characteristics (Paduch et al. 2008).

10.2.3 Diagnosis of KS

Prenatal testing is usually performed as a screening measure to detect trisomies such as 13, 18, and 21 in women of advanced maternal age. Until recently, this testing was done via amniocentesis or chorionic villi sampling. Due to the advent of non-invasive prenatal screening (NiPS), risk for these chromosomal trisomies along with sex chromosome aneuploidies, such as 47,XXY, are being detected early and is becoming standard practice for many prenatal clinics across the country (Bianchi et al. 2012). When parents first learn of risk or receive confirmatory results of 47,XXY, consultation with a specialist in endocrinology becomes a priority concern. Diagnosis, however, is not always made prior to birth. A frequent scenario with 47,XXY occurs when a young man attains adulthood and encounters difficulties in achieving pregnancy with his partner. After consultation with a urologist, the patient may learn that his testes are small and firm, with evidence of low sperm count or azoospermia. These clinical observations usually initate a plan that includes ordering a karyotype to turl our 47,XXY. For undiagnosed boys, many important signs, symptoms, and clinical observations often do not trigger a health care provider to consider inquiry into a genetic diagnosis. Signs that are frequently missed in children include speech and language delay, learning issues, and behavioral struggles.

10.2.4 Case Presentation of KS

JT is a 16-year-old male with a history of learning difficulties and early speech and language delay. He reports that he is unable to keep up with other kids his own age in sports and other physical activ-

ities. Parent reports that during JT's early childhood, he was bullied by other children and frequently not chosen by his peers for group activities. Patient reports that now that he is self-conscious about his body because he is much taller than his peers (>99%), that he is not developing facial hair and that his breast area is becoming protuberant. Parent reports that teachers have described him as lazy and disorganized. JT has expressed to his parents recently that he is too tired to care anymore and that he wishes he could just disappear. At first glance, this case description may sound like a typical disenfranchised teenage boy. On closer examination, however, there are important observations to be made that require further clinical inquiry. On physical examination, this young man was found to have a number of physical features such as tall stature, eunuchoid body proportion, gynecomastia, diminished upper body muscle bulk and strength, Tanner stage V pubertal development, and testicular volume of 8 mL.

Laboratory findings demonstrated elevated luteinizing hormone (LH), and follicle stimulating hormone (FSH) with serum testosterone at 320 mg/dL that suggested hypergonadotropic hypogonadism. Based upon clinical observations, a chromosomal analysis was ordered revealing that this child had 47 chromosomes in the pattern of 47,XXY, also known as Klinefelter Syndrome (KS).

10.2.5 KS Physical Health and Other Health Characteristics

One of the earliest features of KS in child development is a rapid rise in linear growth during the school years with stature greater than the 99th percentile. Tall stature, however, is not always observed. Long legs relative to torso and very long arms may give the child a "eunuchoid" proportion. The onset of puberty and its progression during the Tanner stages of sexual development may demonstrate more emerging features such as low upper body muscle bulk and strength, light facial hair, development of gynecomastia, and small testes. Testicular development in a child should roughly follow Tanner staging. In later Tanner stages IV-V, if testicular volume remains small, this is a sign that genetic testing for 47,XXY should be ordered.

A problem exists, sometimes, in pediatric primary care, when health care providers defer genital examinations in boys to save them from embarrassment. Failure to observe small testes is another reason why the diagnosis of 47,XXY frequently missed during the course of normal care. Physical, neurocognitive, and psychosocial health characteristics associated with 47,XXY vary widely from person to person. Due to the wide range of variability, "textbook" examples are rarely seen. There are, however, several characteristics that, in combination, may elicit a suspicion of 47,XXY in an undiagnosed child. Boys with 47,XXY may also express a variable psychosocial phenotype that is shaped by inherent personality characteristics, yet-to-be-understood mechanisms involved with the supernumerary X, factors of nurture within the family and their social environment. Many boys with 47,XXY show social cognitive deficits that may contribute to social dysfunction (van Rijn et al. 2014b). Social dysfunction has been described as autistic-like without necessarily meeting the full diagnostic requirement for the designation of autism spectrum disorder. Some of these features include deficits in social communication, reciprocal social interaction and restricted, repetitive patterns of behavior (Tartaglia et al. 2017). Neurocognitive features of boys with 47,XXY include normal to low-normal intelligence with specific language-based learning difficulties. Speech and language delays may exist in early childhood along with slow auditory processing, problems with memory, visual-motor difficulties, and fine motor control issues. These variable features may manifest as learning issues that require special attention at school either in the form of individualized education plans, or 504 accommodations for disability. The diagnosis of 47,XXY is not considered a physical or neurocognitive disability per se although many boys and men with 47,XXY demonstrate specific disabilities in learning that impair school and work performance.

10.2.6 Endocrine Basis for Symptoms and Treatment in KS

The feature of hypogonadism and androgen deficiency is due to progressive hyalinization of testicular tissue and the seminiferous tubules. As boys enter puberty, the pituitary gland systematically pulses LH and FSH to signal the testes to begin manufacture and secretion of testosterone. Depending on how fibrotic the testicular tissue has become, the testes become increasingly unable to produce levels of testosterone enough to suppress LH and FSH. As a result, LH and FSH remain high while serum testosterone begins to wane as the child progresses through puberty. Androgen deficiency in adults is associated with fatigue, lack of maintaining upper body muscle bulk, decreased facial hair, lack of libido, azoospermia, osteoporosis irritability, and depression (Styne and Puberty 2015). While boys with 47,XXY are expected to eventually show androgen deficiency in early childhood through adolescence, their serum levels of testosterone remain roughly in the normal to low-normal range. Evidence-based clinical guidelines and clinical consensus documents from professionals in endocrinology currently do not currently exist for how and when to treat children.

Since androgen treatment clinical guidelines and consensus documents do not currently exist for pediatric populations, health care providers are reluctant to treat young boys with testosterone in the absence of identifiable deficiency. Some youth with 47,XXY report bothersome symptoms such as fatigue, lack of motivation, irritability, lack of upper body strength, low self-esteem, and depression. It is unclear, and so far, unsupported by scientific evidence that exogenous testosterone treatment will improve these symptoms in children.

There currently exists conflicting and provocative scientific work with infants with regard to early treatment (Ross et al. 2005; Lahlou et al. 2011), but no body of evidence has yet emerged to support its use unless urogenital anomalies such as microphallus exist. A study completed in 2005 with 29 boys between the ages of 1 month and 23 months suggested that testicular volume and phallic length were diminished, indicating early androgen deficiency (Ross et al. 2005). In 2011, however, researchers found in 72 boys who were less than 2 years of age, that the majority had normal external genitalia (Lahlou et al. 2011). While testosterone replacement therapy is often employed to mitigate physical symptoms, a body of literature is emerging concerning its affect in cognition and behavior in children. In a 2015 study of boys between the ages of 36 and 72 months results suggested that boys with microphallus during infancy who were treated with testosterone had improved scores for social communication, social cognition, and total (T) score on the Child Behavior Checklist along with improvements in the Behavior Rating Inventory of Executive Function compared to untreated controls (Samango-Sprouse et al. 2015). In a 2017 randomized control study with 84 boys between the ages of 4 and 12 years comparing a low-dose oral testosterone treatment group with a no-treatment group. Results from this study showed improvement in only 1 out of 5 endpoints (visual-motor function) (Ross et al. 2017). A secondary analysis of the data in this study showed positive effects of psychosocial function including anxiety, depression, and social problems. No significant effects were observed on cognitive function or behaviors such as hyperactivity or aggression. While evidence continues to be generated, results thus far do not provide strength of evidence to direct the use of testosterone as a clinical treatment for behavior and cognition.

For adolescents aged 18 years and older who demonstrate androgen deficiency with serum levels consistently below normal range for age, there are a variety of testosterone products available as seen in Table 10.1. The Endocrine Society has established clinical guidelines for treating men, age 18 years and older with androgen deficiency syndromes (Bhasin et al. 2010). For adolescents with 47,XXY entering puberty (and/or age of 13 years), it is recommended to begin initial therapy with testosterone enanthate 50 mg intramuscularly every month for about 9 months (Styne and Puberty 2015).

Table 10.1 Testosterone replacement therapy for boys 18 years of age and older

Formulation	Route	Dose and schedule
Testosterone enanthate or cypionate	IM	150–200 mg IM every week OR 75–100 mg IM every 2 weeks
Long-acting testosterone undecanoate in oil	IM	European regimen: 1000 mg IM followed by 1000 mg at 6 weeks, and 1000 mg every 10–14 weeks
1% testosterone gel	Transdermal	5–10 g of testosterone gel containing 50–100 mg testosterone every day
Testosterone patch	Transdermal	1–2 patches designed to deliver 5–10 mg testosterone over 24 h applied every day to non-pressure areas
Testosterone-in-adhesive matrix patch	Transdermal	2 × 60 cm^2 patches delivering approximately 4.8 mg of testosterone per day
Buccal bioadhesive testosterone tablets	Trans-oral mucosa	30 mg controlled release bioadhesive tablets twice daily
Oral testosterone undecanoate[a]	Oral	40–80 mg twice daily or three times daily with meals
Testosterone pellets	Subcutaneous	3–6 pellets implanted subcutaneously; dose and regimen vary with formulation

Adapted from Endocrine Society Clinical Practice Guidelines for men with androgen deficiency syndromes (Bhasin et al. 2010)

[a]Not approved for clinical use in the United States, but available in many other countries

Regular assessment of adolescents' adherence to therapy and monitoring of symptoms is a key part of patient care for the Advanced Practice Nurse (APRN). While monitoring serum testosterone levels when an adolescent is on treatment provides biological feedback in terms of serum levels, it is important to monitor changes in symptoms as well. Some adolescents may report improvements for specific symptoms such as facial hair growth and muscle bulk while other symptoms such as irritability, mood, and tremors may be exacerbated.

10.2.7 Health Surveillance of KS

A number of health risks exist for patients born with 47,XXY that need to be surveilled throughout the lifespan. A recommended health surveillance schedule according to age is shown in Table 10.2. Many physical health risks are endocrine in nature such as: hyperinsulinism, metabolic syndrome, Type II diabetes, thyroid disease, and osteopenia or osteoporosis. Other physical health risks include: hyperlipidemia, hypertension, cardiovascular disease, vascular leg ulcerations, arthritis, breast cancer, tremors, and tics. Psychological health risks include anxiety, depression, suicide, and risk of substance abuse. Recommended best practice for the APRN who monitors boys and adolescents with 47,XXY is to annually conduct a thorough physical exam that includes all systems, screening for depression, anxiety, and substance use.

10.3 Testotoxicosis

Testotoxicosis or familial male-limited precocious puberty is a rare cause of peripheral precocious puberty that affects exclusively boys (Schedewie et al. 1981). It is caused by constitutively activating mutations of the luteinizing hormone receptor gene (*LHCGR*). The pattern of inheritance is autosomal dominant in familial cases, but sporadic cases can occur (Kremer et al. 1999; Laue et al. 1995).

Affected boys typically develop rapid and progressive virilization characterized by penile growth, pubic hair development, minimal testicular enlargement, growth acceleration, and skeletal maturation before the age of 4 (Table 10.3) (Schedewie et al. 1981; Kremer et al. 1999; Laue et al. 1995; Reiter and Norjavaara 2005; Egli et al. 1985). The hormonal profile is characterized by elevated serum levels of testosterone, despite prepubertal basal and GnRH-stimulated LH levels. Normal adrenal precursors and undetectable serum β-hCG should exclude adrenal abnormalities and hCG-producing germ-cell tumors, respectively, in these boys. Testosterone levels can widely range and very high testosterone levels have been reported (>1000 ng/dL)

Table 10.2 Schedule of Recommended Health Surveillance for KS

Areas of specialty or evaluation	Birth–4 years11 months	5 years–9 years 11 months	10–18 years	>18 years
Chromosome testing	Confirm prenatal	Post-natal diagnosis		
Parent/family counseling	Annual	Annual	Annual	Annual
Developmental exam	Annual	Annual	Annual	as needed
Neuropsychology		Initial to biannual	Initial to biannual	Initial to biannual
Endocrinology	Infancy and/or genital anomalies	Annual Beginning at 8 years Peri-pubertal consult	Annual Pubertal progression HRT and bone Sexuality	Semiannual to annual HRT and bone Sexuality
Educational and behavioral psychology and social cognition assessment	as needed	as needed	as needed	as needed
Psychiatry		as needed	as needed	as needed
Urology/fertility	as needed or for urogenital anomalies	as needed or for urogenital anomalies	as needed	as needed
Speech and language	Initial and annual	as needed	as needed	
Occupational therapy	Initial and annual	as needed	as needed	as needed
Physical therapy	as needed	as needed	as needed	as needed
Social work	as needed	as needed	as needed	as needed
Immunology	as needed	as needed	as needed	as needed
Pulmonology	as needed	as needed	as needed	as needed
Neurology	as needed	as needed	as needed	as needed
Sleep apnea			as needed	as needed
Cardiovascular			as needed	as needed

HRT hormone replacement therapy
Reprinted with permission from Pediatric Endocrinology Review (Close et al. 2017)

(Egli et al. 1985). Interestingly, family members with the same mutation may present with phenotypes of variable severity (Laue et al. 1995).

Notably, activating mutations in the LHCG receptor do not cause hyperandrogenism, polycystic ovary syndrome, or reproductive abnormality in women. The lack of clinical manifestations in female carriers suggests that ovarian function is dependent of the activation of both LH and FSH receptors (Eunice et al. 2009).

The LH receptor (LHCGR) is a G protein-coupled receptor with a large amino-terminal extracellular domain, seven-membrane traversing α-helices, and carboxyl-terminal intracellular domain (Themmen and Huhtaniemi 2000; Macedo et al. 2016). The *LHCGR* gene, located on chromosome 2p21, contains 11 exons. Although the reported mutations in familial and sporadic cases had a genetic heterogeneity, they were usually sited in exon 11 of the *LHCGR* gene (Themmen and Huhtaniemi 2000). The p.Asp578Gly mutation in the sixth transmembrane domain has been the most frequent LH receptor alteration. All mutations identified in boys with testotoxicosis were in the heterozygous status, except one (p.Ala568Val), which was caused by maternal isodisomy (Laue et al. 1995; Macedo et al. 2016). However, the clinical and hormonal features of the affected boy with this homozygous mutation were similar with those previously reported. Activating mutations in *LHCGR* have been characterized by a constitutive activity, leading to increased production of c-AMP due to activation of adenylate cyclase (Themmen and Huhtaniemi 2000). Interestingly, a somatic activating mutation (p.Asp578His) of the *LHCGR* has been identified in boys displaying Leydig cell tumors. Concomitant activation of phospholipase C and adenylate cyclase has been proposed as a mechanism determining tumorigenicity in Leydig cell (Liu et al. 1999).

Table 10.3 Clinical, hormonal, and genetic criteria for testotoxicosis

Clinical criterion	
Pubertal development	Progressive and rapid virilization before 4 years of age. Possible family history of precocious puberty
Testicular size	Symmetric and minimally increased (> 2.5 cm or 4 mL)
Growth velocity	Accelerated (> 6 cm per year)
Bone age	Advanced (at least 1 year)
Hormonal criterion	
Testosterone (ng/dL)	Elevated (widely range)
Basal LH (UI/L)	Prepubertal range
LH peak after GnRH or GnRH agonist (UI/L)	Suppressed or blunted
Serum β-hCG (UI/L)	Undetectable
Adrenal androgen precursors	Normal
Genetic criterion	
Gene analysis	Activating mutation of LH receptor gene

10.3.1 Treatment of Testotoxicosis

Treatment typically consists of reducing hyperandrogenism in boys with testotoxicosis with ketoconazole or a combination of anti-androgens and aromatase inhibitors. Long-term treatment with both therapies resulted in similar outcomes and limited efficacy in attaining normal adult height (Almeida et al. 2008). Central precocious puberty typically follows over time, requiring the addition of a GnRH analog (Macedo et al. 2016). After the maturation of hypothalamic-pituitary-testicular axis, normal adult function appears to range from normal paternity to reduced testicular volume or oligospermia (Egli et al. 1985). Untreated boys can present behavioral disturbance and short adult height due to premature closure of the epiphyses (Almeida et al. 2008).

Case Study

A 2.6-year-old boy had penile enlargement, frequent erections, accelerated growth velocity, deepening voice, and aggressive behavior. His height was 115 cm (6 standard deviation (SD)) and weight was 24.3 kg. Penile length was 10.3 cm, testicular size was 2.0 × 1.0 cm^2 at right and 2.0 × 1.0 cm^2 at left, and pubic hair was Tanner stage 4. Bone age (BA) was advanced, 6.0 years. His basal testosterone levels ranged from 1.5 to 40 nmol/L (prepubertal range: <1.0 nmol/L). Basal serum LH and FSH levels were both undetectable. Additionally, a GnRH stimulation test (gonadorelin 0.1 mg, intravenous) indicated suppressed LH and FSH levels (LH < 0.6 IU/L and FSH < 1.0 IU/L) at all-time points. He was treated with cyproterone acetate and aromatase inhibitor (anastrozol 1 mg/day). At the end of treatment, his chronological age was 9.3 years, BA was 16 years, and his height was 158 cm (4 SD).

10.4 Nursing Role

10.4.1 Complexity of Care for Patients Diagnosed with Klinefelter Syndrome or Testotoxicosis

Care for infants, boys, and adolescents diagnosed with 47,XXY or testotoxicosis is best accomplished by building and working with an interprofessional team that may include advanced practice nursing, developmental pediatrics, neuropsychology, endocrinology, urology, psychiatry, psychology, speech and language (47,XXY), occupational therapy, and physical therapy (47,XXY) (Tartaglia et al. 2015). Whether under the auspices of one institution, or by referral to local or regional specialists, the integration and coordination of care is best accomplished by the APRN. As nurses, we see the child and his health care needs within the context of himself, his diagnosis, his family, school, community, and the greater world. To provide patient- and family-centered care, we must be mindful of needs, desires, preferences, and resources available to provide the best care according to the child's developmental status and his developmental trajectory. Patients and families often seek a roadmap to anticipate physical, neurocognitive, and psychosocial needs as children grow. The APRN is called upon to help them navigate this path.

Table 10.4 Web Resources for Information About Klinefelter Syndrome

Resource	Contact information
Association of X and Y variations (AXYS)	www.genetic.org
Genetic Alliance	www.geneticalliance.org
eXtraordinarY Kids Clinic University of Colorado Denver Children's Hospital Denver, CO	www.childrenscolorado.org/conditions/behavior/xychromosome.aspx
eXtraordinarY Kids Clinic Nemours/Alfred DuPont Hospital Wilmington, DE	http://www.nemours.org/about/mediaroom/press/dv/introduces-extraordinary-kids-clinic.html
eXtraordinarY Clinic Emory Health Care Division of Pediatric Genetics Atlanta, GA	https://genetics.emory.edu/patient-care/index.html
Johns Hopkins Klinefelter Syndrome Center Johns Hopkins Medical Center Baltimore, MD	http://klinefelter.jhu.edu
NORD National Association for Rare Disorders	www.rarediseases.org
National Institutes of Health Genetics Home Reference Klinefelter Syndrome	https://ghr.nlm.nih.gov/condition/klinefelter-syndrome

Since endocrinology is a central point of care for boys with 47,XXY or testotoxicosis, the endocrinology APRN is perfectly positioned to assess, monitor, and provide consistent customized treatment plans and support for patients and families. When patients and families first receive the diagnosis of 47,XXY or testotoxicosis they are often stunned, confused, and left to their own devices to probe and learn as much as they can. Much information probing is conducted from Internet-based resources and on social media. The APRN may be most effective during a clinical visit by first assessing major concerns of the patient and family and addressing them systematically with complexity of care in mind. While the Internet is rich with good and poor information, the APRN can be instrumental in guiding patients and families toward information that is up-to-date and reliable. (For 47,XXY several helpful resources can be found in Table 10.4). The National Advocacy Association for X & Y Chromosome Variations known as "AXYS" has formed a Clinical and Research Consortium composed of medical centers interested in developing regional multidisciplinary care for patients and families. The website for this organization and current regional clinics may also be found in Table 10.4. Patient- and family-centered care is the hallmark of practice for APRNs. Our knowledge, accessibility, and willingness to navigate complex patterns of care contributes greatly to achieving best clinical outcomes for patients and families affected by 47,XXY.

10.5 Conclusions

KS and testotoxicosis (familial male precocious puberty) are complex genetic conditions that require careful assessment and follow-up across the lifespan. Beginning in childhood, patient and family-centered care requires navigation by a multidisciplinary team that includes APRNs. Since alterations in hormone levels alone does not account for many characteristics associated with KS or testotoxicosis, the role of APRNs is to help patients and families navigate the process of securing physical, neurocognitive, and psychosocial assessments that will meet targeted needs for each patient. APRNs in endocrinology practice

are perfectly positioned to assess, coordinate, and provide family-centered navigation for health surveillance according to each child's level of development.

References

Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn. 1997;17(4):363–8.

Almeida MQ, Brito VN, Lins TS, Guerra-Junior G, de Castro M. Antonini SR, et al. ong-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clin Endocrinol. 2008;69(1):93–8.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.

Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP, et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol. 2012;119(5):890–901.

Boada R, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. Dev Disabil Res Rev. 2009;15(4):284–94.

Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab. 2003;88(2):622–6.

Close S, Fennoy I, Smaldone A, Reame N. Phenotype and adverse quality of life in boys with Klinefelter syndrome. J Pediatr. 2015;167(3):650–7.

Close S, Talboy A, Fennoy I. Complexities of care in Klinefelter syndrome: an APRN perspective. Pediatr Endocrinol Rev. 2017;14(Suppl 2):462–71.

Egli CA, Rosenthal SM, Grumbach MM, Montalvo JM, Gondos B. Pituitary gonadotropin-independent male-limited autosomal dominant sexual precocity in nine generations: familial testotoxicosis. J Pediatr. 1985;106(1):33–40.

Eunice M, Philibert P, Kulshreshtha B, Audran F, Paris F, Sultan C, et al. Mother-to-son transmission of a luteinizing hormone receptor activating mutation in a prepubertal child with testotoxicosis. J Pediatr Endocrinol Metab. 2009;22(3):275–9.

Herlihy AS, Halliday JL, Cock ML, McLachlan RI. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. Med J Aust. 2011;194(1):24–8.

Jacobs P, Strong J. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature. 1959;183:302–3.

Jacobs PA, Hassold TJ, Whittington E, Butler G, Collyer S, Keston M, et al. Klinefelter's syndrome: an analysis of the origin of the additional sex chromosome using molecular probes. Ann Hum Genet. 1988;52(Pt 2):93–109.

Klinefelter HF, Reifensten EC, Albright F. Syndrome characterized by gynecomastia, asermatogenesis without a-leydigism and increased secretion of follicle-stimulating hormone. J Endocrinol Metab. 1942;2:615–22.

Kremer H, Martens JW, van Reen M, Verhoef-Post M, Wit JM, Otten BJ, et al. A limited repertoire of mutations of the luteinizing hormone (LH) receptor gene in familial and sporadic patients with male LH-independent precocious puberty. J Clin Endocrinol Metab. 1999;84(3):1136–40.

Lahlou N, Fennoy I, Ross JL, Bouvattier C, Roger M. Clinical and hormonal status of infants with non-mosaic XXY karyotype. Acta Paediatr. 2011;100(6):824–9.

Laue L, Chan WY, Hsueh AJ, Kudo M, Hsu SY, Wu SM, et al. Genetic heterogeneity of constitutively activating mutations of the human luteinizing hormone receptor in familial male-limited precocious puberty. Proc Natl Acad Sci U S A. 1995;92(6):1906–10.

Liu G, Duranteau L, Carel JC, Monroe J, Doyle DA, Shenker A. Leydig-cell tumors caused by an activating mutation of the gene encoding the luteinizing hormone receptor. N Engl J Med. 1999;341(23):1731–6.

Macedo DB, Silveira LF, Bessa DS, Brito VN, Latronico AC. Sexual precocity-genetic bases of central precocious puberty and autonomous gonadal activation. Endocr Dev. 2016;29:50–71.

Nieschlag E. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. Dtsch Arztebl Int. 2013;110(20):347–53.

Paduch DA, Fine RG, Bolyakov A, Kiper J. New concepts in Klinefelter syndrome. Curr Opin Urol. 2008;18(6):621–7.

Reiter WO, Norjavaara E. Testotoxicosis: current viewpoint. Pediatr Endocrinol Rev. 2005;3(2):77–86.

Ross JL, Samango-Sprouse C, Lahlou N, Kowal K, Elder FF, Zinn A. Early androgen deficiency in infants and young boys with 47,XXY Klinefelter syndrome. Horm Res. 2005;64(1):39–45.

Ross JL, Kushner H, Kowal K, Bardsley M, Davis S, Reiss AL, et al. Androgen treatment effects on motor function, cognition, and behavior in boys with Klinefelter syndrome. J Pediatr. 2017;185:193–199.e4.

Samango-Sprouse C, Stapleton EJ, Lawson P, Mitchell F, Sadeghin T, Powell S, et al. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. Am J Med Genet C Semin Med Genet. 2015;169(2):150–7.

Schedewie HK, Reiter EO, Beitins IZ, Seyed S, Wooten VD, Jiminez JF, et al. Testicular leydig cell hyperplasia as a cause of familial sexual precocity. J Clin Endocrinol Metab. 1981;52(2):271–8.

Styne D, Puberty GM. Ontogeny, neuroendocrinology, physiology and disorders. In: Kronenberg H, Melmed A, Polonsky K, Larsen P, editors. Williams textbook of endocrinology. Philadelphia, PA: Saunders; 2015. p. 13.

Tartaglia N, Cordeiro L, Howell S, Wilson R, Janusz J. The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). Pediatr Endocrinol Rev. 2010;8(Suppl 1):151–9.

Tartaglia N, Howell S, Wilson R, Janusz J, Boada R, Martin S, et al. The eXtraordinarY Kids Clinic: an interdisciplinary model of care for children and adolescents with sex chromosome aneuploidy. J Multidiscip Healthc. 2015;8:323–34.

Tartaglia NR, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S, et al. Autism spectrum disorder in males with sex chromosome aneuploidy: XXY/Klinefelter syndrome, XYY, and XXYY. J Dev Behav Pediatr. 2017;38(3):197–207.

Themmen APN, Huhtaniemi IT. Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. Endocr Rev. 2000;21(5):551–83.

van Rijn S, Stockmann L, Borghgraef M, Bruining H, van Ravenswaaij-Arts C, Govaerts L, et al. The social behavioral phenotype in boys and girls with an extra X chromosome (Klinefelter syndrome and Trisomy X): a comparison with autism spectrum disorder. J Autism Dev Disord. 2014a;44(2):310–20.

van Rijn S, Stockmann L, van Buggenhout G, van Ravenswaaij-Arts C, Swaab H. Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: a comparison with autism spectrum disorder. Genes Brain Behav. 2014b;13(5):459–67.

Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E. X-chromosome inactivation patterns and androgen receptor functionality influence phenotype and social characteristics as well as pharmacogenetics of testosterone therapy in Klinefelter patients. J Clin Endocrinol Metab. 2004;89(12):6208–17.

McCune–Albright Syndrome

11

Beth Brillante and Lori Guthrie

Contents

11.1 **Introduction** 209

11.2 **McCune–Albright Syndrome: Mutation Effect on Embryonic Development** 209

11.3 **MAS: Diagnostic Criteria, Differential Diagnosis, and Clinical Characteristics** 210
11.3.1 Differential Diagnosis 211
11.3.2 Clinical Characteristics: Bone, Skin, and Endocrine Abnormalities 211
11.3.3 Clinical Outcomes Associated with FD 213

11.4 **Integumentary System: Cafe-Au-Lait Macules** 215

11.5 **Endocrine System: Endocrinopathies** 216
11.5.1 Gonadal Abnormalities 216
11.5.2 Thyroid Abnormalities 216
11.5.3 Pituitary Gland Abnormalities 217
11.5.4 Adrenal Abnormalities 217

11.6 **Other Manifestations** 217
11.6.1 Renal Effect 217
11.6.2 Less Common Manifestations 217

11.7 **Age of Diagnosis** 218
11.7.1 Infancy Presentation 218
11.7.2 Childhood Presentation 218
11.7.3 Adulthood Presentation 219

11.8 **MAS: Diagnostic Methods** 219
11.8.1 Physical Exam and Medical History 219
11.8.2 Laboratory Tests 220
11.8.3 Radiographic Imaging and Nuclear Medicine Bone Scans 220
11.8.4 Additional Diagnostic Workup Based on Clinical Findings 221

B. Brillante (✉) · L. Guthrie
National Institutes of Health, National Institute of Dental and Craniofacial Research, Skeletal Disorders and Mineral Homeostasis Section, Bethesda, MD, USA
e-mail: bbrillante@mail.nih.gov; guthriel@mail.nih.gov

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_11

11.9 **MAS: Management and Treatment** 222
11.9.1 Café-Au-Lait Macules: Management 222
11.9.2 Fibrous Dysplasia: Management and Treatment 222
11.9.3 FD: Preventative and Therapeutic Measures 223
11.9.4 FD: Surgical Management 223
11.9.5 FD: Pain Management 224
11.9.6 Endocrinopathies: Management and Treatment 224
11.9.7 Phosphate Wasting: Management and Treatment 224

11.10 **Psychosocial Considerations of FD/MAS: Management and Treatment** 225
11.10.1 Parental Considerations 225
11.10.2 Genetic Education 225
11.10.3 Adjustment/Management of MAS 225

11.11 **Conclusions** 225

References 226

Abstract

McCune–Albright syndrome (MAS) is a rare, non-hereditable genetic disorder classically defined by a clinical presentation of bone (fibrous dysplasia), skin (café-au-lait macules), and/or endocrine abnormalities. Sporadic occurrence of an activating mutation in the *GNAS* gene creates a mosaic tissue environment marked with normal and mutated cells. Mutation effect is variable with ability to cause significant disruption to various organs. Bone abnormalities include deformities and fractures, which may lead to pain, disability, and immobility. Visible irregularly shaped skin markings may be large and pronounced. Hyperfunctioning endocrinopathies pose challenges to normal growth, development, and function. Individual presentation is unique in extent and severity with a range from mild, barely recognizable symptoms to severe, disfiguring disease. MAS commonly presents in childhood with a fracture or endocrine abnormality, which leads to a diagnosis. Individual variation drives the need for medical and nursing care that is centered on an accurate diagnosis. Management and treatment of bone and endocrine disease enhances and promotes patient well-being and optimal physical functioning. Despite the complexity and challenges, the majority of individuals affected appear to be psychologically well adjusted and live productive lives (Kelly et al., Bone 37(3):388–394; 2005).

Keywords

McCune–Albright syndrome · Gsα mutation
Fibrous dysplasia · Endocrinopathy (ies)
Café-au-lait macules

Abbreviations

CF	Craniofacial
FD	Fibrous dysplasia
GHX	Growth hormone excess
GNAS	Guanine nucleotide binding protein alpha stimulating activity polypeptide
MAS	McCune–Albright syndrome
NTX	N-telopeptide
OTC	Over-the-Counter
PP	Precocious puberty

Key Terms

- ***GNAS* activating mutation:** Genetic mutation resulting in abnormal version of the G protein, which causes the Gsα pathway to be constantly turned on, leading to overproduction of hormones or increased cell proliferation that results in abnormal cell differentiation and malfunction.
- **Fibrous dysplasia:** Skeletal disorder where normal bone and bone marrow is replaced with fibrous or connective tissue that may

result in pain, misshapen bone, functional impairment, and fractures.
- **Café-au-lait macules:** light hyperpigmented (light or dark brown) skin lesions.

Key Points
- McCune–Albright syndrome (MAS) is a rare, complex, non-hereditary genetic disorder.
- MAS is characterized by the presence of two or more abnormalities of the bone (fibrous dysplasia), skin (café-au-lait), endocrine (endocrinopathies), and/or more rarely, other systems.
- Individual variation drives the need for medical and nursing intervention that is centered on an accurate diagnosis and appreciation of the spectrum of the disease.
- Optimal individual well-being and physical functioning is achievable through individualized management and treatment plans focused on bone, endocrine, and other abnormalities.
- Most individuals with MAS adjust psychologically well to their disease and lead productive lives.

11.1 Introduction

McCune–Albright syndrome is a rare non-hereditary genetic disorder affecting approximately 1/100,000 to 1/1,000,000 individuals worldwide (Dumitrescu and Collins 2008). Diagnosis most often occurs in childhood and is classically defined by a clinical presentation of simultaneously occurring bone, skin, and/or endocrine features (Weinstein et al. 1991). Due to the random nature and sporadic rise of a *GNAS* (guanine nucleotide binding protein alpha stimulating activity polypeptide) mutation, clinical manifestations are dependent on the specific tissues affected and the extent of tissue involvement (Collins et al. 2013). Individual presentation is unique. Prognosis and clinical management is based on location and severity of disease.

The syndrome was first described in the medical literature by Donovan McCune (1936) and Fuller Albright et al. (1937). Both reported an unusual syndrome in females characterized by three distinguishing features: irregular pigmentations of the skin; symptoms of precocious puberty (PP); and bone abnormalities with bowing, fractures, and deformities. Since these initial reports a broader scope of the syndrome has emerged. In contrast to what was originally postulated, MAS affects males equally as much as females and features associated with the syndrome are more extensive than previously reported (Collins et al. 2013; Collins 2006; Collins and Shenker 1999). Due to the unique clinical presentation, a thorough clinical assessment coupled with a comprehensive evaluation and individualized approach to treatment/management is required.

11.2 McCune–Albright Syndrome: Mutation Effect on Embryonic Development

MAS is the result of a postzygotic somatic mutation (Dumitrescu and Collins 2008). There is no identified cause for this non-heritable mutation which occurs randomly in the general population (Riminucci et al. 2007). Genetic changes are caused by an activating mutation of the gene *GNAS* (Weinstein et al. 1991). Specifically, the Gsα, which is responsible for cellular development/function, is affected. Gsα serves as the "on/off" switch for cell activity and proliferation for tissues including the bone, skin, pituitary, thyroid, and gonadal organs. In MAS, the Gsα pathway is constantly turned on leading to overproduction of hormones, or increased cell proliferation and resulting in abnormal cell differentiation and malfunction. Tissue effect is sporadic, dependent upon when the mutation occurs during embryogenesis.

In normal human embryogenesis, growth and development originate as a single stem cell. This single cell proceeds through an orderly process of differentiation to form three germ layers known as the ectoderm (outer), endoderm (inner), and

mesoderm (middle). The ectoderm and endoderm form first followed by the mesoderm. Each layer has a predetermined role in the development of specific tissues that emerge into mature organs. Examples of tissue development for each layer are provided in Table 11.1.

A generally accepted model of pathogenesis proposes that once a mutation occurs within a stem cell the mutated cell is carried through the normal process of differentiation creating various alterations in cellular development along the way. Figure 11.1 illustrates this effect in MAS.

Table 11.1 Germ layer tissue development

Germ layer	Examples of tissue development
Ectoderm	Epidermis, pituitary gland, adrenal medulla, jaw
Mesoderm	Bone, reproductive organs, adrenal cortex
Endoderm	Thymus, thyroid, parathyroid glands, digestive tract, liver, pancreas, epithelial lining of respiratory, excretory and reproductive organs

Adapted from Tortora and Derrickson (2017)

MAS mutations may cause abnormalities in any or all tissues under the influence of Gsα (Weinstein et al. 1991; Weinstein and Shenker 1993; Shenker et al. 1993). Commonly affected include bone, skin, pituitary, thyroid, and gonadal organs. Mutations occurring early in development have the potential for significant disruption to all three layers, therefore affecting multiple tissues (widespread disease). Mutations emerging later in development establish limited disease. Germline *GNAS* mutations are believed to result in neonatal lethality (Happle 1986).

11.3 MAS: Diagnostic Criteria, Differential Diagnosis, and Clinical Characteristics

Diagnosis is clinical, based on the presence of any combination of ***two or more*** of the following: skeletal (fibrous dysplasia), skin (café-au-lait macules), and endocrine abnormalities (Collins and Shenker 1999). Diagnostic imaging

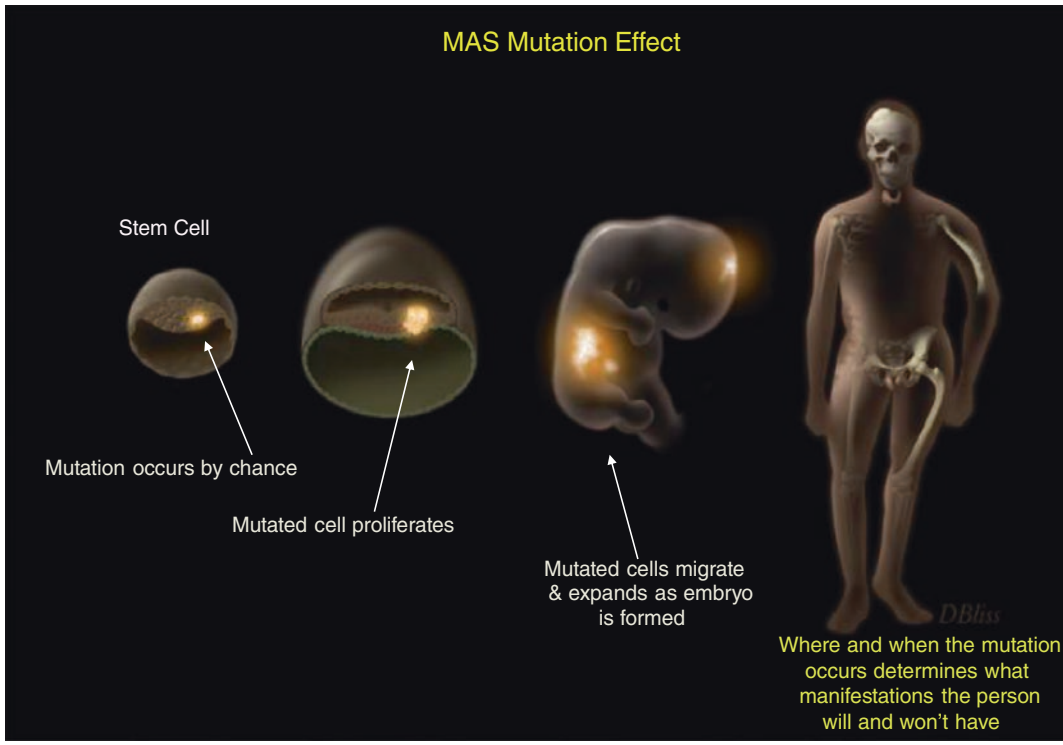


Fig. 11.1 MAS mutation effect (Dumitrescu and Collins 2008)

can also be used to diagnose and/or confirm FD or endocrine findings. Histological (i.e., biopsy) testing of *GNAS* may confirm a diagnosis but is not required. Genetic tests for mutation detection exist but are not routinely available; reliability of these tests depends on the degree of tissue mosaicism and sensitivity of technique (Agopiantz et al. 2016). Genetic testing is not required to establish a diagnosis, but may be useful when there is clinical uncertainty.

11.3.1 Differential Diagnosis

Differential diagnosis includes:

- Neurofibromatosis type I
- Osteofibrous dysplasia
- Non-ossifying fibromas
- Idiopathic central precocious puberty
- Osteogenesis imperfecta
- Ovarian neoplasm
- Cherubism

11.3.2 Clinical Characteristics: Bone, Skin, and Endocrine Abnormalities

Individuals usually present with at least two out of the three characteristics of bone, skin, and/or endocrine abnormalities. Bone lesions are the most common finding followed by café-au-lait macules, and endocrinopathies (Collins et al. 2012). Less common other manifestations include renal, liver, and pancreatic abnormalities but are not part of the diagnostic criteria (Agopiantz et al. 2016). Manifestations of the syndrome are usually evident by 5 years of age, but occasionally the diagnosis is made later in life. Understanding the clinical characteristics of MAS is important for diagnosis, management, and treatment.

11.3.2.1 Skeletal System: Fibrous Dysplasia

11.3.2.1.1 Characteristics and Features

Fibrous dysplasia (FD) is characterized by benign, scar-like (fibrotic) lesions in the bone. Excess activation of Gsα generates an increased production and clustering of immature bone cells which limit hematopoietic cell action within the bone marrow (Riminucci et al. 2007). This process forms a weak abnormal fibrotic lesion that replaces normal bone. Due to poor infrastructure, these lesions are unable to provide optimal bone support or function which leads to weakness, deformities, and breaks. Clinical morbidities include fractures, disabilities, limps, and pain.

FD lesions do not usually present clinically or radiographically at birth (Boyce and Collins 2015). Diagnosis of FD in infancy is rare except in severely affected individuals with deformities or fractures. Within the first few years of life, FD lesions become more apparent due to bone expansion during linear growth in childhood. Lesion expansion is progressive through adolescence with a typical slowing into adulthood (Boyce and Collins 2015). The extent of FD disease can usually be determined by the age of 10 years, with no new clinically significant lesions emerging after the age of 15 years (Leet and Collins 2007). The one skeletal exception may be rib involvement (Kelly et al. 2008).

The timing of the mutation during embryogenesis dictates which bones are affected, the number of bones affected, and the extent of disease in affected bones. FD lesions may form in any one or all the bones of the human skeleton (Robinson et al. 2016). Lesions may occur in one bone (monostotic), multiple bones (polyostotic), or nearly every bone in the body (panostotic).

Clinical (physical exam) and radiologic evaluations are the most common methods of diagnosis of FD (Boyce and Collins 2015). Skeletal X-ray images best capture clinically evident lesions, whereas bone scans (99TcMDP or Sodium Fluoride (NaF)) best capture lesions that are not clinically obvious. In individuals age 6 and above, an initial bone scan is recommended to determine the extent of bone disease (Stanton et al. 2012). In children under age 6, radiographs may be used to determine extent of bone disease. A bone biopsy of a lesion may be done in cases where a diagnosis cannot be determined; however, it is not required for an FD diagnosis (Stanton et al. 2012). Figure 11.2 illustrates examples of FD bone disease on radiographic imaging (a, b, c, d) and bone

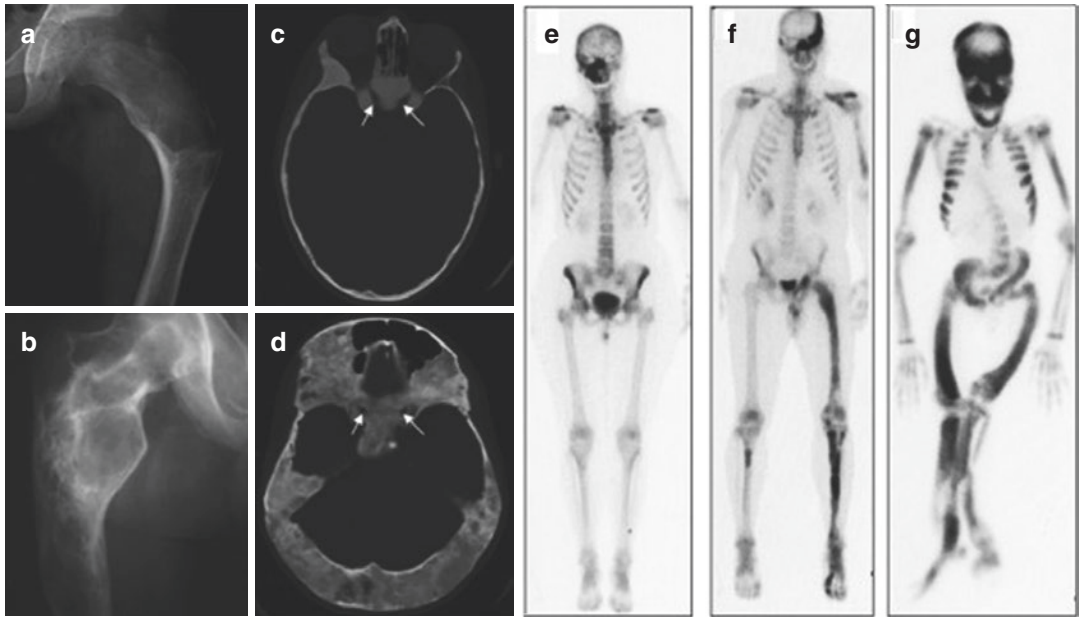


Fig. 11.2 FD bone disease on radiographic and nuclear medicine imaging, (Dumitrescu and Collins 2008)

scan images of three individuals with varying degrees of FD ((e) mild, (f) moderate, (g) severe), FD lesions appear as dark areas in the bones.

Identification of the specific bone(s) to which FD lesion(s) are present is important to establish and predict functional and mechanical effects. The most commonly affected are the skull and facial bones (~85%), pelvic (~57%), and femur (~56%) (Kelly et al. 2008). Skeletal bones are often classified together regionally as appendicular, axial, or craniofacial. Individuals may have lesions in one, two, or three of these areas. Important differences in FD features and characteristics exist for these regions.

11.3.2.2 Appendicular Fibrous Dysplasia

Appendicular lesions are found in the shoulder, pelvic, and long bones (i.e., arms, legs) of the skeleton. On physical exam, these bones may appear normal, especially in infants and young children. However, as the child grows, the bones may become more distorted with changes in contour and width size. On radiographs, appendicular lesions appear in the bone shaft as lytic or ground glass circumscribed lesions surrounded by a very thin bone cortex (Boyce and Collins 2015). Appendicular lesions expand within the bone cortex but do not cross out of the bone into other tissues (Hart et al. 2007). Expansion within the bone cortex may become quite large. Progressively through the age spectrum these lesions change in appearance becoming more sclerotic possibly due to slowing of bone activity (Boyce and Collins 2015; Leet and Collins 2007; Hart et al. 2007). Complications that arise from these lesions result in leg length discrepancies, deformities, and fractures (Leet et al. 2004).

11.3.2.3 Axial Fibrous Dysplasia

Axial lesions are located in the sternum, spine, and ribs. On radiographs they appear as cystic lesions within the bone cortex; they do not expand out of the bone (Collins et al. 2013). Lesions in the spine are a common finding (~63%) with scoliosis being the most significant clinical complication (Leet et al. 2004). Rib fractures with pain are common in adulthood (Kelly et al. 2008).

11.3.2.4 Craniofacial Fibrous Dysplasia

Craniofacial (CF) lesions are located in the skull, face, and/or jawbones. They are dense and hard

fibrous tissue (Collins 2006). Initially these lesions present as small lumps or bumps on the head, cheekbone, or jaw bone. In infants, CF FD lesions may not be detected on exam; however, with growth they may become more evident. CF lesions are best characterized on computed tomography (CT) appearing as homogeneous ground glass tissue with expansile features (Lee et al. 2012). On radiographs they appear as sclerotic lesions (Akintoye et al. 2003). These lesions have the potential to expand and compress vital structures, most critically the cranial nerves (Lee et al. 2002; Cutler et al. 2006). Most complications that occur with CF FD are related to bone expansion. Fortunately, in the majority of individuals with optic nerve encasement, CF FD disease appears to remain stable without progressive optic neuropathy (Cutler et al. 2006). Unlike appendicular lesions, CF lesions may continue to progress through adulthood (Collins 2006).

11.3.3 Clinical Outcomes Associated with FD

11.3.3.1 Bone Pain

Bone pain is a common feature reported in up to 67% of the FD population (Kelly et al. 2008). Pain related to FD is hard to predict, is not well understood and does not directly correlate with the number of bone lesions or extent of disease (Kelly et al. 2008). The etiology of pain may be due to the lesion itself, fracture, phosphate wasting, or hypophosphatemia (Boyce and Collins 2015). Pain perception is individualized. Some individuals do not report bone pain and in those that do report pain, intensity varies from mild to severe. Children with FD report bone pain less frequently (49%) than adults (81%) (Kelly et al. 2008; Chapurlat et al. 2012). In children, FD does not typically present with pain unless associated with a fracture. Pain appears to become a more significant consequence starting in late adolescence. In adults FD bone pain is more likely, with lower extremity, rib, and spinal pain as the most common sites (Kelly et al. 2008). Headaches associated with CF FD appear to emerge in late adolescence and early adulthood, especially in patients with growth hormone excess (GHX) (Kelly et al. 2005).

11.3.3.2 Fractures

Pathologic fractures are a common feature of FD. Appendicular bones are the most common sites of fracture, with femoral fractures occurring most frequently in childhood. Long bone fractures most often occur between the ages of 6 and 10 years of age with a slowing into adulthood (Leet et al. 2004). Rib fractures occur frequently in adults but rarely occur in children (Hart et al. 2007). Individuals with hypophosphatemia are at higher risk for fractures (Leet et al. 2004). Fractures of the skull are rare.

11.3.3.3 Clinical Morbidities Associated with Fibrous Dysplasia

Alteration in normal bone growth causes clinical morbidities. In the appendicular bones, leg length discrepancy may become obvious during growth and is usually a sign of bone disease progression (Stanton et al. 2012). FD lesions located in the proximal femur frequently cause weakness, bowing, and changes to the femoral neck shaft angle, which results in two commonly known deformities: (1) Shepherd Crook deformity occurs when the femoral head of the bone bows outward as shown in Fig. 11.3a. (2) Windswept deformity occurs when the femur head bows inward, as shown in Fig. 11.3b.

FD lesions in the spine may lead to scoliosis with varying degrees of deformity. The prevalence rate of scoliosis is estimated at 40–52% (Leet et al. 2004). Respiratory compromise due to collapse of spine may occur which has led to death in few cases (Mancini et al. 2009). CF lesions initially appear as facial asymmetry with a small population progressing to disfigurement (Collins et al. 2013; Boyce and Collins 2015; Kelly et al. 2008; Lee et al. 2012). CF FD may also cause narrowing of the auditory canal, deformities of the jaw and cranial area, dentition changes, and facial deformities (Lee et al. 2012). A very small subset of individuals is at risk for partial or complete blindness or hearing loss due to compression of the cranial nerves (Lee et al. 2002; Boyce et al. 2013a). These risks are particularly significant in the setting of untreated GHX.

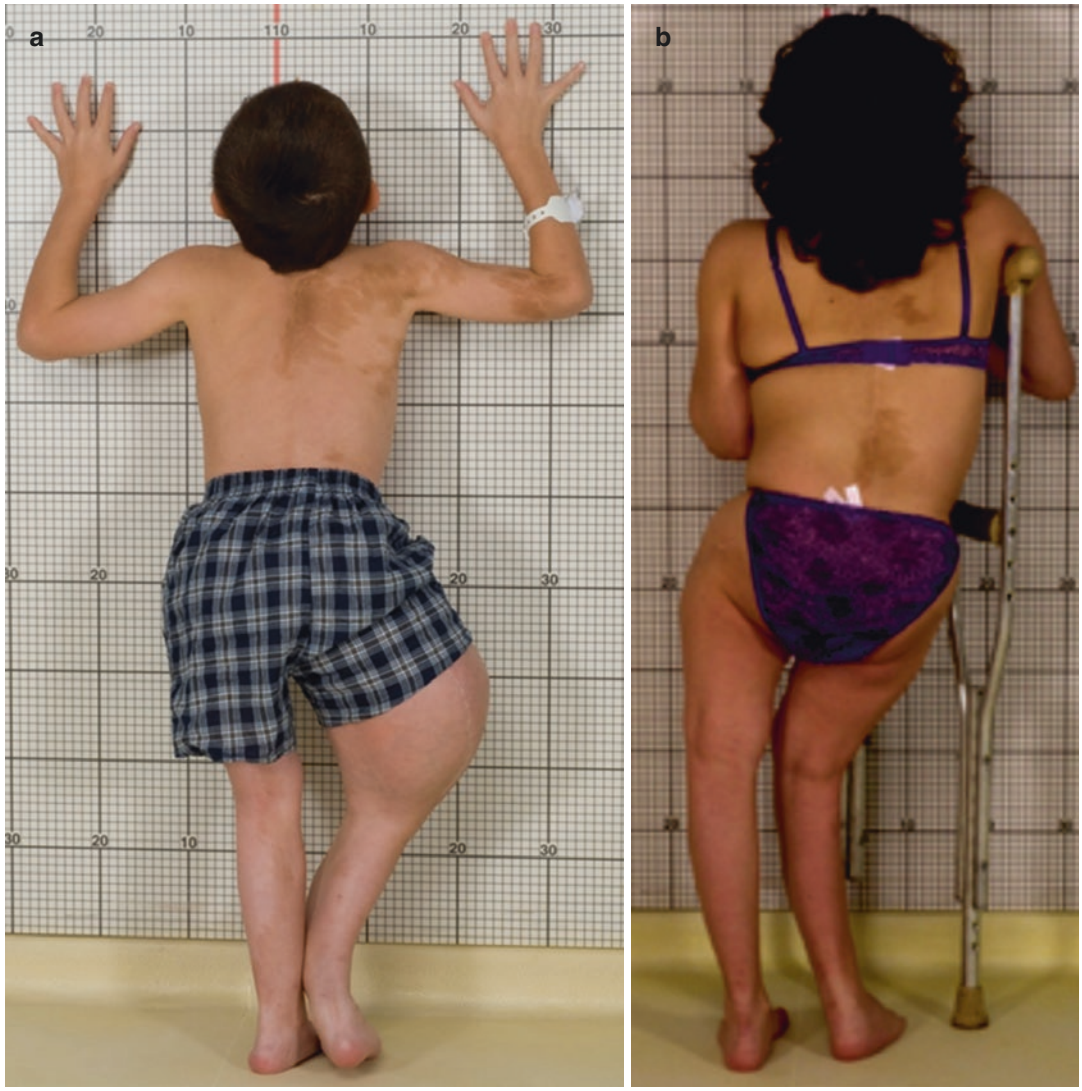


Fig. 11.3 (**a**) Shepherd Crook. (**b**) Windswept deformity. Copyright permission received from ENDOTEXT

11.3.3.4 Aneurysmal Bone Cysts

On occasion a rapidly expanding fluid-filled cyst known as an aneurysmal bone cyst forms in FD bone, often in the skull or long bones. Symptoms are acute with rapid onset of pain, increased size and deformity of bone. Aneurysmal bone cysts carry the potential for severe morbidity related to expansion into neighboring tissues. Although rare, there have been reports of sudden blindness due to a rapidly expanding skull cyst compressing the optic nerve (Lee et al. 2002, 2012). Aneurysmal bone cysts are considered emergent and should be followed with immediate MRI and evaluation by a surgeon (Lee et al. 2012).

11.3.3.5 Psychosocial Impact on Quality of Life

FD is a complex bone disorder with the potential to affect physical as well as social aspects of life. Social and emotional functioning were studied and correlated to individual skeletal disease in a large FD population by Kelly et al. (2005). The data show that adult and children with FD report high levels of self-esteem and social func-

tion despite impaired physical function. Quality of life (QOL) parameters were equivalent to the normal (United States) population despite low physical scores, suggesting that individuals adapt well to their disease. Social data from the study indicates that affected individuals succeed at all levels of education and employment and perceive themselves as leading meaningful, productive lives (Kelly et al. 2005).

11.4 Integumentary System: Cafe-Au-Lait Macules

The Gsα mutation effect on the integumentary system results in the formation of light brown skin spots referred to as café-au-lait macules. These spots can also be identified by their irregularly shaped jagged borders, which bear resemblance to topographical areas of the United States (i.e., "the coast of Maine"). Café-au-lait macules are not unique to MAS and are a very common finding among the general population.

Café-au-lait macules are present at birth and may be the first symptom in the diagnosis of MAS. However, some macules may be small, faint, or not easily visible, and can be missed on early assessment. These macules are uniquely individual with a wide variation in color, size, shape, and anatomical location. Macules frequently appear to start or end at a midpoint on the body. Some spots expand unilaterally down the body while others wrap entirely around the torso. Figure 11.4 illustrates the wide range in presentation of MAS-associated café-au-lait macules. Even though café-au-lait lesions are commonly located on the same side as bone involvement, skin and bone involvement do not necessarily correlate (Collins et al. 2012; Boyce and Collins 2015).

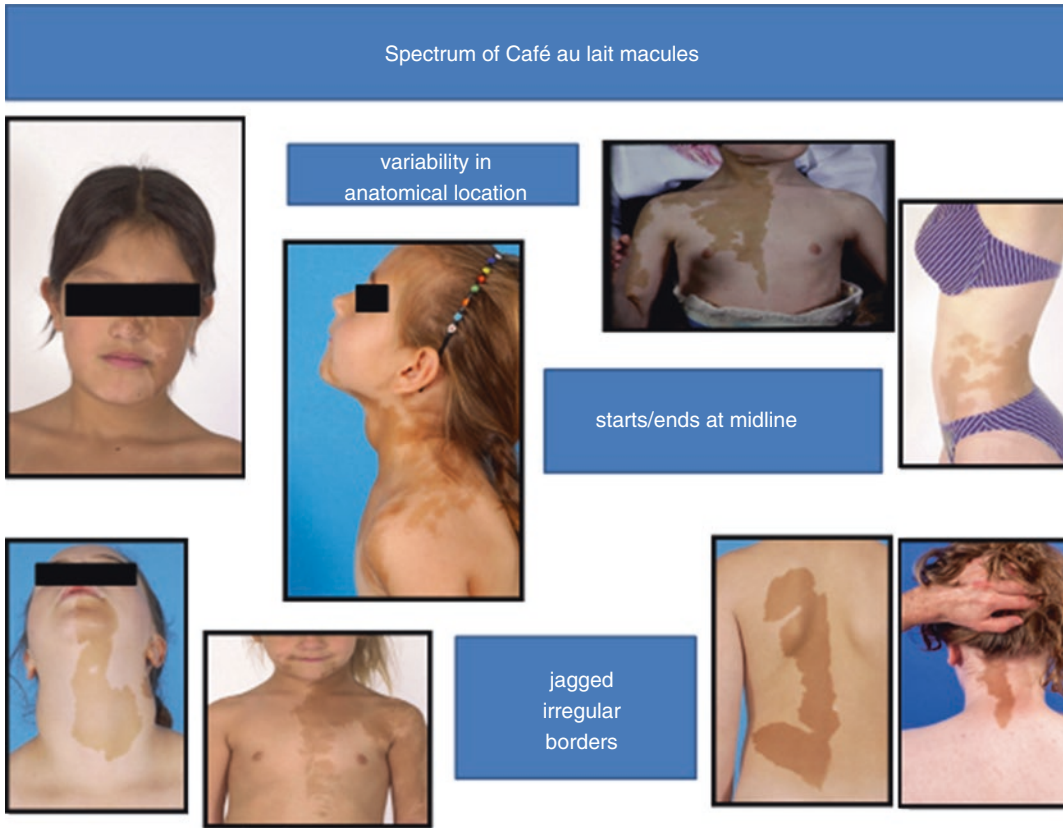


Fig. 11.4 Spectrum of Café-au-lait Macules (Leet and Collins 2007; Dumitrescu and Collins 2008; Collins et al. 2012)

11.5 Endocrine System: Endocrinopathies

Dysfunction of endocrine tissue is the result of altered signal transduction pathways responsible for regulating endocrine cell functions and bodily hormones. Overproduction of hormones alters the intrinsic pathways causing deleterious effects to organs. Any or all endocrine organs may be affected. Individuals may present with one or multiple endocrinopathies.

11.5.1 Gonadal Abnormalities

Gonadal abnormalities are common. Gonadotropin-independent precocious puberty arises from early activation of the gonads in both males and females. PP occurs in ~ 85% of the girls and ~10–15% of the boys with MAS (Boyce and Collins 2015). Manifestations of PP occur before age 8 in girls and before age 9 in boys.

In girls, intermittent autonomous activation of ovarian tissue produces high serum estradiol levels resulting in early vaginal bleeding, breast development and/or (recurrent) ovarian cysts (Boyce and Collins 2015; Foster et al. 1986). PP is often the first clinical symptom of MAS in infants and young girls. Symptoms such as vaginal bleeding, rapid breast development, and abdominal pain (ovarian pain) are usually concerning to the child and parents and often get the attention of a clinician.

In boys, autonomous testosterone production results in increased growth of testicles and/or penis, early sexual behavior/aggression, and/or growth of pubic and axillary hair. PP in boys sometimes goes undetected. Untreated PP in both males and females results in increased growth velocity and bone age advancement leading to a reduced final adult height. Occasionally a child with peripheral PP (with or without adequate treatment) will later develop central PP due to the early activation of the pituitary gland.

Gonadal involvement occurs at an approximate equal rate in both males and females (Boyce et al. 2012; Akintoye et al. 2013). Adult women may experience menstrual irregularities with or without recurrent ovarian cysts (Foster et al. 1986). Ultrasounds of the ovaries often show benign ovarian cysts. Erratic functioning of ovaries may cause a delay in fertility for some women (Boyce and Collins 2015). Most women with MAS can become pregnant, maintain a viable pregnancy, and produce healthy offspring.

In adult males, testicular lesions interspersed with hyperplasia of the Leydig/sertoli cells (gonadal tissue) are commonly observed on ultrasound (Boyce et al. 2012). These lesions are not normally visible or palpable on exam and do not cause symptoms. Lesions may be associated with gonadotropin-independent PP and should be clinically correlated. Testicular lesions are usually benign; however, there have been rare cases that have emerged as malignant (Boyce et al. 2012).

11.5.2 Thyroid Abnormalities

Thyroid abnormalities include clinical hyperthyroidism (with and without goiter) and abnormal thyroid tissue with cysts and nodules. Hyperthyroidism occurs in approximately one-third of the population (Boyce and Collins 2015). The mutation causes sustained hypersecretion of thyroid hormones with cellular proliferation (Feuillan et al. 1990). Diagnosis of hyperthyroidism prior to the age of 5 is rare and primarily subclinical. Hyperthyroidism becomes more evident after the age of 5 but may remain undetected until laboratory tests or ultrasounds are performed to confirm disease (Boyce and Collins 2015). Young children rarely exhibit signs of hyperthyroidism. In older children and adults, common symptoms of hyperthyroidism include goiter, weight loss, sweating, nervousness, anxiety, and fatigue. Persistent hyperthyroidism is common and many individuals will eventually require a thyroidectomy (Boyce and Collins 2015).

Thyroid cysts and/or nodules observed on ultrasound (with or without hyperthyroidism) occur in approximately 54% of the MAS population (Boyce and Collins 2015). Measurement of serum thyroid levels should be performed to cor-

relate thyroid function with ultrasound findings. Lesions appearing in the absence of hyperthyroidism are rarely symptomatic. There is slight risk of thyroid cancer in the MAS population therefore periodic follow-up with examination, laboratory tests, and ultrasound should be performed in the setting of abnormal ultrasound findings (Collins et al. 2003).

11.5.3 Pituitary Gland Abnormalities

Growth hormone excess occurs less frequently (~10–15%) than other endocrinopathies (Boyce and Collins 2015). Mutation effect results in unregulated production of excess growth hormone by the pituitary gland (Akintoye et al. 2002). Presentation is subtle, typically with subclinical findings until the age 7. The main symptoms include accelerated bone growth exhibited by increased height; significant increase in bone growth of the hands, feet, and head; and/or excessive sweating. Radiographic images may reveal "tufting" of fingers or toes. In the absence of clinical symptoms, diagnosis is based on laboratory and overnight serum growth hormone testing.

Untreated GHX in children may result in gigantism due to accelerated growth of the long bones before closure of growth plate. Individuals with GHX are at higher risk for certain morbidities due to the rapidly expanding and thickening bone. CF bone is most susceptible to GHX often causing asymmetry of the face with widened facial bones of the forehead, nose, and jaw. Thickened jaw bones may cause loosening of teeth and changes to dentition (Lee et al. 2012). In rare cases, rapid expansion in bone growth may cause impingement of cranial nerves, causing blindness and/or diminished hearing (Lee et al. 2012; Akintoye et al. 2002). Individuals with MAS and GHX are also at risk for hypertension and high cardiac output due the higher bone burden, which taxes the cardiovascular system (Collins et al. 2012). Rarely a benign pituitary tumor may be detected. In these cases, surgery is recommended which is typically curative (Boyce and Collins 2015).

11.5.4 Adrenal Abnormalities

Cushing's syndrome (neonatal hypercortisolism) is a rare complication of MAS and occurs almost exclusively during the first year of life. It is the result of bilateral autonomous neonatal adrenal hyperfunction caused by the Gsα mutation (Brown et al. 2010). Adrenal tissue manifests with diffuse nodular hyperplasia and cortical atrophy (Carney et al. 2011). Symptoms may be subtle to include moon or rounded face, low birth weight, and abnormal weight gain, especially in the face and trunk. Diabetes and hyperlipidemia may be present. Infants with Cushing's syndrome can become severely ill with the risk of death. Approximately half of MAS related cushing's syndrome cases have spontaneously resolved on their own (Boyce and Collins 2015).

11.6 Other Manifestations

11.6.1 Renal Effect

Phosphate wasting by the kidneys is a prevalent finding in up to 50% of the population, especially those with significant bone disease (Collins et al. 2001, 2012; Riminucci et al. 2003). The MAS mutation causes overproduction of fibroblast growth factor-23 (FGF23), a hormone responsible for regulating phosphorus in the kidneys (Riminucci et al. 2003). Increased levels of FGF23 trigger the kidney(s) to release extra phosphorus into the urine. This effect signals the bones to release additional phosphorus to the kidney. Constant recurrence of this cycle leads to osteomalacia/rickets of the bone (Robinson et al. 2016). Phosphate wasting may or may not lead to hypophosphatemia. Symptoms of phosphate wasting include bone pain, muscle weakness, and increased fractures (Boyce et al. 2013b).

11.6.2 Less Common Manifestations

Less common manifestations have been reported in the literature. These include various abnormal-

Table 11.2 Less common manifestations

Organ system	Manifestations
Liver	Hepatitis (infancy) and hepatic adenomas (Parvanescu et al. 2014)
Gastrointestinal	Gastroesophageal tract abnormalities (Wood et al. 2017) Gastrointestinal polyps (Zacharin et al. 2011)
Pancreas	Pancreatitis, intraductal papillary mucinous neoplasms (Gaujoux et al. 2014; Parvanescu et al. 2014; Wood et al. 2017)
Muscle	Intramuscular myxomas (Biazzo et al. 2017)

Adapted from Boyce and Collins (2015)

ities of the liver, gastrointestinal tract, pancreas, and musculature. Table 11.2 summarizes these findings.

Although rare, malignancies have been reported in association with MAS to include bone (Ruggieri et al. 1995), thyroid (Collins et al. 2003), testicle (Boyce et al. 2012), and breast (Majoor et al. 2018).

11.7 Age of Diagnosis

Diagnosis may occur anytime throughout the lifespan and is based on manifestations of the disease.

11.7.1 Infancy Presentation

Diagnosis shortly after birth is possible based on the presence of café-au-lait macules, Cushing's syndrome, and/or early vaginal bleeding. In females, early vaginal bleeding may be the first and only presenting symptom.

Case Scenario 1
A 12-month female presents with bloody discharge in her diaper. Physical exam findings include increased growth velocity of 14–15 cm per year (>95%), Tanner stage 2 breasts, and a large, light brown irregular bordered macule on posterior neck and chest. Bone age is advanced 2 years from chronological age.

Nursing Assessment: What MAS manifestations does this infant have? Would you anticipate further workup? If so, what other manifestations would you be looking for? What type of education would you provide to the family?

11.7.2 Childhood Presentation

Childhood is the most common time for diagnosis. Rapid growth coupled with high levels of physical activity contributes to identification of symptoms. Incidental findings of FD are commonly found on X-rays and/or other images. Bone features leading to diagnosis include abnormal gait with limp, signs of leg length discrepancy, and scoliosis. Pain is a rare first finding in children, however if present, imaging should be done to rule out fractures and/or any other bone abnormalities. Other findings include those related to endocrinopathies. PP with bleeding and/or breast development is often the first signs in girls. Attention should be made in children with accelerated growth which may indicate GHX, PP, or hyperthyroidism.

Case Scenario 2
A 7-year-old boy presents with a left femur mid-shaft fracture obtained while playing soccer. Radiographs show the fracture at the site of a bony lesion is described as "ground glass." Physical exam reveals two light brown jagged edged birthmarks near the crease of his buttocks that respect the midline and an increased testicular volume. Endocrine testing reveals high testosterone levels. Bone scan and X-rays show numerous, bilateral bone lesions in extremities and the skull; bone age is advanced by 3 years.

Nursing Assessment: What MAS manifestations does this child have? What germ layers would you predict were affected in embryogenesis? Which manifestations require follow-up?

Case Scenario 3
A 10-year-old girl presents to the emergency department with complaints of sudden decreased

vision in one eye. The ER physician notes some mild facial asymmetry. An MRI shows an extensive bony lesion surrounding the right orbit and a fluid-filled cyst compressing the right optic nerve. An ophthalmology exam reveals a pale optic disk. Uncorrected vision shows 20/500 vision on the right with normal vision on the left. Further evaluation reveals a small brown skin macule and tall stature. Routine bloodwork is normal.

Nursing Asssessment: Does this child meet the criteria for diagnosis of MAS? Why? If so, what manifestations does she exhibit? What manifestation would be the most critical to manage and how? What other endocrinopathy/ies should be ruled out?

11.7.3 Adulthood Presentation

Diagnosis of MAS in adulthood occurs mostly as the result of symptoms related to FD including fractures, pain, or an incidental finding on imaging. Initial findings of endocrine abnormalities are rare, but possible (e.g., thyroid).

11.8 MAS: Diagnostic Methods

A comprehensive initial evaluation should be done to establish a diagnosis and to determine the facets of disease. This should include a physical exam with medical history, blood and urine laboratory tests, and diagnostic imaging. Additional evaluations are required based on specific clinical findings.

11.8.1 Physical Exam and Medical History

A detailed clinical history coupled with a thorough physical exam are critical diagnostic tools in the establishment of a MAS diagnosis. In children, Tanner staging should be performed in addition to height, weight, and bone age on X-ray (captured on a growth chart). Common findings are indicated below.

Box 11.1 Physical Exam/Medical History

Manifestation	Common findings
BONE	• Limp or abnormal patterns of walking • Asymmetric overgrowth or deformity of bone(s) • Decreased vision or hearing • Decreased activities of daily living (ability) • Pain (note location and severity) • Growth chart—accelerated growth with bone age advancement
SKIN ENDOCRINE	• Variable size lesions, brown in color with jagged, irregular borders
Precocious puberty	• Advanced growth velocity • Advanced bone age • Short or tall stature • Reduced predicted final adult height • Advanced Tanner staging • **(Girls)** presence (or history) of vaginal bleeding, breast development, pubic hair • **(Boys)** pubic and axillary hair, increased testicular/penis size for age, early sexual behavior/aggression
Growth hormone excess	• Tall stature for age • Rapid increase in height • Enlarged hands and feet • Widened or expanded cranial/facial bones • Bone age advancement • Sweating
Hyperthyroidism	• Palpable nodules • Goiter • Accelerated growth on growth chart • Bone age advancement • Symptoms of hyperthyroidism
Cushing's syndrome	• Moon/round face • Low birth weight
OTHER	• Abnormal weight gain
Liver	• Symptoms of hepatitis (jaundice, etc.)
Gastrointestinal	• Complaints of gastroesophageal reflux • Pain
Pancreatitis	• Symptoms of pancreatitis
Myxomas	• Palpable mass in muscle

11.8.2 Laboratory Tests

Perform to assess general health, bone and endocrine abnormalities.

Box 11.2 Laboratory Tests

Test	Common results/rationale
Blood tests	
Routine (CBC, PT/PTT, chemistries)	• Hematological values within normal range • High alkaline phosphatase due to bone effect • Low phosphorus, calcium, and/or vitamin D if phosphate wasting is present • Abnormal chemistry values consistent with endocrine/bone organ effect (repeat testing or additional testing and/or imaging required) *Note: Not all abnormal laboratory values are indicative of MAS. Values should be correlated with clinical workup*
Endocrine	• Abnormal thyroid results support hyperthyroid diagnosis • Elevated cortisol (with hyperlipidemia) indicates • Cushing's syndrome (neonates/early toddlerhood) • Elevated prolactin suggests pituitary tumor • Elevated luteinizing hormone, follicle stimulating hormone, testosterone, estrogen—perform further clinical workup for GHX and PP *Note: a single elevated GH with elevated IGF-1 requires further testing to determine source of GHX; a single GH value is not conclusive in the diagnosis of GHX*
Overnight serial serum test for hormonal axes (if GHX suspected)	• Non-suppressible GH levels indicate GHX
Bone and mineral blood tests (assess bone turnover, formation, resorption)	• Low ionized calcium with high PTH may indicate secondary hyperparathyroidism due to vitamin D deficiency • High alkaline phosphatase, bone specific alkaline phosphatase (BSAP) and osteocalcin (due to bone disease) *Note: BSAP is specific to bone disease; high BSAP levels indicate extensive bone disease; low BSAP indicate low bone disease*
Urine tests	
Random urine and/or 24-h sample for: • Mineral metabolism (calcium, magnesium, phosphorous) • Cortisol • Bone turnover markers—N-telopeptide (NTX), pyridinoline, and deoxypyridinoline (24 h)	• High-normal levels of phosphate (urine) with low TMP-GFR indicate phosphate wasting • High cortisol levels in 24-h specimen indicate Cushing's syndrome • High bone turnover markers indicative of bone disease

11.8.3 Radiographic Imaging and Nuclear Medicine Bone Scans

Perform to assess bone and endocrine effect.

Box 11.3 Imaging

Test	Rationale	Common findings
Skeletal radiographs (limited or whole body)	Easy, quick, minimal risk	• Appendicular and axial lesions appear ground glass in bone shaft with thin cortex; fractures • Craniofacial lesions appear sclerotic
Bone age (children ≤18 years of age)	Provides bone growth information Provides guidance in the treatment of bone growth and endocrinopathies	• Advanced bone age > 2 years could indicate PP, GHX, hyperthyroidism, pituitary tumor—further workup indicated
99TcMDP or NaF bone scan (≥ 5 years of age)	Determine extent of bone disease	• Increased tracer uptake in bones indicative of FD lesions or other bone abnormalities (fractures)

11.8.4 Additional Diagnostic Workup Based on Clinical Findings

Additional diagnostic workup should be done to characterize the extent of disease. Guidance for specific findings is provided below.

Box 11.4 Additional Diagnostic Workup

Clinical findings	Additional diagnostic/medical testing	Common findings
Craniofacial FD	• Computed tomography (skull)	CF FD lesions appear ground glass Aneurysmal bone cysts Pituitary gland adenomas Cranial nerve compression
	• Ophthalmology, audiology, otolaryngology examination and testing	Cranial nerve compression Narrowing of auditory canal Sinus narrowing/obliterations
	• Dental examination	Dentition and jaw abnormalities
	• Craniofacial surgical exam (if needed)	
Appendicular FD	• Rehabilitation medicine • Physical therapy • Occupational therapy (as needed) • Pain consultation (as needed) • Orthopedic consultation (as needed)	Abnormalities in function and mobility (range-of-motion, activities of daily living, gait)
Scoliosis	• Scoliosis radiographs • Pulmonary function test to assess lung volume/parameters • Rehabilitation medicine evaluation • Orthopedic consultation (as needed)	Lesions in the spine, varying degrees of curve angle Diminished lung volume Abnormalities in gait, posture, function
Rib fractures/rib abnormalities	• Chest radiographs • Bone scan • Rehabilitation medicine evaluation • Pain consultation (as needed)	Rib fractures/abnormal growth Abnormalities in gait, posture, function Rib pain
Growth hormone excess	• Serial blood testing (growth hormone suppression test, growth hormone stimulation test) • MRI pituitary, to identify pituitary adenoma • Echocardiogram to evaluate cardiac output	Increased height and bone age advancement Hands/feet show tufting on imaging GH does not suppress Pituitary adenoma Note: IGF-1 blood test should be used to monitor treatment effect in GHX Abnormal cardiac results
Thyroid disease	• Thyroid ultrasound, if abnormal lab tests/ultrasound	Tissue appears swiss cheese like with cystic and solid lesions embedded in normal tissue
Precocious puberty/ gonadal abnormalities (female)	• Ovarian (bilateral) pelvic ultrasound	Ovarian cysts (recurrent) Large or mature uterus for girls Thickened endometrial tissue *Note: Ultrasound abnormalities may or may not correlate to clinical symptoms*
Precocious puberty/ gonadal abnormalities (male)	• Testicular (bilateral) ultrasound	Hyperechoic and hypoechoic lesions interspersed with hyperplastic testicular tissue *Note: Ultrasound abnormalities may or may not correlate to clinical symptoms*

(continued)

Box 11.4 (continued)

Clinical findings	Additional diagnostic/medical testing	Common findings
Cushing's syndrome	• 24-h urine collection for free cortisol • Low-dose dexamethasone suppression test (measures AM serum level) • Diurnal serum or salivary cortisol test • Additional tests to determine the source of tumor (pituitary or adrenal): – ACTH blood test – MRI (pituitary) – CT (adrenals)	High cortisol levels
Pancreatic abnormalities	Laboratory tests	Elevated amylase + lipase
	MRI abdomen/MRCP with contrast	Pancreatic pathology
Gastrointestinal abnormalities	Endoscopy/colonoscopy	Gastroesophageal reflux Polyps

11.9 MAS: Management and Treatment

MAS is a complex disorder with many manifestations. There is no treatment or cure for MAS. Clinical intervention requires a multidisciplinary team experienced in endocrine, orthopedics, pain management, and rehabilitation. After the initial evaluation, clinical evaluations should occur at regular intervals to assess, manage, and treat manifestations.

In children, a comprehensive yearly evaluation with repeat testing related to diagnosed or suspected bone and/or endocrine disease is recommended (Boyce and Collins 2015; Stanton et al. 2012). Attention to CF FD, GHX, and/or scoliosis should be made due to the high risk for morbidities; frequent interval consultations with appropriate specialists are prudent. Into adolescence and adulthood, gonadal and thyroid abnormalities warrant frequent (1–2 year) imaging for progression of disease and possibility of malignancy, which is rare (Boyce and Collins 2015). Those with GHX should be monitored frequently for changes in vision, hearing, and/or cardiovascular issues. Successful management of symptoms may be achieved through established therapies, treatments, and/or surgeries which enhance overall well-being, improve physical function, and ameliorate clinical symptoms. Management and treatment is based on presenting manifestations.

11.9.1 Café-Au-Lait Macules: Management

There is no cure or treatment for café-au-lait macules. Methods to diminish lesion color and size have not been effective (Collins et al. 2012). Cosmetic makeup may help to temporarily diminish lesion color.

11.9.2 Fibrous Dysplasia: Management and Treatment

There are no proven medical treatments and/or therapies that eradicate or alter FD lesions. Management efforts are focused on optimizing physical function while minimizing morbidities. In the absence of pain, fracture, or deformity, frequent clinical observation with interval radiograph imaging is sufficient for the management of FD bone disease over time (Stanton et al. 2012). Bone scans (≥ age 6) may be repeated in 3–5 year intervals to monitor bone disease throughout childhood (Stanton et al. 2012). Into adulthood repeat bone scan images may not be needed if disease is stable. Throughout the life spectrum, CF and axial FD lesion progression are best followed by radiographs and conservative use of CT imaging.

11.9.3 FD: Preventative and Therapeutic Measures

Early identification of bone involvement is the key to understanding the effect of the disease on bone. With knowledge of bone location and extent of disease, functional impact is better anticipated and predicted to identify preventative measures aimed at lowering overall morbidity.

Prophylactic non-weight bearing activities is ***not recommended*** in the absence of pain, fractures, or deformities (Stanton et al. 2012). Active, natural, low risk movement based on individual ability should be encouraged and optimized by all. Routine muscle conditioning and strengthening is also important for bone support (Paul et al. 2014). Individuals should be encouraged to participate in activities with low risk of injury to bones such as swimming or stationary biking to avoid fractures and other injuries (Paul et al. 2014). Those with moderate or severe appendicular and/or axial FD should be instructed to minimize or eliminate contact sports and other high-risk activities (e.g., horseback riding, skiing).

Individuals with appendicular and axial FD should be evaluated by rehabilitation medicine as early as possible to assess overall function and mobility. Those with appendicular FD are at risk for limb length discrepancies, deformities, and fracture. Those with spinal FD are at risk for progression of scoliosis. Routine physical therapy can minimize pain and enhance mobility (Paul et al. 2014). Physical therapists should develop individualized plans to include exercises for proper movement and form as well as those to increase muscle strength. Dependent on the involved bone(s), equipment such as canes, walkers, and wheelchairs may be recommended as preventative or therapeutic measures for individuals with lower extremity disease (Paul et al. 2014). Physical supports such as customized orthotics or shoe lifts can easily correct leg length differences or assist with hip/pelvis malalignment (Paul et al. 2014). In addition to physical therapy, individuals may benefit from a consultation with an occupational therapist if FD disease interferes with their ability to carry out functions of daily living and/or performance in a job or school. Nurses can encourage and assist individuals in finding accessory aids and developing functional plans to meet their specific needs to achieve optimal function.

11.9.4 FD: Surgical Management

11.9.4.1 Appendicular FD

In the setting of fractures and/or deformities, surgical intervention is required (Stanton et al. 2012). Surgical intervention is challenging and should be performed by a surgeon experienced working with FD bone. Traditional orthopedic techniques such as bone grafting and curettage of FD lesions have proven ineffective due to regeneration and regrowth of dysplastic bone lesion (Boyce and Collins 2015). Similarly, standard screws and plates have been found ineffective due to the soft consistency of the FD bone (Leet and Collins 2007; Stanton et al. 2012). External fixation devices and bracing have also proven ineffective (Boyce and Collins 2015). Closed management systems such as casting and conventional surgical procedures have proven suitable for limited situations of FD including non-weight bearing upper limb lesions as well as monostotic lesions located in other bones (Stanton et al. 2012). Treatment with these modalities warrants careful clinical monitoring to ensure proper alignment of the newly formed dysplastic bone.

Internal fixation devices, specifically intramedullary (IM) devices, have been shown to be the most effective as corrective surgical treatment particularly for weight bearing bones, as these devices provide additional support to strengthen the weakened bone (Stanton et al. 2012). In individuals with upper limb weight bearing ability (i.e., crutches), internal fixation is useful. Despite surgical corrective measures, recurrent fractures and deformities of the surgically corrected bones may still occur requiring individuals to have multiple surgeries.

11.9.4.2 Axial FD

Progression of scoliosis can be stopped by surgical fusion in effort to prevent morbid outcomes (Stanton and Diamond 2007).

11.9.4.3 CF FD

Surgical management of CF FD is often difficult due to lesion location and expansile features. In the setting of CF FD, a craniofacial surgeon with expertise in FD should be consulted prior to surgery. In most instances, FD lesions cannot be fully excised, there is a 68% probability of regrowth of partially resected lesions (Boyce et al. 2016). In individuals with GHX, regrowth incidence increases to 88% (Boyce et al. 2016). The most common indication for surgery is debulking of bone. Other indications include the removal of aneurysmal bone cysts and correction of jaw malformations. Optic canal encasement, a common feature, should be conservatively managed as the risk of blindness from surgery is high (Cutler et al. 2006; Lee et al. 2002). The benefits of CF surgery should be carefully measured against the potential outcomes of surgery.

11.9.5 FD: Pain Management

There is no medical treatment or therapy that permanently eradicates FD bone pain. Several treatments are effective in managing pain including non-pharmaceutical and pharmaceutical options. Non-pharmaceutical therapies include the use of heat, gentle massage, acupuncture, and biofeedback. Pharmaceutical treatments include the use of over-the-counter (OTC) pain relievers, bisphosphonates, and narcotic medications. OTC pain relievers such as acetaminophen, ibuprofen, and naproxen are the most commonly used and the most effective treatment for mild to moderate FD bone pain (Kelly et al. 2008). OTC pain relievers may also be combined with non-pharmaceutical therapies to enhance pain relief.

For severe pain, intravenous (IV) bisphosphonates such as pamidronate or zoledronate can be used for pain relief in the appendicular and axial skeleton. The pharmacological action of bisphosphonates is aimed at reducing bone turnover and has been proven effective in reducing bone pain (Boyce et al. 2014). One dose of IV bisphosphonate provides a longer duration of pain relief than OTCs with effects usually lasting several months. Bisphosphonate intervals should be scheduled based on pain (Boyce 2000). There are a few significant side effects of IV bisphosphonate treatment. A common first administration reaction may occur resulting in a "flu-like" reaction with chills, fever, and general ill-feeling. To avoid this reaction, individuals should be pre-medicated with a non-steroidal anti-inflammatory drug (NSAID) treatment before the first administration. Most individuals tolerate repeat IV bisphosphonate therapy without reaction. A long-term serious side effect of this drug class is osteonecrosis of the jaw. The incidence of development of osteonecrosis of the jaw in the FD population is unknown but appears infrequent (Boyce and Collins 2015). Individuals should have a thorough dental hygiene exam to address any dental abnormalities (i.e., cavities, extractions, root canal) before starting treatment and should be monitored routinely while receiving therapy. If OTC pain relievers and bisphosphonates are not effective, narcotic medications may be considered as a last option. A pain consultant should be sought in these cases.

11.9.6 Endocrinopathies: Management and Treatment

The goal of treatment is to control hormone overproduction and minimize target organ effects. Treatment for endocrinopathies should be individualized based on organ involvement. Standard medical treatment can ameliorate and/or manage endocrinopathies associated with MAS.

11.9.7 Phosphate Wasting: Management and Treatment

The goal of treatment is to control phosphorus retention by the kidney. Treatment includes the use of oral phosphate supplement and active vitamin D (Boyce et al. 2013b).

11.10 Psychosocial Considerations of FD/MAS: Management and Treatment

11.10.1 Parental Considerations

A significant finding among parents with children diagnosed with FD/MAS is that they suffer more emotionally than the child himself, and more emotionally than parents without a chronic illness (Kelly et al. 2005). These parental reactions are like those observed in parents with children that have similar other chronic illnesses (i.e., asthma or rheumatoid arthritis). Parental reactions may be of concern, fear, worry, and/or a sense of being overwhelmed. Nurses should make every effort to reassure parents that despite physical impairments children and adults with MAS appear to adjust and cope well with their medical condition. Individuals with MAS have been shown to be fully capable of succeeding in education and employment (Kelly et al. 2005). Factual information should be provided to child and family. Discussions related to bone and endocrine disease should emphasize a realistic prognosis highlighting appropriate supports, medical management plans, and treatment. Parents should be empowered to become advocates for their child. Families should be encouraged to connect with local, regional, and international FD and MAS support groups.

11.10.2 Genetic Education

Parents should be educated and reassured that MAS is non-heritable; there are no instances of vertical transmission of MAS (Happle 1986; Boyce and Collins 2015; Boyce 2000). Emphasis should be made that neither parent passed the mutation onto the child. Parents should be informed that siblings have the same probability of acquiring MAS as the general public (Boyce and Collins 2015; Boyce 2000). Individuals with MAS should be reassured that the mutation cannot be passed on to the offspring of an affected individual.

11.10.3 Adjustment/Management of MAS

MAS is a complex disorder. Understanding the various facets and management of disease may be a challenge for parents as well as individuals. Clinicians should provide clear instructions as well as rationale for diagnoses, tests, evaluations, and therapies/treatments. Written information for both the parent and child (age appropriate) should be provided. Parents and children (age appropriate) should be involved in the decision-making and should be encouraged to keep copies of their medical records at home.

For individuals with moderate-severe FD, a change in physical activity may be warranted. Clinical recommendation may include having a child change his current activity from high impact (i.e., soccer) to low impact (i.e., swimming). In some individuals, preventative measures may require assistive equipment including wheelchair, crutch, or cane use. In both situations, parents may have difficulty psychologically adjusting to this change, even more so than the child (Kelly et al. 2005). Despite the psychological difficulty, parents should be supported and strongly encouraged to move toward these changes to avoid future physical complications for their child. Nurses can play an active role in providing recommendations for activities based on the child's and parent's interest. Physical activity, even with supports, should be encouraged within the individual's ability.

11.11 Conclusions

MAS is a complicated disease that may present a complex clinical picture to those not familiar with the syndrome. Due to the multiple facets of the disease, individual presentation is unique; no two individuals present with the same clinical features. Individual prognosis is contingent upon an early accurate diagnosis followed by long-term management. Diagnosis is dependent upon identification of the clinical signs and symptoms related to fibrous dysplasia, café-au-lait macules,

and endocrinopathies, particularly in infancy and childhood. A comprehensive initial evaluation should include detailed assessments, evaluations, laboratory tests, and radiologic imaging to define the manifestations of the disease. Long-term management involves routine interval follow-up for identified endocrine or bone abnormalities. Clinical interventions are aimed at minimizing potential adverse outcomes related to bone and endocrine disease. Management of fibrous dysplasia includes therapies for pain control coupled with surgical and rehabilitation interventions. Management of endocrinopathies is accomplished with standard medical therapies and surgical interventions. Even though adults and children with MAS appear well adjusted and live productive lives, parents of children with MAS are emotionally affected by the disease and may need additional support. Successful management of the disease is possible with medical and nursing care which is individually tailored.

References

Agopiantz M, Journeau P, Lebon-Labich B, Sorlin A, Cuny T, Weryha G, et al. McCune-Albright syndrome, natural history and multidisciplinary management in a series of 14 pediatric cases. Ann Endocrinol. 2016;77(1):7–13.

Akintoye SO, Chebli C, Booher S, Feuillan P, Kushner H, Leroith D, et al. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. J Clin Endocrinol Metab. 2002;87(11):5104–12.

Akintoye SO, Lee JS, Feimster T, Booher S, Brahim J, Kingman A, et al. Dental characteristics of fibrous dysplasia and McCune-Albright syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(3):275–82.

Akintoye SO, Boyce AM, Collins MT. Dental perspectives in fibrous dysplasia and McCune–Albright syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(3):149–55.

Albright FBA, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction with precocious puberty in females: report of 5 cases. N Engl J Med. 1937;216:727–46.

Biazzo A, Di Bernardo A, Parafioriti A, Confalonieri N. Mazabraud syndrome associated with McCune-Albright syndrome: a case report and review of the literature. Acta Biomed. 2017;88(2):198–200.

Boyce AM. Fibrous dysplasia. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. Endotext. South Dartmouth, MA: MDText.com; 2000.

Boyce AM, Collins MT. Fibrous dysplasia/McCune HYP Albright syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReview. Seattle, WA: University of Washington; 2015.

Boyce AM, Chong WH, Shawker TH, Pinto PA, Linehan WM, Bhattacharryya N, et al. Characterization and management of testicular pathology in McCune-Albright syndrome. J Clin Endocrinol Metab. 2012;97(9):E1782–90.

Boyce AM, Glover M, Kelly MH, Brillante BA, Butman JA, Fitzgibbon EJ, et al. Optic neuropathy in McCune-Albright syndrome: effects of early diagnosis and treatment of growth hormone excess. J Clin Endocrinol Metab. 2013a;98(1):E126–34.

Boyce AM, Bhattacharyya N, Collins MT. Fibrous dysplasia and fibroblast growth factor-23 regulation. Curr Osteoporos Rep. 2013b;11(2):65–71.

Boyce AM, Kelly MH, Brillante BA, Kushner H, Wientroub S, Riminucci M, et al. A randomized, double blind, placebo-controlled trial of alendronate treatment for fibrous dysplasia of bone. J Clin Endocrinol Metab. 2014;99(11):4133–40.

Boyce AM, Burke A, Cutler Peck C, DuFresne CR, Lee JS, Collins MT. Surgical management of polyostotic craniofacial fibrous dysplasia: long-term outcomes and predictors for postoperative regrowth. Plast Reconstr Surg. 2016;137(6):1833–9.

Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab. 2010;95(4):1508–15.

Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011;35(9):1311–26.

Chapurlat R, Gensburger D, Jimenez-Andrade J, Ghilardi J, Kelly MH, Mantyh P. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7:S3.

Collins MT. Spectrum and natural history of fibrous dysplasia of bone. J Bone Miner Res. 2006;21(Suppl 2):99–104.

Collins MT, Shenker A. McCune HYP Albright syndrome: new insights. Curr Opin Endocrinol Diabetes. 1999;6:119–25.

Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res. 2001;16(5):806–13.

Collins MT, Sarlis NJ, Merino MJ, Monroe J, Crawford SE, Krakoff JA, et al. Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations. J Clin Endocrinol Metab. 2003;88(9):4413–7.

Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7(Suppl 1):S4.

Collins MT, Riminucci M, Bianco P. Fibrous dysplasia. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 8th ed. Ames, IA: Wiley-Blackwell; 2013. p. 786–91.

Cutler CM, Lee JS, Butman JA, FitzGibbon EJ, Kelly MH, Brillante B, et al. Long-term outcome of optic nerve encasement and optic nerve decompression in patients with fibrous dysplasia: risk factors for blindness and safety of observation. Neurosurgery. 2006;59(5):1011–7.

Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet J Rare Dis. 2008;3:12.

Feuillan P, Shawker T, Rose S, Jones J, Jeevanram RK, Nisula BC. Thyroid abnormalities in the McCune-Albright syndrome: ultrasonography and hormonal studies. J Clin Endocrinol Metab. 1990;71(6):1596–601.

Foster CM, Feuillan P, Padmanabhan V, Pescovitz OH, Beitins IZ, Comite F, et al. Ovarian function in girls with McCune-Albright syndrome. Pediatr Res. 1986;20(9):859–63.

Gaujoux S, Salenave S, Ronot M, Rangheard AS, Cros J, Belghiti J, et al. Hepatobiliary and pancreatic neoplasms in patients with McCune-Albright syndrome. J Clin Endocrinol Metab. 2014;99(1):E97–101.

Happle R. The McCune HYP Albright syndrome: a lethal gene suviving by mosaicism. Clin Genet. 1986;29(4):321–4.

Hart ES, Kelly MH, Brillante B, Chen CC, Ziran N, Lee JS, et al. Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. J Bone Miner Res. 2007;22(9):1468–74.

Kelly MH, Brillante B, Kushner H, Gehron Robey P, Collins MT. Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone. Bone. 2005;37(3):388–94.

Kelly MH, Brillante B, Collins MT. Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions. Osteoporos Int. 2008;19(1):57–63.

Lee JS, FitzGibbon E, Butman JA, Dufresne CR, Kushner H, Wientroub S, et al. Normal vision despite narrowing of the optic canal in fibrous dysplasia. N Engl J Med. 2002;347(21):1670–6.

Lee JS, FitzGibbon EJ, Chen YR, Kim HJ, Lustig LR, Akintoye SO, et al. Clinical guidelines for the management of craniofacial fibrous dysplasia. Orphanet J Rare Dis. 2012;7(Suppl 1):S2.

Leet AI, Collins MT. Current approach to fibrous dysplasia of bone and McCune-Albright syndrome. J Child Orthop. 2007;1(1):3–17.

Leet AI, Chebli C, Kushner H, Chen CC, Kelly MH, Brillante BA, et al. Fracture incidence in polyostotic fibrous dysplasia and the McCune-Albright syndrome. J Bone Miner Res. 2004;19(4):571–7.

Majoor BC, Boyce AM, Bovee JV, Smit VT, Collins MT, Cleton-Jansen AM, et al. Increased risk of breast cancer at a young age in women with fibrous dysplasia. J Bone Miner Res. 2018;33(1):84–90.

Mancini F, Corsi A, De Maio F, Riminucci M, Ippolito E. Scoliosis and spine involvement in fibrous dysplasia of bone. Eur Spine J. 2009;18(2):196–202.

McCune DJ. Osteitis fibrosa cystica: the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. Am J Dis Child. 1936;52:743–4.

Parvanescu A, Cros J, Ronot M, Hentic O, Grybek V, Couvelard A, et al. Lessons from McCune-Albright syndrome-associated intraductal papillary mucinous neoplasms: GNAS-activating mutations in pancreatic carcinogenesis. JAMA Surg. 2014;149(8):858–62.

Paul SM, Gabor LR, Rudzinski S, Giovanni D, Boyce AM, Kelly MR, et al. Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia. Bone. 2014;60:41–7.

Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003;112(5):683–92.

Riminucci M, Robey PG, Bianco P. The pathology of fibrous dysplasia and the McCune-Albright syndrome. Pediatr Endocinol Rev. 2007;4(Supplement 4):401–11.

Robinson C, Collins MT, Boyce AM. Fibrous dysplasia/McCune-Albright syndrome: clinical and translational perspectives. Curr Osteoporos Rep. 2016;14(5):178–86.

Ruggieri P, Sim FH, Bond JR, Unni KK. Osteosarcoma in a patient with polyostotic fibrous dysplasia and Albright's syndrome. Orthopedics. 1995;18(1):71–5.

Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. J Pediatr. 1993;123(4):509–18.

Stanton RP, Diamond L. Surgical management of fibrous dysplasia in McCune-Albright syndrome. Pediatr Endocinol Rev. 2007;4(Supplement 4):446–52.

Stanton RP, Ippolito E, Springfield D, Lindaman L, Wientroub S, Leet A. The surgical management of fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7(Suppl 1):S1.

Tortora GJ, Derrickson BH. Principles of anatomy & physiology. 15th ed. New York: Wiley; 2017. p. 658–60. 1107–1126.

Weinstein LS, Shenker A. G protein mutations in human disease. Clin Biochem. 1993;26(5):333–8.

Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med. 1991;325:1688–95.

Wood LD, Noe M, Hackeng W, Brosens LA, Bhaijee F, Debeljak M, et al. Patients with McCune-Albright syndrome have a broad spectrum of abnormalities in

the gastrointestinal tract and pancreas. Virchows Arch. 2017;470(4):391–400.
Zacharin M, Bajpai A, Chow CW, Catto-Smith A, Stratakis C, Wong MW, et al. Gastrointestinal polyps in McCune Albright syndrome. J Med Genet. 2011;48(7):458–61.

Key Reading

1. Boyce AM, Collins MT. Fibrous dysplasia/McCune HYP Albright syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReview. Seattle, WA: University of Washington; 2015.
2. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7(Suppl 1):S4.
3. Chapurlat R, Gensburger D, Jimenez-Andrade J, Ghilardi J, Kelly MH, Mantyh P. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7:S3.
4. Kelly MH, Brillante B, Kushner H, Gehron Robey P, Collins MT. Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone. Bone. 2005;37(3):388–94.
5. Robinson C, Collins MT, Boyce AM. Fibrous dysplasia/McCune-Albright syndrome: clinical and translational perspectives. Curr Osteoporos Rep. 2016;14(5):178.

Part III

Hypothalamus and Pituitary

Christine Yedinak and Judith P. van Eck

Anatomy and Physiology of the Hypothalamic-Piuitary Axis

12

Kathryn Evans Kreider

Contents

12.1 **Introduction** 233
12.1.1 Pituitary Gland Introduction and Gross Anatomy 233

12.2 **Anterior Pituitary** 236
12.2.1 Corticotropin/Adrenocorticotrophic Hormone (ACTH) 237
12.2.2 Thyroid Stimulating Hormone 238
12.2.3 Follicle Stimulating Hormone and Luteinizing Hormone 238
12.2.4 Growth Hormone 238
12.2.5 Prolactin 240
12.2.6 Physiology of the Posterior Lobe 241
12.2.7 Oxytocin 241
12.2.8 Vasopressin 242

12.3 **Nursing Process** 242

12.4 **Conclusions** 243

References 243

Abstract

The pituitary gland is a small gland located in the sella turcica, a cavity in the base of the brain. The pituitary gland measures less than 1 cm and weighs less than 1 g but is responsible for maintaining critical homeostatic functions that sustain life. Almost all of the functions of the pituitary are regulated by input from the hypothalamus, and the two glands are connected through the hypophyseal (pituitary) stalk. The pituitary has 3 lobes—anterior (adenophyophysis), posterior (neurohypophysis), and intermediate (pars intermedia) lobe. The anterior, intermediate, and posterior sections of the pituitary act synergistically and are independently functional, each section producing different hormones and regulatory processes. The anterior pituitary produces six hormones in peptide form, including thyroid stimulating hormone (TSH), corticotropin or adrenocorticotrophic hormone (ACTH), follicle stimulating hormone (FSH), lutenizing hormone (LH), growth hormone (GH), and prolactin (PRL). All of the anterior pituitary hormones except PRL act by

K. E. Kreider (✉)
Duke University School of Nursing and Duke University Medical Center, Durham, NC, USA
e-mail: kathryn.evans@duke.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_12

stimulating other glands to release additional hormones. The release and production of these hormones is controlled through a classic feedback loop. The posterior lobe of the pituitary, also known as the neurohypophysis, secretes oxytocin and anti-diuretic hormone (ADH), also known as vasopressin. Release of the posterior pituitary hormones is regulated by neuronal activity.

Disruption to the pituitary gland may cause dysregulation to hormone production or secretion. The etiology of dysregulation is varied but the majority of dysfunction is related to the presence of a pituitary tumor or adenoma. However, hypopituitarism may be congenital, caused by an unrelated illness, injury and in some cases is the result of treatment for other diseases. Patients may present with a wide range of pathophysiologic symptoms, including bone growth disruption, infertility, galactorrhea, muscle wasting, headaches, fatigue, poor blood pressure homeostasis, or disruption to normal fluid balance. Patients with pituitary diseases often require lifelong treatment and require intense education regarding their disease and treatment, management of comorbidities and psychological support.

Advances in medicine now allow replacement of all pituitary deficiencies so that patients, even with panhypopituitarism, have the potential to lead a full and productive life. Early detection and appropriate medical therapies for all pituitary dysfunctions are critical.

Keywords

Anterior pituitary · Posterior pituitary
Infundibulum · Neurohypophysis · Pituitary hormones

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Anti-diuretic hormone
AP	Anterior pituitary
FSH	Follicle stimulating hormone
GH	Growth hormone
GIH	Growth hormone inhibiting hormone/ somatostatin
GRH	Growth hormone releasing hormone
LH	Luteinizing hormone
POMC	Pro-opiomelanocortin
PP	Posterior pituitary
PRL	Prolactin
TRH	Thyroid releasing hormone
TSH	Thyroid stimulating hormone

Key Terms

- **Hypophyseal-portal circulation**: The circulatory system connecting the hypothalamus and pituitary gland.
- **Anterior pituitary**: The front lobes of the pituitary gland, responsible for secreting TSH, LH, FSH, PRL, GH, and ACTH.
- **Posterior pituitary:** The rear lobes of the pituitary, responsible for producing ADH and oxytocin.
- **Thyroid stimulating hormone**: The hormone responsible for the secretion of free T3 and Free T4, primary regulators of metabolism, cardiovascular function, and growth/development.
- **Adrenocorticotropic hormone:** The hormone responsible for stimulating cortisol production from the adrenal glands.
- **Follicle** stimulating hormone: The hormone responsible for female ovulation and menstruation, as well as male testosterone production.
- **Luteinizing hormone:** A hormone important in regulating ovulation and menstruation in females and spermatogenesis in males.
- **Growth hormone:** A hormone critical for human growth and development, including bone development and remodeling, metabolism, and muscle strength.
- **Prolactin:** A hormone responsible for milk production in pregnant women.
- **Pro-opiomelanocortin**: A precursor glycoprotein that assists in the production of other hormones.
- **Thyroid stimulating hormone:** A hormone regulating the synthesis of T4 and T3 in the thyroid.

- **Thyroid releasing hormone:** The hormone originating in the hypothalamus, triggering the pituitary to release TSH.
- **Vasopressin/Anti-diuretic hormone (ADH):** This hormone is responsible for maintaining fluid homeostasis in the body.
- **Oxytocin:** A hormone that facilitates uterine contractions and delivery.

Key Points

- The pituitary gland measures less than 1 cm and weighs less than 1 g, but is responsible for secreting hormones that maintain critical homeostatic functions to sustain life. As a result, it is commonly referred to as the "master gland."
- Almost all functions of the pituitary are regulated by input from the hypothalamus, and the two glands are connected through the hypophyseal (pituitary) stalk.
- The anterior pituitary (AP), also known as the adenohypophysis, comprises the largest territory of the gland. The anterior pituitary produces six hormones in peptide form, including thyroid stimulating hormone, corticotropin/adrenocorticotrophic hormone, follicle stimulating hormone, lutenizing hormone, growth hormone, and prolactin.
- The posterior lobe of the pituitary, also known as the neurohypophysis, secretes oxytocin and anti-diuretic hormone, also known as vasopressin.
- Disruption of these hormone cascades can cause a variety of pathophysiologic processes including (but not limited to) disorders of growth and development, gonadal and reproductive dysfunction, dysregulation of metabolism, emotional disturbances, fluid imbalance, cardiovascular disorders, and possibly death.

12.1 Introduction

12.1.1 Pituitary Gland Introduction and Gross Anatomy

The pituitary gland is a small gland located in the sella turcica, a cavity in the base of the brain (Fig. 12.1). The pituitary gland measures less than 1 cm (0.4 in.) and weighs less than 1 g (0.03 oz), but is responsible for maintaining critical homeostatic functions that sustain life (Amar and Weiss 2003). Almost all of the functions of the pituitary are regulated by input from the hypothalamus, and the two glands are connected through the infundibulum or the hypophyseal (pituitary) stalk. There are several connections from the hypothalamus to the pituitary, including one from the median eminence, the primary functional link between the two glands. It contains connecting axons and releasing factors which are responsible for hormone production and/or release. Hormone releasing factors are rapidly distributed from the hypothalamus to the pituitary via the hypophyseal-portal circulation, which is derived from the internal carotid arteries and provides blood circulation to the pituitary (Melmed 2017) (Fig. 12.2). The anterior pituitary is the most richly vascularized of all mammalian tissues, receiving approximately 0.8 mL/g/min of blood from the portal system (Amar and Weiss 2003).

The hypothalamic-pituitary axis facilitates signaling between the brain and hormone-secreting target glands through positive and negative feedback responses (Fig. 12.3). These signals sustain end-organ function and the cycle of hormone production and inhibition to support the bodies cycle of hormonal needs. The pituitary gland is controlled by positive feedback from the hypothalamus and negative feedback from end-organ hormone production. The negative feedback system works through self-regulation, whereby, when a released hormone achieves a preset level, either the hormone itself or products of the hormone release will trigger the system to stop releasing the stimulating hormone and/or trigger the release of inhibiting hormones to avoid oversecretion (Amar and Weiss 2003). In contrast, a

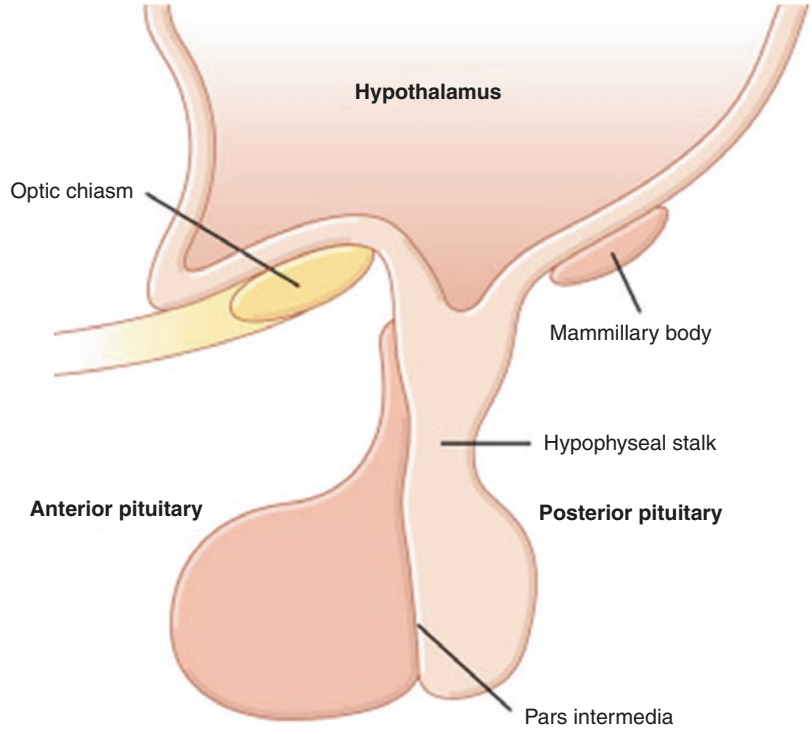


Fig. 12.1 Anatomy of the pituitary gland. Reprinted from Hall J. Pituitary hormones and their control by the hypothalamus. Guyton and Hall textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

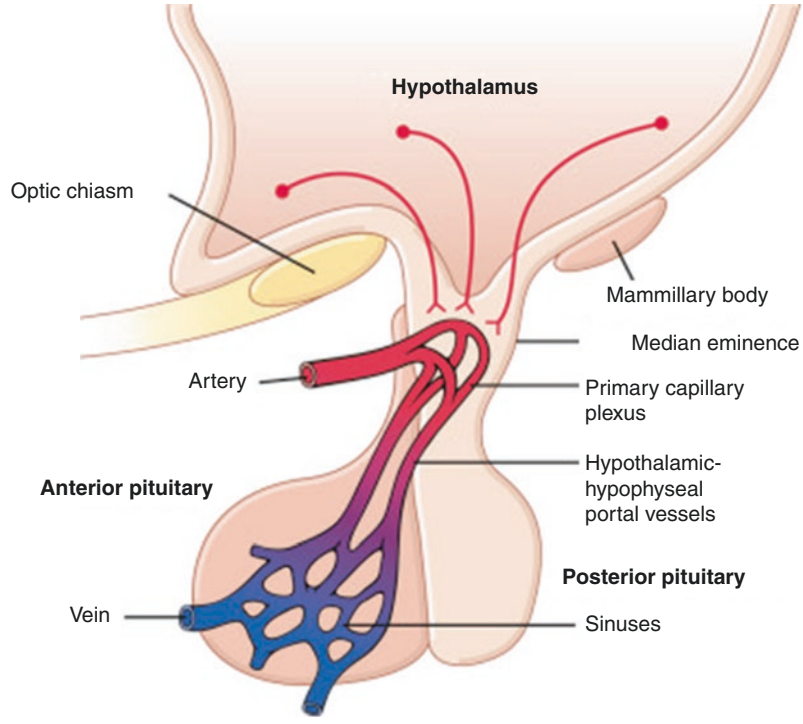


Fig. 12.2 Hypophyseal portal vessels. Reprinted from Hall J. Pituitary hormones and their control by the hypothalamus. Guyton and Hall textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

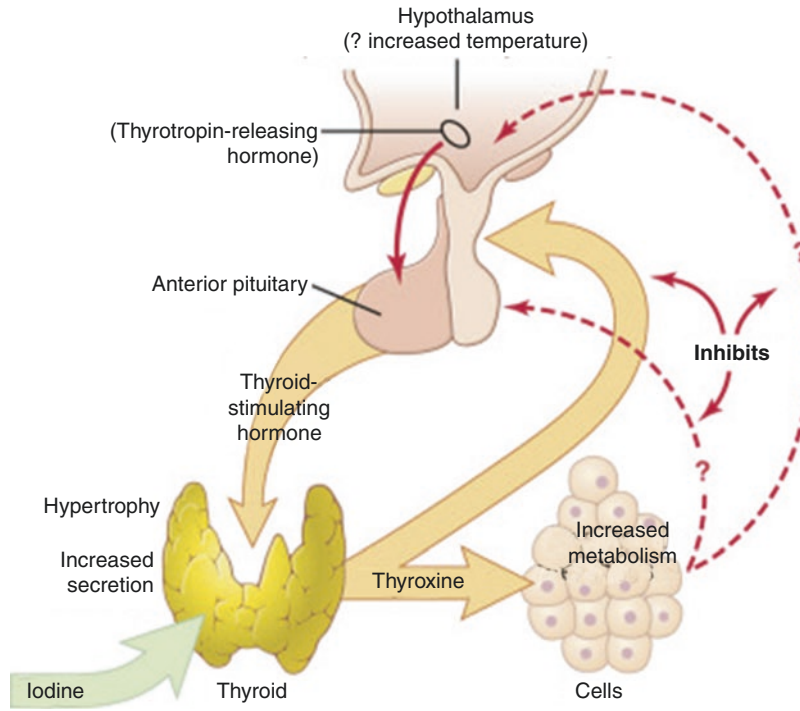


Fig. 12.3 Negative feedback system (thyroid hormone). Hall J. Pituitary hormones and their control by the hypothalamus. Textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

positive feedback loop stimulates the production of a specific releasing hormone from the hypothalamus and pituitary when levels at the end organ decline below a set threshold. For example, during the female menstrual cycle, low estrogen and progesterone levels from the ovaries and uterus provide a negative feedback signal to the hypothalamus to produce GnRH and provide positive feedback to the pituitary to manufacture luteinizing hormone (LH) and follicle stimulating hormone (FSH). These subsequently rise, triggering ovulation. If the egg is not fertilized, there is a sharp drop in estrogen and progesterone levels (negative feedback), stimulating menses and resetting the cycle when threshold low levels of estrogen and progesterone are reached. Therefore, the release of a hormone serves to control its own production (Hall 2016). Other factors are involved in maintaining the delicate balance of hormones release and inhibition, including cytokines, growth factors, nutrients, and neurotransmitters (Melmed 2017).

The pituitary has 3 lobes—anterior (adenophyophysis), posterior (neurohypophysis), and intermediate (pars intermedia). The anterior, intermediate, and posterior sections of the pituitary act synergistically and independently, each section producing different hormones and regulatory processes or functioning as a specific hormonal axis.

The endocrine hormones are carried by the circulatory system to cells throughout the body where they bind to cell receptors and initate cell reactions, usually resulting in an end-organ function completing the axis (Fig. 12.4). Proper functioning of the hypothalamus, pituitary, and end organ is required for completion of the axis. Some endocrine hormones produce effects throughout the body (example: growth hormone) while others act directly on target tissues (such as adrenocorticotropic hormone) (Hall 2016).

Most of the hormones of the pituitary gland are released in a cyclical manner. These cycles may vary based on a clock mechanism, such as a 24-h circadian rhythm, by season, development and age, diurnal patterns, or association with the sleep-wake cycle (Hall 2016). Other patterns of hormone release also exist, such as pulsatile or with acute brain stimulation (Melmed 2017). Most hormones also have a continuous or tonic

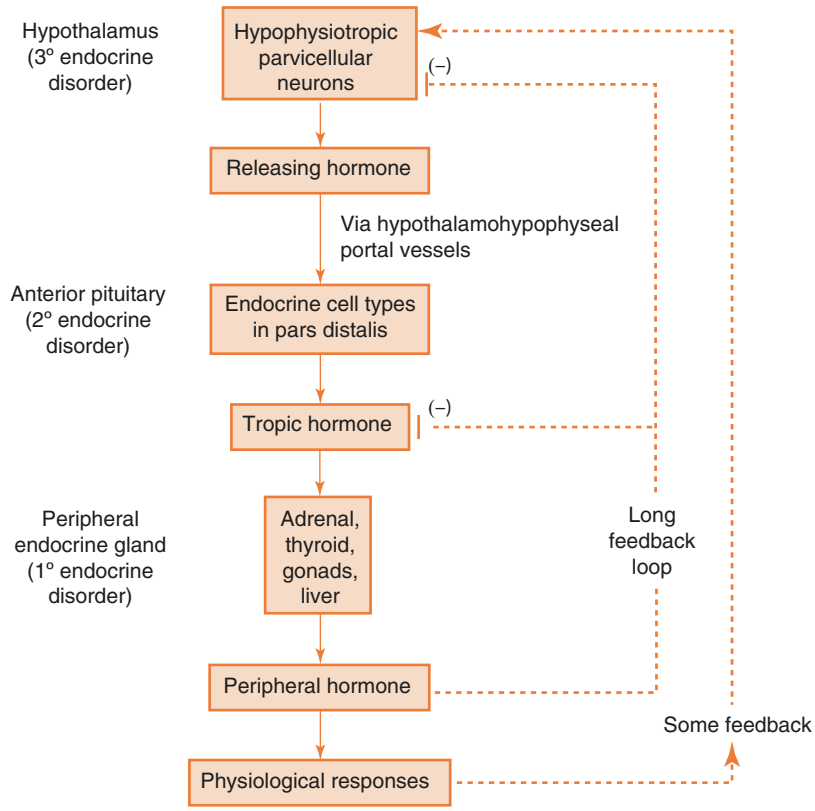


Fig. 12.4 Endocrine axis. Reprinted from White BA, Porterfield SP. Endocrine and reproductive physiology. 2013. Figure 5.10

production so levels never fall to zero (White and Porterfield 2013).

12.2 Anterior Pituitary

The anterior pituitary (AP), also known as the adenohypophysis, comprises the largest territory of the gland. The anterior pituitary produces six hormones in peptide form including thyroid stimulating hormone (TSH), corticotropin or adrenocorticotrophic hormone (ACTH), follicle stimulating hormone (FSH), lutenizing hormone (LH), growth hormone (GH), and prolactin (PRL) (Amar and Weiss 2003). All of the hormones except PRL act by stimulating other glands to release additional hormones (Fig. 12.5). PRL acts on breast tissue directly to stimulate milk production (Hall 2016).

Secretion of anterior pituitary hormones occurs episodically, stimulated by the hypothalamus. Hypothalamic releasing hormones and hypothalamic inhibiting hormones are sent to the anterior pituitary through the hypothalamic-hypophyseal portal vessels. These hormones act on the specific cells to control release or inhibition of their respective hormones (positive feedback). Each secretion may last a few minutes, with a longer duration of action (90–140 min), depending on physiologic stimulation (Amar and Weiss 2003).

There are six currently recognized cell types in the anterior pituitary. The first and most common are somatotropes which secrete GH. The somatotropes make up 40–50% of the cells in the AP and are located primarily in the lateral section of the AP. Mammotrophs (also known as lactotrophs) secrete PRL and make up 10–25% of the cells in the AP. Mammotrophs are located throughout the AP. Corticotrophs, which manufacture corticotrophin (ACTH) and POMC, comprise an additional 15–20% of cells. Corticotrophs are generally located in the anteriomedial part of the AP. Gonadotrophs secrete FSH and LH, make

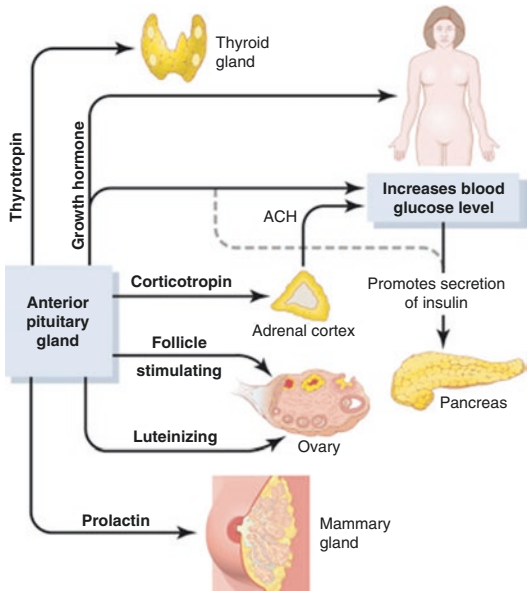


Fig. 12.5 Metabolic functions of the anterior pituitary gland. Reprinted from Hall J. Pituitary hormones and their control by the hypothalamus. Guyton and Hall textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

up 10–15% of cells, and are located throughout the gland. Thyrotrophs secrete TSH, only accounting for 3–5% of AP cells (Hall 2016).

12.2.1 Corticotropin/ Adrenocorticotrophic Hormone (ACTH)

Corticotrophic cells in the anterior lobe produce pro-opiomelanocortin (POMC), a precursor glycoprotein that cleaves to produce hormones such as ACTH. In addition, POMC produces melanocyte stimulating hormones in the pars intermedia and is responsible for the production of opioid peptides (endorphins) in the brain. POMC is also produced in the hypothalamus, placenta, lungs, and gastrointestinal tract (Amar and Weiss 2003). Corticotroph cells are responsive to stimulation from corticotrophin-releasing hormone (CRH) from the hypothalamus, and are inhibited by the production of the glucocorticoid cortisol from the zona fasciculata of the adrenal glands.

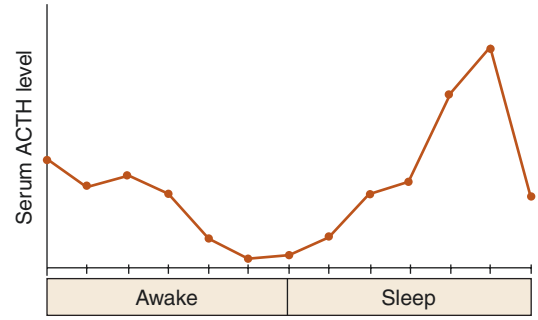


Fig. 12.6 Diurnal pattern for serum adrenocorticotropic hormone (ACTH). Reprinted from White BA, Porterfield SP. Endocrine and reproductive physiology. 2013. Figure 5.14

Corticotropin (adrenocorticotrophic hormone) is essential to life. The primary action of this hormone is to stimulate the adrenal glands to produce glucocorticoids, aldosterone, and androgens. The half-life of corticotropin is approximately 10 min, allowing for rapid adjustments in levels based on physiologic needs. Corticotropin is released on a 24-h circadian recurring pattern. The lowest levels usually occur around normal bedtime or 11 pm to midnight and the highest levels in the morning hours, typically 2–4 h before awakening (Fig. 12.6). Secretion of corticotropin is regulated by corticotropin-releasing hormone (CRH), produced in the hypothalamus in medial paraventricular nuclei and in response to low circulating levels of cortisol. Additionally, CRH, and thus corticotropin, is released in response to physiologic stressors such as physical injury, pain or emotional fear, stress and strain, and is a central mechanism in the "flight or fight" phenomena (Fig. 12.7). The physiology of ACTH in the body is broad and includes maintaining blood pressure, heart rate, and blood sugar levels for cell metabolism to maintain environmental adaptation and create conditions that favor survival in times of acute threat or stress (Melmed 2017). In addition, ACTH, supported by the hypothalamic, pituitary, adrenal axis (HPA axis), responds to stressors by reducing blood flow or constricting blood vessels particularly of the GI tract, increasing heart rate blood pressure, blood sugar, increasing cellular metabolism, and focusing attention and cognition. The production of CRH and corticotropin are

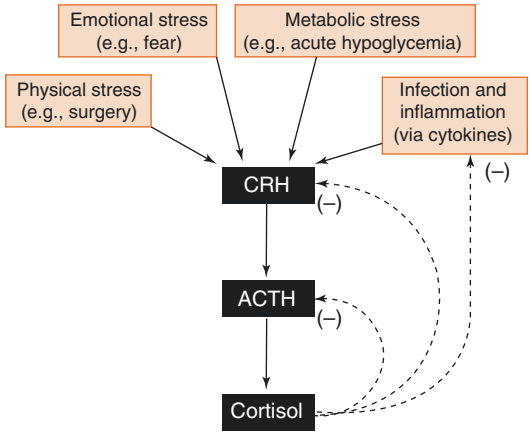


Fig. 12.7 Factors regulating secretion of CRH and ACTH. Reprinted from White BA, Porterfield SP. Endocrine and reproductive physiology. 2013. Figure 5.15

inhibited when glucocorticoids (cortisol) ciculating in the blood stream are sufficient to maintain homeostasis and/or the threat has resolved (Amar and Weiss 2003).

12.2.2 Thyroid Stimulating Hormone

The TSH molecule is a glycoprotein that has a half-life of 60 min. The primary action of TSH is to promote the synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) in the thyroid. Thyroid hormone secretion is dependent on the feedback loop between TSH and thyrotropin releasing hormone (TRH). Secretion of TSH is stimulated by TRH, while somatostatin (produced in the hypothalamus) inhibits the release (Amar and Weiss 2003). Cold temperatures can increase the production of TRH, stimulating more TSH production. TSH binds to the receptors on thyroid cells, which causes production of thyroxine (T4) and triiodothyronine (T3). T3 and T4 are recognized by the hypothalamus and pituitary, which block the secretion of TSH when appropriate or supraphysiologic levels are achieved. Thyroid hormone acts on almost all cells and tissues in the body. Thyroid hormone is essential for supporting oxygenation of cardiovascular tissue by increasing cardiac output (White and Porterfield 2013). In addition, thyroid hormone is responsible for maintaining basal metabolic rate, respiratory effort and oyxgen supply, function and growth of bone and muscle, regulation of the reproductive system, and fetal brain development (White and Porterfield 2013).

12.2.3 Follicle Stimulating Hormone and Luteinizing Hormone

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are responsible for the gonadal development in both men and women, gametogenesis (germ cell production), the production of androgens and estrogens, and regulating ovulation in women (Amar and Weiss 2003). In women, FSH and LH both increase prior to ovulation, with FSH being the primary driver for follicular development each month. LH stimulation occurs in concert with FSH, creating a more rapid increase in follicular secretion. LH is primarily responsible for the final stages of follicular growth leading to ovulation (Fig. 12.8).

In men, LH is the primary stimulator of testosterone production in the testes and FSH stimulates spermatogenesis (Hall 2016). LH has a half-life of around 60 min while the half-life of FSH is around 170 min. Stimulation of FSH and LH is regulated by gonadotropin-releasing hormone (GnRH), a peptide produced in the hypothalamus. Secretion of FSH and LH occurs in a pulsatile manner. Inhibition of FSH occurs with the hormone inhibin, a polypeptide produced in the gonads of both sexes (Hall 2016).

12.2.4 Growth Hormone

Growth hormone (GH) is the most abundant of the hormones produced in the anterior pituitary gland. GH leads to the production of polypeptide growth factors secreted by the liver, cartilage, and other tissues. The effects of GH are seen throughout the body in protein synthesis and promoting the growth of cells and tissues (Fig. 12.9). Actions include growth of long bones, increase in lean body mass and decrease in body fat, increasing hepatic glucose output and acting as an anti-

insulin effect in muscles (Amar and Weiss 2003). GH also stimulates general metabolic rate. The half-life of GH is between 10 and 20 min (Faria et al. 1989). Secretion of GH is stimulated by growth hormone releasing hormone (GRH) and growth hormone inhibiting hormone (GIH, also known as somatostatin), both produced in the hypothalamus. GH release is pulsatile and there are very low basal levels in between bursts (Melmed 2017) (Fig. 12.10). GH release is stimulated by hypoglycemia, sleep, exercise, and stressors. Chronic malnutrition or fasting causes dramatically elevated GH levels. GH is inhibited by glucose and cortisol. IGF-1 also inhibits secretion of GH from the pituitary (Hall 2016). Growth hormone is essential for human development, but continues to be a critical hormone throughout adulthood. In adulthood, GH is essential for bone metabolism and remodeling; metabolism of carbohydrates, protein, and lipids; and muscle strength and exercise. There is some data to suggest that GH is essential for cognitive development and function (Wass and Reddy 2010) as well as maintaining quality of life (McKenna et al. 1999). Insulin-like growth factors (IGF-1 and IGF-2) regulate many of the actions of GH. IGF-1

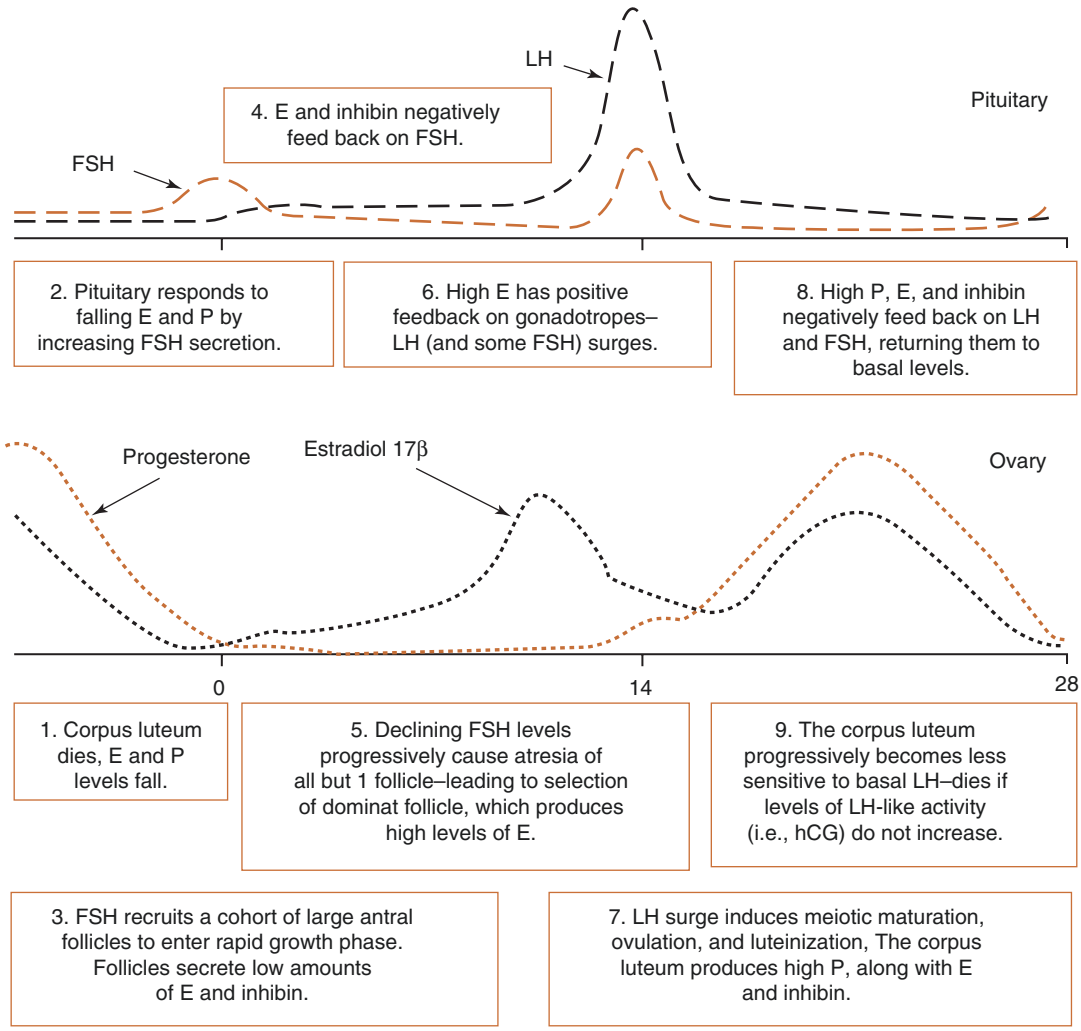


Fig. 12.8 Menstrual cycle regulation by FSH and LH. Reprinted from White BA, Porterfield SP. Endocrine and reproductive physiology. 2013. Figure 10.14

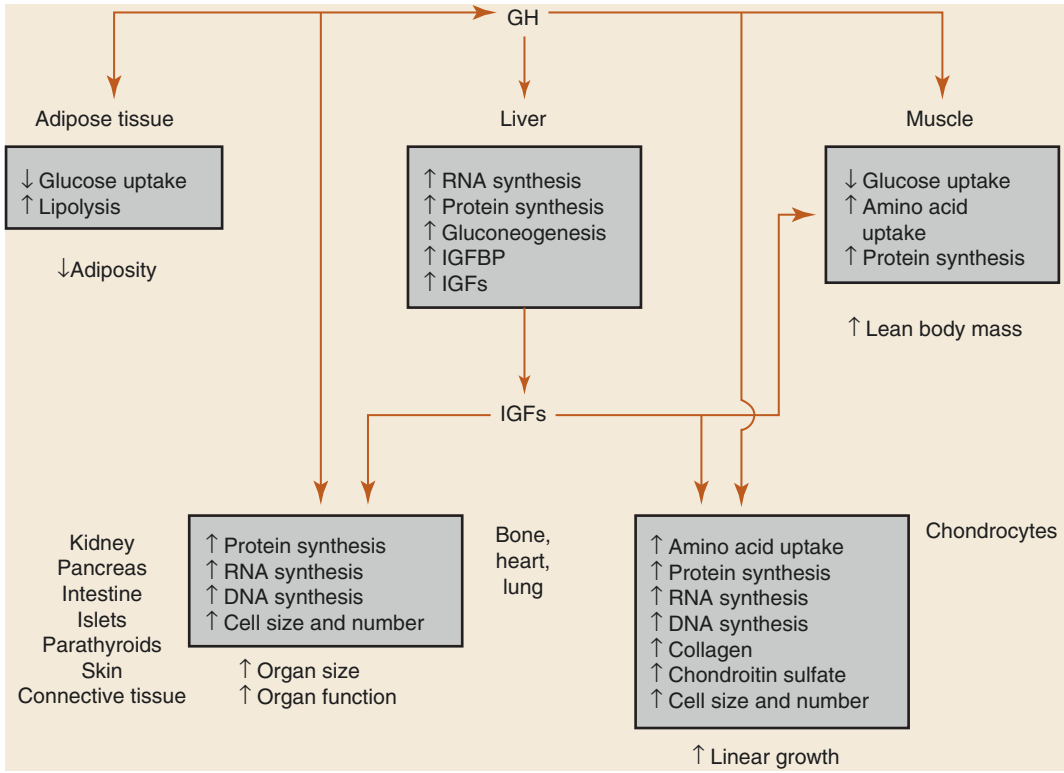


Fig. 12.9 Biologic actions of growth hormone. Reprinted from White BA, Porterfield SP. Endocrine and reproductive physiology. 2013. Figure 5.21

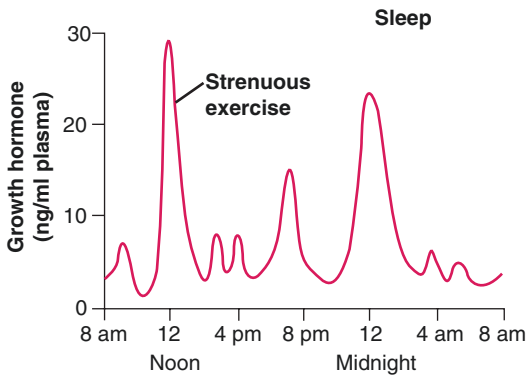


Fig. 12.10 Pulsatile release of growth hormone. Reprinted from Hall J. Pituitary hormones and their control by the hypothalamus. Guyton and Hall textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

peaks in puberty and declines with advancing age. IGF-2 plays a large role in the development of the fetus before birth. IGF-1 is monitored more commonly than GH in laboratory testing because it does not fluctuate significantly during the day in the same manner that GH does, allowing for more consistent testing results.

12.2.5 Prolactin

Prolactin (PRL) works with progesterone and estrogen to assist in the development of the female breast and promote milk secretion from the breast. It also works to inhibit the actions of gonadotropins on the ovary. The role of prolactin in men is unclear, but high levels can lead to impotence and infertility. High levels of prolactin can also lead to female infertility and should be assessed during an infertility evaluation. Hyperprolactinemia may contribute to an increased risk of osteoporosis due to the secondary lowering of estrogen and testosterone. Women with hyperprolactinemia are 2–4.5 times more likely to develop an osteoporotic fracture, compared to age and BMI-matched controls

(Hui et al. 1988). The risk of osteoporosis related to elevated prolactin levels dissipates with normalization of the prolactin levels. TRH stimulates PRL and prolactin-inhibiting factor (PIF, or dopamine) inhibits-proalctin production. Exercise, stress, sleep, pregnancy, and nipple stimulation can all increase PRL release (Amar and Weiss 2003).

12.2.6 Physiology of the Posterior Lobe

The posterior lobe of the pituitary, also known as the neurohypophysis, secretes oxytocin and antidiuretic hormone (ADH), also known as vasopressin. Both of these peptides are produced in the hypothalamus, pass through nerve fibers in the hypothalamo-hypophyseal tract, and are released from the pars nervosa (posterior lobe) in response to stimuli (Amar and Weiss 2003). Release of these hormones is regulated by calcium-dependent exocytosis in response to action potentials arriving at the nerve ending. Exocytosis occurs into the extracellular fluid, gaining access to the peripheral circulation. The posterior lobe is primarily made up of axon endings that originate in the hypothalamus. The axon terminals are in close proximity to blood vessels, which allows the hormones to be secreted into the bloodsteam (Hall 2016) (Fig. 12.11).

12.2.7 Oxytocin

Oxytocin acts on the breast and uterus. In breast tissue, oxytocin causes the flow of milk from the alveoli to the nipples. Oxytocin release is caused by nipple stimulation, which communicates with neurons in the hypothalamus that discharge action potentials and cause the release of oxytocin from the posterior pituitary gland (Amar and Weiss 2003). Oxytocin also assists in labor, causing contractions of the uterine muscles. Some research supports the idea that oxytocin may stimulate the passage of sperm to the fallopian tubes in nonpregnant women. In men, oxytocin also increases around ejaculation, which may assist with contraction of smooth muscle tissue that propels sperm to the urethra (Ganong 2001).

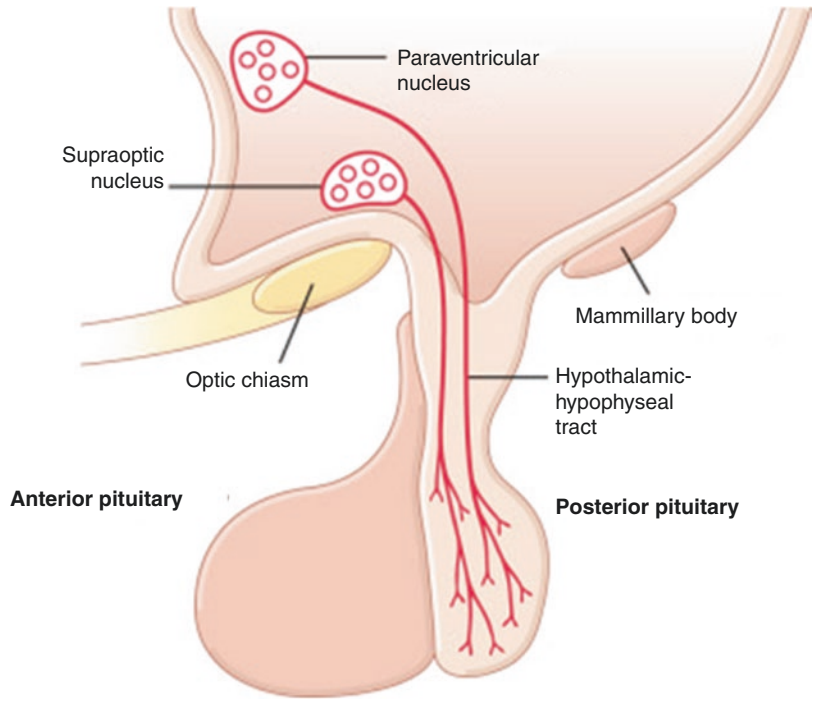


Fig. 12.11 Posterior pituitary relationship to hypothalamus. Reprinted from Hall J. Pituitary hormones and their control by the hypothalamus. Guyton and Hall textbook of medical physiology. 13th ed. pp. 939–950. Copyright (2016), with permission from Elsevier

12.2.8 Vasopressin

Vasopressin, also known as anti-diuretic hormone or ADH, has its primary action in the renal system, where it acts to concentrate urine. Its primary objective is to balance concentration by regulating circulating volume. In the collecting ducts of the kidney, vasopressin causes aquaporins (water channels) to translocate from the endosomal to the luminal membranes. This action causes increased permeability of the collecting duct which allows water to enter the hypertonic interstitium. This causes urine volume to decrease and the urine concentration to increase. Subsequently, specific gravity increases and triggers a decrease in plasma osmolality (the concentration of solutes in the solution), increasing circulating blood volume and subsequently decreasing serum sodium.

Vasopressin is secreted in a variety of situations such as decreased circulating volume in hemorrhage, pain, exercise, and nausea and vomiting. In addition to the renal actions, vasopressin also acts to constrict vascular muscle tissue, which can assist in blood pressure regulation (Amar and Weiss 2003). Alcohol is an inhibitor of ADH release, which subsequently decreases circulating volume and increases serum sodium or promotes dehydration.

12.3 Nursing Process

An understanding of normal pituitary anatomy and physiology establishes a basis for helping the patient navigate personalized treatment goals. Patient-centered care and adherence to the principles as described by the Picker Institute are purposed to engage and empower patients to achieve self-efficacy with respect to these goals (Picker Institute 2017).

Pituitary dysfunction can lead to significant morbidity and mortality. Recognition of the normal physiology and impact of hormone secretion is often revealing for both nurse and patient. In the context of the nursing process assessment of patient reported signs and symptoms, vital signs, growth and development (auxology), vision, reproductive functions, metabolic indices, bone density, sleep parameters, mental status, stress response, and fluid balance all involve an understanding of normal pituitary function. Each hormonal axis requires assessment for dysfunction, which will be further described in subsequent chapters.

A nursing action plan for patients with pituitary dysfuntion is dynamic and goal directed and includes an appropriate education program that aims to empower participation in self-care and collaborative decision making regarding their treatment (Marks et al. 2005a, b; Bennett et al. 2010). Promotion of treatment adherence improves outcomes and quality of life. The dynamics inherent in this concept require the nurse to participate in ongoing evaluation, reviewing the literature for new knowlege with respect to pituitary function and for changes in the individual's function over time and the life cycle.

Assessing symptoms based on pituitary hormone function may include the determination of alterations to the HPA axis function during an acute phase of illness, when the patient is undergoing a surgical procedure or with the diagnosis of a pituitary tumor. Monitoring for signs and symptoms of other hormonal dysfunction enables early diagnosis and prompt treatment.

Patient education and understanding of normal gland function and alterations in function in all with pituitary disease, as in those with other diseases, lays the foundation for self-care and treatment adherence for best outcomes (Adams 2010). Patients must be counseled on actual or potential symptoms that can result from their disease process. Advances in medicine now allow patients with every type of pituitary deficiency, including panhypopituitarism, to lead a full life, although quality of life can vary. However, the best outcomes can be achieved with early detection and prompt and appropriate medical therapies. Additionally, patients identified with pituitary dysfunction should be immediately referred to a specialty provider in endocrinology for a prompt evaluation.

12.4 Conclusions

The pituitary gland is a small but crucial master gland in the body that is closely associated with the hypothalamus and is responsible for regulating many essential physiologic and end-organ processses. The anterior pituitary gland has six types of cells that assist in a variety of hormone production and regulation including corticotropin, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, growth hormone, and prolactin. The posterior pituitary produces two additional types of hormones: vasopressin and oxytocin. Each of these pituitary hormones plays a key role in a variety of physical functions and sustaining life. Any disruption of these hormone cascades can cause a variety of pathophysiologic processes. Apoplexy or bleeding into the pituitary gland can lead to death if not immediately identified and treated with glucocorticoids (cortisol replacement). Nurses in all environments, particularly advanced practice nurses, should understand the key features of the pituitary gland as a primary foundation for the study of endocrinology.

References

Adams RJ. Improving health outcomes with better patient understanding and education. Risk Manag Healthc Policy. 2010;3:61–72. https://doi.org/10.2147/RMHP.S7500

Amar AP, Weiss MH. Pituitary anatomy and physiology. Neurosurg Clin N Am. 2003;14(1):11–23.

Bennett HD, Coleman EA, Parry C, Bodenheimer T, Chen EH. Health coaching for patients with chronic illness. Fam Pract Manag. 2010;17(5):24–9.

Faria AC, Veldhuis JD, Thorner MO, Vance ML. Half-time of endogenous growth hormone (GH) disappearance in normal man after stimulation of GH secretion by GH-releasing hormone and suppression with somatostatin. J Clin Endocrinol Metab. 1989;68(3):535–41.

Ganong WF. Central regulation of visceral function. In: Review of medical physiology. 20th ed. New York: McGraw Hill; 2001. p. 224–47.

Hall JE. Guyton and hall textbook of medical physiology. 13th ed. Philadelphia: Elsevier; 2016. p. 925–50.

Hui SL, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest. 1988;81:1804–9.

Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part I). Health Promot Pract. 2005a;6(1):37–43.

Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). Health Promot Pract. 2005b;6(2):148–56.

McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L, Wíren L. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. Qual Life Res. 1999;8(4):373–83.

Melmed S. The pituitary. 4th ed. San Diego: Elsevier Academic Press; 2017.

Picker Institute. Picker Institute's eight principles of patient-centered care. 2017. http://cgp.pickerinstitute.org/?page_id=1319. Accessed 23 Oct 2017.

Wass JA, Reddy R. Growth hormone and memory. J Endocrinol. 2010;207(2):125–6.

White BA, Porterfield SP. Endocrine and reproductive physiology. 4th ed. Philadelphia: Elsevier; 2013. p. 99–128.

Key Reading

1. Amar AP, Weiss MH. Pituitary anatomy and physiology. Neurosurg Clin N Am. 2003;14(1):11–23.
2. Ben-Shomo A, Melmed S. In: Melmed S, editor. Hypothalamic regulation of the anterior or pituitary function in pituitary. 4th ed. San Diego: Elsevier Academic Press; 2017.
3. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part I). Health Promot Pract. 2005a;6(1):37–43.
4. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). Health Promot Pract. 2005b;6(2):148–56.

Metabolic Effects of Hypothalamic Dysfunction

13

Cecilia Follin

Contents

13.1 **Introduction** 247

13.2 **Hypothalamus** 247
13.2.1 Thirst Control/Fluid Balance 247
13.2.2 Appetite Control 249
13.2.3 Temperature Regulation 250
13.2.4 Hypothalamic Obesity 251
13.2.5 Hypothalamic Hormones and Actions 252

13.3 **Nursing Process** 252

13.4 **Conclusions** 253

References 253

Abstract

The hypothalamus is a very small, key regulator of endocrine, metabolic, and behavioral functions. The hypothalamus controls the release of 8 major hormones by the pituitary and is involved in temperature regulation, control of food and water intake, sexual behavior and reproduction. Hypothalamus neuronal bodies that produce factors controlling the pituitary are clustered in different nuclei which have specific functions. The clinical syndrome will depend on the location and extent of the underlying lesion. The lesion may be very small and only affect specific hypothalamic nuclei. The lateral hypothalamus contains the thirst center and controls thirst. Neurons from the supraoptic and PVN of the hypothalamus terminate in the posterior pituitary and control the release of ADH (antidiuretic hormone) which then acts on the kidneys to prevent loss of water. Osmotic sensors in the hypothalamus work with ADH to maintain water metabolism.

Destruction of the VMN in hypothalamus induces hyperphagia, hyperinsulinemia, and weight gain. The same neurons in the hypothalamus express high levels of leptin and ghrelin receptors. Hypothalamic damage can result in "leptin resistance," which means a decreased sensitivity to leptin and resulting in an inability to detect satiety despite high energy stores. Ghrelin is known as the "hunger hormone" and is mainly produced by the stomach. Circulating

C. Follin (✉)
Department of Oncology, Skane University Hospital, Lund, Sweden
e-mail: cecilia.follin@med.lu.se

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_13

ghrelin is increased under fasting and reduced after refeeding. When the hypothalamus is damaged and disturbances in energy expenditure and appetite-regulation occur, a syndrome of severe weight gain ensues, termed "hypothalamic obesity." Hypothalamic obesity can occur as a consequence of acquired anatomic hypothalamic damage including various types of hypothalamic tumors, inflammatory diseases, head injury, cranial radiotherapy, and cerebral aneurysm.

Childhood onset craniopharyngioma (CP) is a rare intracranial tumor that frequently affects hypothalamic/pituitary regions. CP patients suffer from increased morbidity, primarily due to hypothalamic damage. Understanding the central role of the hypothalamus in the regulation of feeding and energy metabolism is important in the care of the patients with hypothalamic disorders. The care should be conducted by experienced multidisciplinary teams, with the nurse as a key team member.

Keywords

Hypothalamus · Hypothalamic obesity
Energy homeostasis · Appetite control
Temperature regulation · Thirst center
Neuronal bodies

Abbreviations

ALL	Acute lymphoblastic leukemia
ACTH	Adrenocorticotropin hormone
ADH	Antidiuretic hormone
ARC	Arcuate nucleus
AGRP	Agouti-related peptide
CO	Childhood onset
CRH	Corticotropin-releasing hormone
CRT	Cranial radiotherapy
CP	Craniopharyngioma
DMN	Dorsomedial nucleus
GnRH	Gonadotropin-releasing hormone
GH	Growth hormone
GHRH	Growth hormone releasing hormone
HT	Hypothalamus
INF	Infundibular nucleus
NPY	Neuropeptide Y
PVN	Paraventricular nucleus
PWS	Prader–Willi syndrome
TRH	Thyrotropin-releasing hormone
VMN	Ventromedial nucleus

Key Terms

- **Energy homeostasis:** A biological process that involves the coordinated homeostatic regulation of food intake and energy expenditure.
- **Afferent neurons:** Sense stimuli and send information to the brain.
- **Hyperphagia:** Abnormally increased appetite.
- **Leptin:** The "satiety hormone," is a hormone made by adipose cells that helps to regulate energy balance by inhibiting hunger.
- **Ghrelin:** The "hunger hormone," is a hormone produced by ghrelinergic cells in the gastrointestinal tract regulating appetite.
- **Hypothalamic obesity:** A syndrome of severe weight gain due to damage to the hypothalamus when disturbances in energy expenditure and appetite-regulation occur.

Key Points

- Hypothalamus is important in coordinating signals between nervous system and the endocrine system and it influences hormonal and behavioral system, as well as, the control of body temperature, hunger and thirst.
- Damage to the hypothalamus will lead to significant clinical morbidity and can result in metabolic complications, such as disturbed energy balance, hypothalamic obesity, insulin and leptin resistance.
- Hypothalamus releases ADH (antidiuretic hormone) which acts on the kidneys to prevent loss of water through the urine. Diabetes insipidus is a rare water metabolism disorder which is caused by ADH deficiency.
- The pathogenic mechanism underlying hypothalamic obesity is complex and multifactorial. Weight gain results from

damage to hypothalamus, which leads to hyperphagia, low-resting metabolic rate, and hormone deficiency. The weight gain is unlike that of normal obesity. The patients gain weight even if caloric restriction and lifestyle modification are provided.

- As no non-surgical therapeutic option is currently available for hypothalamic obesity, prevention of hypothalamic injury should be the preferred strategy. The care should be conducted by experienced multidisciplinary teams, including nurses providing comprehensive coordinated care and promoting healthy lifestyle behavior.

13.1 Introduction

The hypothalamus is a very small, but important area of the brain and a key regulator of endocrine, metabolic, and behavioral functions. The hypothalamus controls the release of 8 major hormones by the pituitary (Fig. 13.1) and is involved in temperature regulation, control of food and water intake, sexual behavior and reproduction, control of behavior, and mediation of emotional responses. It may be very difficult to differentiate between hypothalamic and pituitary disease as the endocrine abnormalities are often similar. As the hypothalamus regulates both endocrine and autonomic function, there is usually a combination of endocrine and neurological disturbance in hypothalamic damage.

The hypothalamus is a small cone shaped structure, weights about 4 g, below the thalamus and on both sides of the third cerebral ventricle. The hypothalamus is connected to the pituitary through the pituitary stalk. The portal system is a unique arrangement of capillaries and veins located in the stalk, allowing the hypothalamic hormones to pass directly to the anterior pituitary. Hypothalamus neuronal bodies that produce factors controlling the pituitary are clustered in different nuclei which have specific functions (Schneeberger et al. 2014). The clinical syndrome will depend on the location and extent of the underlying lesion. The lesion may be very small and only affect specific hypothalamic nuclei (Schneeberger et al. 2014).

Disturbed energy balance with intractable weight gain, termed hypothalamic obesity, is one of the most agonizing late complications after hypothalamic damage (Lustig 2002). The pathogenesis of hypothalamic obesity involves the inability to transduce afferent hormonal signals of adiposity. However, efferent sympathetic activity persists resulting in reduced energy expenditure and increased vagal activity results in increased insulin secretion and adipogenesis.

The hypothalamus is thought to contain the "biological clock" that regulates certain body functions that vary at different times of the day (e.g., body temperature, hormone secretion, hunger) or those that vary over a period of many days (e.g., menstrual cycle). Lesions of the hypothalamus often disrupt the state of the sleep-waking cycle (Schneeberger et al. 2014).

13.2 Hypothalamus

13.2.1 Thirst Control/Fluid Balance

The lateral hypothalamus contains the thirst control center. When blood that is too concentrated or dehydrated reaches the hypothalamus, the patient becomes thirsty. In response, the PVN and supraoptic nuclei of the hypothalamic are activated producing antidiuretic hormone (ADH) which is released as a chemical signal at the terminus of their respective neurons in the posterior pituitary and subsequently secreted into the blood stream. ADH, in turn, acts on the kidneys to prevent loss of water through the urine. ADH constantly regulates and balances the amount of water in the blood. Higher water concentration increases the volume and pressure of the blood and osmotic sensors in the hypothalamus work with ADH to maintain water metabolism. The effect on the body is to conserve water by returning it to the blood and stop it from being lost by excretion. Decreased levels of ADH in the blood can also be caused by compulsive water drinking or low serum osmolality in the blood, e.g., concentration of particles in the blood.

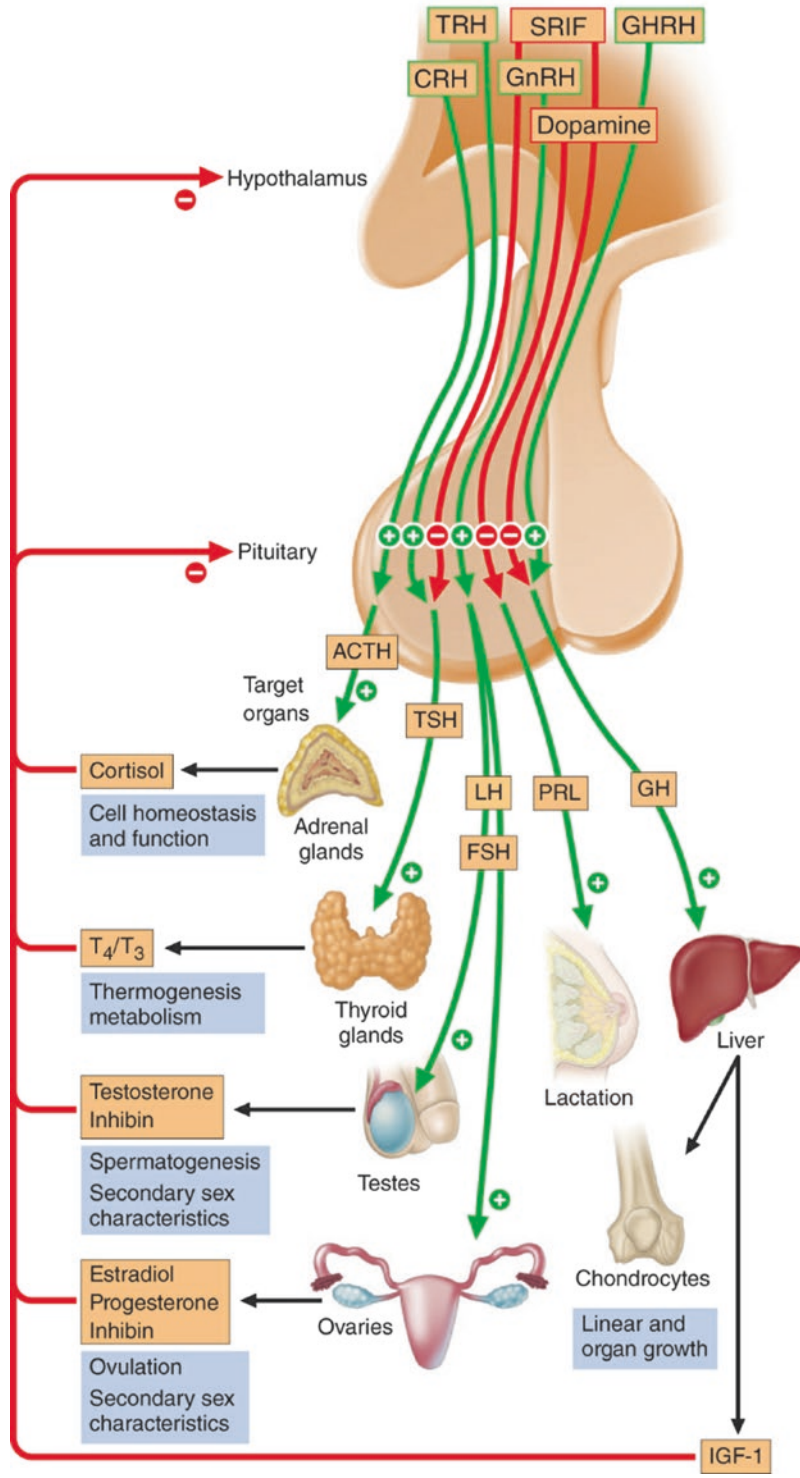


Fig. 13.1 The hypothalamus controls the release of 8 major hormones by the pituitary and is involved in temperature regulation, control of food and water intake, sexual behavior and reproduction, control of behavior, and mediation of emotional responses. (Used with permission from Jameson, J. L. (ed.) *Harrison's Endocrinology, 4th Edition*. New York: McGraw Hill Education)

Central diabetes insipidus is a rare water metabolism disorder which is caused by ADH deficiency. The symptoms include excessive urination (polyuria) followed by extreme thirst (polydipsia). The patients are often extremely tired because their sleep is frequently interrupted by the need to urinate. In severe cases urination may occur more frequently than every 30 min. The urine is clear and has an abnormally low concentration of particles. Specific gravity is low. Diabetes insipidus can lead to severe dehydration with high serum levels of sodium if it is left untreated (Higham et al. 2016).

13.2.2 Appetite Control

Energy homeostasis is a biological process that adjusts food intake over time to promote stability in the amount of body fuel stored as fat. The regulation of appetite and body weight involves the human brain and in particular the hypothalamus. Information regarding nutrient status and energy stores is communicated to the brain through diverse afferent neuronal signals. The hypothalamus consists of groups of nerve cells bodies forming distinct nuclei including the arcuate nucleus (ARC), (also known as infundibular nucleus (INF)), the paraventricular nucleus (PVN), the dorsomedial nucleus (DMN), and the ventromedial nucleus (VMN). Destruction of these nuclei induces hyperphagia, hyperinsulinemia, and weight gain (Schneeberger et al. 2014). Animal studies have shown the ventromedial nucleus as the satiety center which inhibits feeding when stimulated and leads to hyperphagia when destroyed. The ARC is a very important area in the control of energy homeostasis. It is located on both sides of the third ventricle (Fig. 13.2). In the ARC there are two populations of neurons controlling appetite and energy expenditure. Neuropeptide Y (NPY) and agouti-related peptide (AGRP) control energy expenditure and anorexigenic neuropeptides, cocaine-and amphetamine-regulated transcript (CART), and α-melanocyte-stimulating hormone (α-MSH). This neuronal circuit is crucial for sensing and integrating a number of peripheral signals allowing for a precise control of food intake and energy expenditure. The neurons in the ARC express high levels of leptin and ghrelin receptors (Kamegal et al. 2000; Horvath et al. 2001). Leptin is derived from adipose cells and interacts with leptin receptors to regulate energy balance by inhibiting hunger. Hypothalamic damage can result in "leptin resistance," which means a decreased sensitivity to leptin and resulting in an inability to detect satiety despite high energy stores. Ghrelin is known as the "hunger hormone" and is mainly produced by the stomach. Circulating ghrelin is increased under fasting and reduced after refeeding (Tschöp et al. 2000). Central and peripheral administration of ghrelin in rodents has been shown to robustly promote food intake causing adiposity and weight gain (Tschöp et al. 2000). Ghrelin also enhances appetite in humans, but ghrelin levels have been shown to decrease in obese humans (Wren et al. 2001) (Figs. 13.3 and 13.4).

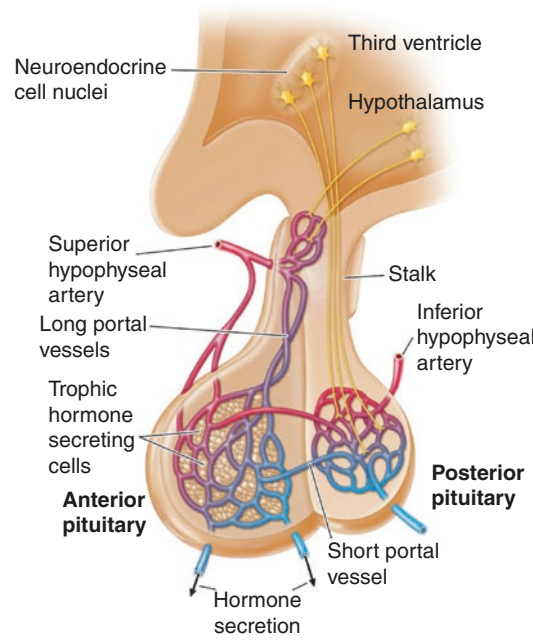


Fig. 13.2 The hypothalamus is a small cone shaped structure, weights about 4 g, below the thalamus and on both sides of the third cerebral ventricle. The hypothalamus is connected to the pituitary through the pituitary stalk. The portal system is a unique arrangement of capillaries and veins located in the stalk, allowing the hypothalamic hormones to pass directly to the anterior pituitary. (Used with permission from Jameson, J. L. (ed.) *Harrison's Endocrinology, 4th Edition*. New York: McGraw Hill Education)

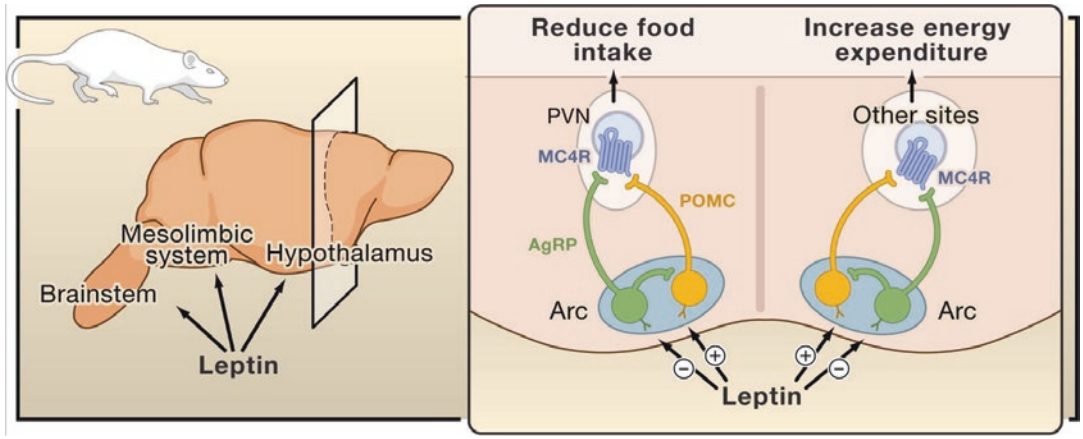


Fig. 13.3 Control of food intake by the hypothalamic leptin-melanocortin pathway. The hypothalamus receives and integrates neural, metabolic, and hormonal signals to regulate energy homeostasis. In particular, the adipocyte-derived hormone leptin and the melanocortin pathway have a critical role in the control of food intake. *AgRP* Agouti-related protein; *Arc* arcuate nucleus; *MC4R* melanocortin 4 receptor; *POMC* pro-opiomelanocortin; *PVN* paraventricular nucleus. Reprinted by Creative Commons License: Coll AP, Farooqi IS, O'Rahilly S. Hormonal control of food intake. Cell. 2007;129(2):251–262

13.2.2.1 Childhood Onset Craniopharyngioma

Childhood onset craniopharyngioma (CP) is a rare intracranial embryonal malformation of the sellar region. These tumors frequently affect hypothalamic/pituitary regions. CP patients suffer from increased morbidity, primarily due to hypothalamic (HT) damage (Holmer et al. 2010; Müller et al. 2000). Contributing factors to a high BMI among CP patients do not include higher energy intake but rather low basal metabolic rate and low levels of physical activity (Holmer et al. 2010). Another important factor is autonomic imbalance, including vagally mediated hyperinsulinemia (Lustig et al. 2003; Bray and Gallagher 1975). Further, CP patients are leptin resistant and ghrelin levels decrease in parallel with the HT involvement by the tumor (Holmer et al. 2010).

13.2.2.2 Cranial Radiotherapy and Hypothalamic Dysfunction in Children

Childhood brain tumor survivors treated with cranial radiotherapy (CRT) with hypothalamic damage are at increased risk for obesity (Holmer et al. 2010; Müller et al. 2000). It is established that the largest childhood cancer group, the acute lymphoblastic leukemia (ALL) survivors, treated with CRT suffer from obesity and lipid abnormalities (Link et al. 2004). Further, the metabolic hormones insulin and leptin have shown resistance (Follin et al. 2016; Sklar et al. 2000) among ALL survivors (Brennan et al. 1999), suggesting a radiation-induced hypothalamic dysfunction.

Prader–Willi syndrome (PWS) is a genetic neurodevelopmental disorder due to loss of genes within a critical chromosomal region. These genes are widely expressed in the brain, including the hypothalamus. This results in a number of neuroendocrine abnormalities, including hyperphagia and morbid obesity, hypogonadism and GH deficiency. In contrast, ghrelin levels are increased in populations with a possible hypothalamic dysfunction e.g., PWS (Delparigi et al. 2002), and in childhood leukemia survivors treated with cranial radiotherapy (Link et al. 2004).

13.2.3 Temperature Regulation

The functions of the hypothalamus are of a homeostatic nature, such as temperature regulation. If the internal temperature drops or rises outside the normal range, the hypothalamus will take steps to adjust it to avoid potentially dangerous

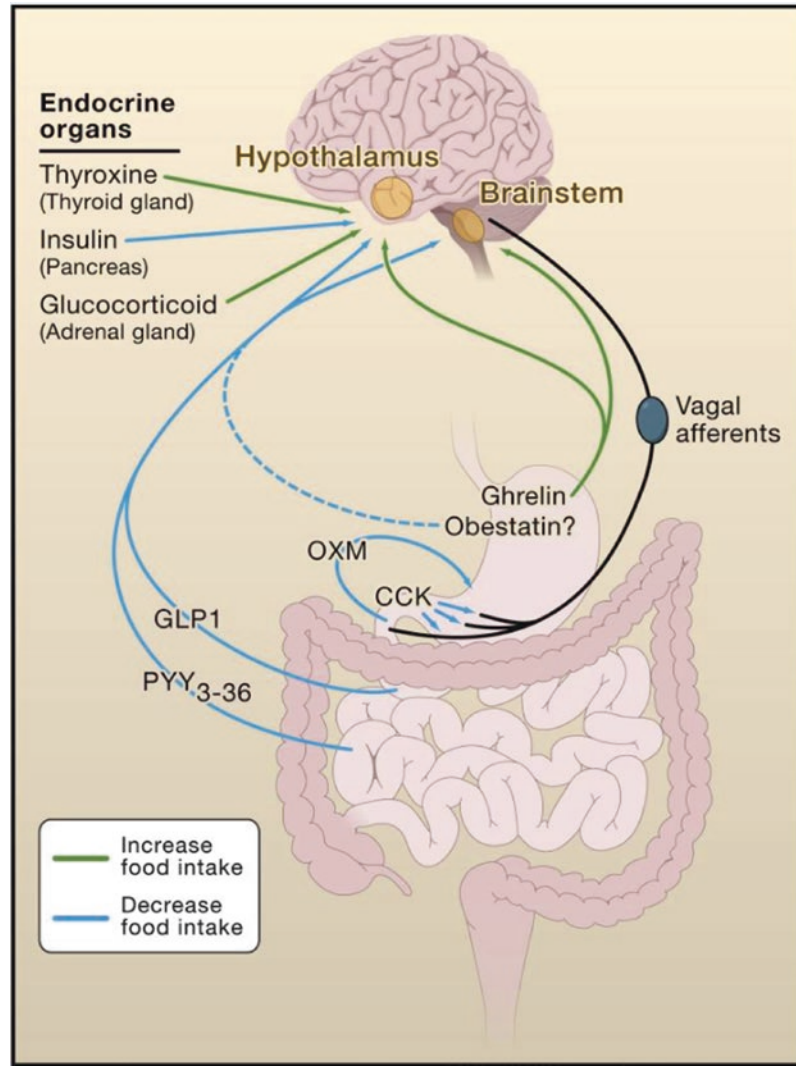


Fig. 13.4 Hormones from the gut and endocrine organs affect food intake. Reprinted by Creative Commons License: Coll AP, Farooqi IS, O'Rahilly S. Hormonal control of food intake. Cell. 2007;129(2):251–262

conditions by sending signals to muscles, organs, glands, and nervous system. When body temperature increases, neurons in the anterior part of the hypothalamus turn on mechanisms for heat dissipation that include sweating and dilation of blood vessels in the skin. When body temperature decreases, neurons in the posterior part of the hypothalamus are responsible for heat production through shivering, vasoconstriction in the skin, and blockage of perspiration. Lesions in the anterior part can result in hyperthermia and lesions in the caudal part can result in hypothermia when the environmental temperature is low (Morrison and Nakamura 2011).

13.2.4 Hypothalamic Obesity

When the hypothalamus is damaged and disturbances in energy expenditure and appetite-regulation occur, a syndrome of severe weight gain ensues. This syndrome is termed "hypothalamic obesity" and its weight gain is unlike that of normal obesity. The patient gains weight even if caloric restriction and lifestyle modification are implemented. Hypothalamic obesity can occur as a consequence of acquired anatomic hypothalamic damage and includes various types of hypothalamic tumors, inflammatory diseases, head injury, cranial radiotherapy, and cerebral

aneurysm. Complications related to obesity are the major causes of morbidity, such as diabetes type 2 and cardiovascular disease (Kim et al. 2016). Obesity alone is also associated with increased mortality (Adams et al. 2006).

Studies of childhood acute lymphoblastic leukemia (ALL) and brain tumor populations report an abnormal increase in weight long after cancer therapy has been discontinued. Many of these studies demonstrate that cranial radiotherapy is an important risk factor (Lustig et al. 2003). The finding of increased levels of leptin/kg fat mass or fat mass associated with a reduced HT volume among the ALL survivors indicates a hypothalamic involvement after CRT treatment (Follin et al. 2016).

In childhood onset CP, an extremely high frequency of hypothalamic obesity of 30–77% has been reported after treatment. Tumor location, e.g., HT involvement, has been suggested to be the most important risk factor for obesity (Müller et al. 2000). Elevated serum leptin levels have been found in CP patients with suprasellar tumor component (Roth et al. 2015), suggesting that normal inhibition fails to occur due to disruption of the negative feedback loop in which leptin binds to hypothalamic receptors. Studies also report that CP patients continue to have a lower than normal level of physical activity (Harz et al. 2003). Attempts to control hypothalamic obesity with diet, exercise, and pharmacological treatments have not been successful in patients with a history of CP.

In patients with PWS, hypothalamic dysfunction manifests as temperature dysregulation, central sleep apnea and obesity with insatiable hunger and reduced muscle mass. Caloric needs of persons with PWS are significantly lower than norms for age or weight (Cataletto et al. 2011). Endocrine issues include GH deficiency, hypogonadotropic hypogonadism and less often, central hypothyroidism and central adrenal insufficiency.

13.2.5 Hypothalamic Hormones and Actions

Neurons from the nuclei in the supraoptic region of the hypothalamus stimulate the secretion of vasopressin (ADH, antidiuretic hormone), oxytocin from the posterior pituitary, and CRH (corticotropin-releasing hormone) from the hypothalamus. ADH and oxytocin are transported down the axons from cells in the supraoptic and paraventricular nuclei through the stalk to the posterior pituitary, where they are stored and released as needed into the blood stream (Fig. 13.1). Damage to the anterior hypothalamus blocks the production of ADH, resulting in central diabetes insipidus, which is characterized by rapid water loss from the kidneys. Hypothalamic neurons that produce growth hormone releasing hormone (GHRH), corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH) send their axons through the median eminence to terminate and release their hormones into the hypophyseal-portal circulation. This network of blood vessels penetrates into the anterior lobe of the pituitary. The hypothalamic neurohormones stimulate responsive anterior pituitary cells to secrete growth hormone (GH), adrenocorticotropin hormone (ACTH), thyroxin-stimulating hormone (TSH), lutenizing hormone (LH), and follicular-stimulating hormone (FSH). Dopaminergic neurons are responsible for tonic inhibition of prolactin secretion from the anterior pituitary, while somatostatin released from somatostatinergic neurons inhibits GH and TRH release (Higham et al. 2016).

Exposure to cranial radiotherapy impacts the hypothalamus more than the anterior pituitary and GH deficiency is often the first endocrine sequelae post therapy (Littley et al. 1988; Chrousos et al. 1982). It has been shown that patients treated with cranial radiotherapy, e.g., ALL survivors, have a blunted GH response to insulin tolerance test (ITT) and a low GH peak during GHRH-arginine testing (Björk et al. 2005). Damage of the lateral hypothalamus by cranial radiotherapy is a possible explanation for this phenomenon, because this area contains neurons responsible for promoting GH secretion after stimulation by hypoglycemia (Maghnie et al. 2002).

13.3 Nursing Process

Evaluate the patient's health status. Take a detailed medical and family history. Identify the patient's behavior regarding food intake, physical activity, and lifestyle. Identify deficits in fluid

balance and temperature regulation. Recognize abnormal findings, including psychological effects such as depression. Provide a detailed explanation to the patient and family of the function of the hypothalamus, how damage occurs and affects behaviors. Identify the patient/family knowledge gaps regarding healthy lifestyle behaviors and plan together a personalized education program. Offer follow-up with continuity and support. Facilitate referrals and contact with the endocrinologist, dietician, physiotherapist, and psychologist.

13.4 Conclusions

The hypothalamus is a key regulator of body clock functions, pituitary functions, weight and water homeostasis. Information regarding nutrient status and energy stores is communicated to the brain through diverse afferent neuronal signals. The hypothalamus consists of groups of nerve cells bodies forming distinct nuclei including the arcuate nucleus, (also known as infundibular nucleus), the paraventricular nucleus, the dorsomedial nucleus, and the ventromedial nucleus. Destruction of these nuclei induces hyperphagia, hyperinsulinemia, and weight gain. Hypothalamic injury can result in "leptin resistance," which means a decreased sensitivity to leptin and results in an inability to detect satiety despite high energy stores. Further, ghrelin levels have been shown to decrease in obese humans. In craniopharyngioma patients, a rare intracranial embryonal malformation of the sellar region, frequently affects the hypothalamic/pituitary regions with ghrelin levels decreasing in parallel with tumor involvement on the HT. The weight gain of hypothalamic obesity is unlike that of normal obesity. The patients gain weight even if caloric restriction and lifestyle modification are provided.

Understanding the central role of the hypothalamus in the regulation of food and energy metabolism is important in the care of the patients with hypothalamic disorders. As no medical/nonsurgical therapeutic option is currently available to treat hypothalamic obesity, prevention of hypothalamic injury should be the preferred strategy. Care should be provided by experienced multidisciplinary teams that include nurses. The nurse should provide psychological support and a personalized plan of care that includes facilitating communication with the multidisciplinary team and educating the patients in healthy lifestyle choices and behaviors.

References

Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355(8):763–78.

Björk J, Link K, Erfurth EM. The utility of the growth hormone (GH) releasing hormone-arginine test for diagnosing GH deficiency in adults with childhood acute lymphoblastic leukemia treated with cranial irradiation. J Clin Endocrinol Metab. 2005;90(11):6048–54.

Bray GA, Gallagher TF. Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. Medicine. 1975;54(4):301–30.

Brennan B, Rahim A, Blum W Adams JA, Eden OB, Shalet SM. Hyperleptinemia in young adults following cranial irradiation in childhood cancer survivors: growth hormone deficiency or leptin insensitivity? Clin Endocrinol (Oxf). 1999;61:683–91.

Cataletto M, Angulo M, Herz G, Whitman B. Prader-Willi syndrome: a primer for clinicians. Int J Pediatr Endocrinol. 2011;2011(1):12.

Chrousos GP, Poplack D, Brown T, O'Neill D, Schwade J, Bercu BB. Effects of cranial radiation on hypothalamic-adenohypophyseal function: abnormal growth hormone secretory dynamics. J Clin Endocrinol Metab. 1982;54:1135–9.

Delparigi A, Tschöp M, Heiman M, Salbe AD, Vozarova B, Sell SM, et al. High circulating ghrelin: a potential cause for hyperphagia and obesity in Prader-Willi syndrome. J Clin Endocrinol Metab. 2002;87:5461–4.

Follin C, Gabery S, Petersén Å, Sundgren P, Björkman-Burtcher I, Lätt J, Mannfolk P, Erfurth EM. Metabolic risk is associated with reduced hypothalamic volume in individuals treated with cranial radiotherapy for childhood leukemia. PLoS One. 2016;29:7–12.

Harz KJ, Müller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. J Clin Endocrinol Metab. 2003;88(11):5227–31.

Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet. 2016;388(10058):2403–15.

Holmer H, Pozarek G, Wirfält E, Popovic V, Ekman B, Björk J, et al. Reduced energy expenditure and impaired feeding-related signals but not high energy intake reinforces hypothalamic obesity in adults with childhood onset craniopharyngioma. J Clin Endocrinol Metab. 2010;95:5395–402.

Horvath T, Diano S, Sotonyi P, Heiman TM. Minireview: ghrelin and the regulation of energy balance—a hypothalamic perspective. Endocrinology. 2001;142:4163–9.

Kamegal J, Tamura H, Shimizu T, Ishi S, Hitochi S, Wakabayashi I. Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. Endocrinology. 2000;114:4797–9.

Kim SH, Despres JP, Koh KK. Obesity and cardiovascular disease: friend or foe? Eur Heart J. 2016;37(48):3560–8.

Link K, Moell C, Garwicz S, Cavallin-Ståhl E, Björk J, Thilén U, Erfurth EM. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. J Clin Endocrinol Metab. 2004;89:5003–12.

Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumors in adults. Q J Med. 1988;262:145–60.

Lustig RH. Hypothalamic obesity: the sixth cranial endocrinopathy. Endocrinologist. 2002;12:210–2174.

Lustig R, Post S, Srivannaboon K, Rose SR, Danish RK, Burghen GA. Risk factors for the development of obesity in children surviving brain tumours. J Clin Endocrinol Metab. 2003;88:611–6.

Maghnie M, Cavigioli F, Tinelli C, Autelli M, Arico M, Aimarett G, Ghigo E. GHRH plus arginine in the diagnosis of acquired GH deficiency of childhood-onset. J Clin Endocrinol Metab. 2002;87:2740–4.

Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci. 2011;16(1):74–104.

Müller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, Pietsch T, Pohl F, Sörensen N, Calaminus G, Study Committee of KRANIOPHARYNGEOM. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. Eur J Endocrinol. 2000;165(1):17–24.

Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J, Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity. 2015;23(6):1226–33.

Schneeberger M, Gomis R, Claret M. Hypothalamic and brainstem neuronal circuits controlling energy balance. J Endocrinol. 2014;220:T25–46.

Sklar CA, Mertens AC, Walter A, Mitchell D, Nesbit ME, O'Leary M. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol. 2000;35:91–5.

Tschöp M, Weyer C, Tataranni A, Devanarayan V, Ravussin E, Heiman M. Circulating ghrelin levels are decreased in human obesity. Diabetes. 2000;50:707–9.

Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, Dhillo WS, Ghatel MA, Bloom SR. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab. 2001;86:5992.

14 Sella and Suprasellar Brain Tumours and Infiltrarive Disorders Affecting the HPA-Axis

Christine Yedinak

Contents

14.1 **Introduction** ... 257

14.2 **Empty Sella Syndrome: Primary Empty Sella (PES) and Secondary Empty Sella (SES)** ... 258
14.2.1 Definition ... 258
14.2.2 Epidemiology ... 258
14.2.3 Presenting Symptoms ... 258
14.2.4 Assessment and Testing ... 259
14.2.5 Treatment ... 259
14.2.6 Summary ... 259

14.3 **Infiltrative Disorders** ... 262
14.3.1 Definition ... 262
14.3.2 Hypophysitis ... 263
14.3.3 Sarcoidosis ... 265
14.3.4 Histiocytosis ... 266
14.3.5 Fungal Infection ... 267
14.3.6 Pituitary Abscess ... 267
14.3.7 Infectious Disorders ... 267
14.3.8 Primary Pituitary and Metastatic Carcinomas ... 267
14.3.9 Hemochromatosis ... 268

14.4 **Development and Hypothalamic Tumors** ... 268
14.4.1 Germ Cell Tumors ... 268
14.4.2 Rathke's Cleft Cyst (RCC) ... 268
14.4.3 Epidermoid and Dermoid Cysts ... 269

14.5 **Meningioma** ... 270
14.5.1 Definition ... 270
14.5.2 Epidemiology ... 270
14.5.3 Symptoms ... 270
14.5.4 Treatment ... 270
14.5.5 Outcome and Recurrence ... 270

C. Yedinak (✉)
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_14

14.6 **Harmatoma** 271

14.7 **Craniopharyngioma** 271
14.7.1 Definition and Epidemiology 271
14.7.2 Etiology 271
14.7.3 Symptoms 271
14.7.4 Assessment 271
14.7.5 Treatment 272
14.7.6 Nursing and Long-Term Care 272

14.8 **Conclusions** 272

References 273

Abstract

The pituitary is a unique organ that is key to maintaining end organ function. However, it is particularly susceptible to some tumors, cysts, and infiltrates. Disruption of pituitary function may help target symptom etiology, but can lead to significant morbidity and mortality if not treated effectively.

Patients can present with similar symptom of mass effect, headaches, and pituitary deficiencies despite disparate types of lesions. In some cases, the patient is asymptomatic, and the lesion is found incidentally on Computerized Tomography (CT)/Magnetic resonance imaging (MRI) imaging. Treatment may depend on the type of lesion found on MRI or after surgical pathology when a definitive diagnosis is acquired.

Disorders such as empty sella syndrome may be primary or secondary to other disorders such as intracranial hypertension or occur after tumor resection. Infiltrative and infective disorders may be primary or localized to the pituitary, or may result secondarily from other system diseases. Cysts or tumors beginning in embryonic development can become symptomatic, with growth impacting the optic apparatus resulting in mass effect symptoms such as headaches and/or visual changes. Other tumors may originate in the hypothalamus, grow downward and impact the optic apparatus and the pituitary gland.

Assessment includes a detailed history and physical, MRI and biochemical and dynamic testing for pituitary dysfunction. MRI may have characteristics suggestive of a diagnosis but surgical pathology is often required for a definitive diagnosis. Treatment is often dictated by tumor or lesion histology.

Nursing assessment includes patient emotional, social and executive functions, resources, family history including parental and personal exposures. Together these form the basis of patient education, preparation for further testing and treatment planning decisions. The patient's family can be important historians of patient symptoms particularly in the event of cognitive and memory dysfunction.

Keywords

Pituitary infiltrative disorders · Hypothalamic tumors · Intracranial hypertension · Pituitary dysfunction · Parasellar cysts

Abbreviations

ACTH	Adrenocorticotrophic hormone
AIP	Aryl hydrocarbon–interacting protein gene
CP	Craniopharyngioma
CSF	Cerebrospinal fluid
CT	Computerized tomography
DI	Diabetes insipidus
ES	Empty sella
FSH	Follicle stimulating hormone
GSU	Glycoprotein hormone subunits
HPA	Hypothalamic-pituitary-adrenal (axis)
ICP	Intracranial pressure
IIH	Idiopathic intracranial hypertension
LAR	Long acting release
LCH	Langerhans Cell Histiocytosis
LDL	Low density lipoprotein
LH	Luteinizing hormone

LHH	Lymphocytic hypophysitis
LINH	Lymphocytic infundibuloneurohypophysitis
MEN-1	Multiple endocrine neoplasia-type 1
MRI	Magnetic resonance imaging
PC	Pituitary carcinoma
PES	Primary empty sella
PH	Pituitary hypophysitis
QoL	Quality of life
RCC	Rathke's cleft cysts
SES	Secondary empty sella
SSA	Somatostatin analogues (ligands)
SSTR	Somatostatin receptor
TSH	Thyroid stimulating hormone
WHO	World Health Organization

Key Terms

- **Sella turcica:** the saddle like bony compartment in which the pituitary sits.
- **Suprasellar:** above the sella turcica.
- **Parasellar:** the region next to the pituitary.
- **Histopathology:** microscopic examination of tissue obtained during surgery.
- **Dynamic testing:** involves the stimulation or suppression of one or more pituitary hormones after the administration of a specific agent.
- **Hypopituitarism:** insufficient hormone production from one or more pituitary hormonal axes.
- **Panhypopituitarism:** inadequate hormonal production of all pituitary hormones.
- **Optic apparatus:** includes the optic nerves and optic chiasm.
- **Optic chiasm:** the point above the pituitary gland where the optic nerves from the eye cross over each other and enter the opposite side of the brain.

Key Points

- Pituitary function can be disrupted by benign cysts and tumors, locally aggressive and cancerous lesions or infiltrative disorders from remote system disease.
- Tumors may be asymptomatic until they exert mass effect or pressure on surrounding structures within the Sella such as the pituitary stalk or optic nerves.
- Patient symptoms may be similar at presentation despite different etiologies and often center symptoms of mass effect. Surgical pathology may be needed to guide treatment.
- A detailed patient intake history, including exposure risks, recent illnesses, family history, current symptoms of systems dysfunction and functional limitations for all patients is recommended to aid diagnosis. Family input is valuable.
- Pituitary dysfunction may be evident at presentation and require immediate evaluation and treatment, particularly if HPA axis dysfunction is present.
- Children are afflicted with some tumors with greater frequency than adults. Consideration may need to be given to growth hormone deficiency and replacement therapy after tumor control.

14.1 Introduction

The pituitary gland is aptly lauded as the body's *master gland*. However, the function of the gland is influenced by numerous genetic and genomic, anatomic, vascular, biochemical and metabolic and environmental factors. These factors can interact at all levels in relation to the gland modifying its actions and downstream impact on end organs.

The pituitary largely lies outside the protection of the blood–brain barrier, and thus is not protected from invasion of some pathologic species. Systemic inflammatory diseases, infectious, metastatic and immune disorders can infiltrate the pituitary, inflicting transient or devastating consequences on pituitary function. Biochemical changes from chemotherapeutic agents can result in partial or panhypopituitarism. Genetic and genomic changes secondary to metabolic and environmental exposures have been shown to negatively impact the pituitary hormonal functions.

Sella, parasellar, and suprasellar tumors can significantly change the pituitary structure, its functions, and patient symptomatology. Tumors

can arise from multiple cell types, mostly from local cells within the sella and suprasellar region, but can also result from distant metastasis or infection, albeit less frequently. Germ cell tumors, and epidermoid cysts and Rathke's cleft cysts (RCCs) are tumors that arise from developmental cells. Meningiomas are tumors derived from the protective meninges covering of the brain, including the pia mater, the arachnoid and the dura mater. Gliomas are tumors that arise from the supporting cells in the brain. Metastatic tumors originate in another part of the body and spread to the brain, but are extremely rare. Diseases such as tuberculosis, fungal infections, and inflammatory disorders usually originate in other body systems and may migrate to the pituitary.

The treatment goal in all cases is to minimize pituitary hormonal dysfunction, restore function and vision, and prevent secondary end organ dysfunction. This may involve the removal of a tumor or cyst and/or pituitary hormone replacement. Patient and family education and support is a vital component in treatment adherence to aid preservation of functional capacity and to improve quality of life.

14.2 Empty Sella Syndrome: Primary Empty Sella (PES) and Secondary Empty Sella (SES)

14.2.1 Definition

Empty sella (ES) occurs when there is a weakness or failure of the diaphragma sella and the subarachnoid space that allows cerebral spinal fluid (CSF) to herniate into the sella turcica resulting in compression or flattening of the pituitary gland (Tyrrell et al. 1994; Auer et al. 2018). This may produce a partial or a complete empty sella (>50% of sella fluid filled) (Carmichael 2017). As a result, the sella itself may become enlarged (Carmichael 2017). ES can be primary (PES) such as in the case of a congenital weakness (or absence) of the diaphragma sella or of an unknown etiology. Secondary empty sella (SES) may occur after a surgical tumor removal, radiation, trauma, increased intracranial pressure or pituitary infarction or necrosis, such as in postpartum Sheehan's syndrome (Tyrrell et al. 1994; Carmichael 2017). Other contributory conditions include hydrocephalus, intracranial hypertension (pseudotumor cerebri), thrombus, brain tumor, and Chiari malformation, all of which promote ES by increasing intracranial pressure (ICP). Other factors that have been associated with PES include obesity, hypertension, and sleep apnea, but the mechanisms are unclear (Fig. 14.1).

14.2.2 Epidemiology

Empty sella is relatively common, with a prevalence ranging from 5 to 35% of the general population as drawn from cases found on autopsy and from clinical practice imaging reports (Tyrrell et al. 1994). However, this may be an overestimate (Auer et al. 2018). Females are affected 5 times more than males particularly if they have a history of pregnancy (Tyrrell et al. 1994). Peak age at diagnosis is 30–40 years, perhaps earlier in females than in males. However, PES can also be found associated with genetic disorders or perinatal complications in children (Tyrrell et al. 1994). An estimated 8–15% of patients presenting with ES subsequently develop intracranial hypertension (IIH).

14.2.3 Presenting Symptoms

PES may be asymptomatic and an incidental finding on imaging obtained for other reasons. However, when symptoms occur, they include headaches, fatigue, and/or symptoms of anterior pituitary dysfunction. Women may present with menstrual irregularities, galactorrhea (often with normal prolactin), infertility, and hirsutism. Male presentation is often sexual dysfunction and gynecomastia (Tyrrell et al. 1994). On rare occasions, the pulsatile nature of CSF fluid in the sella may erode the bony sella floor, resulting in CSF rhinorrhea (a "CSF" leak) (Tyrrell et al. 1994). In the presence of a CSF leak, patients report a

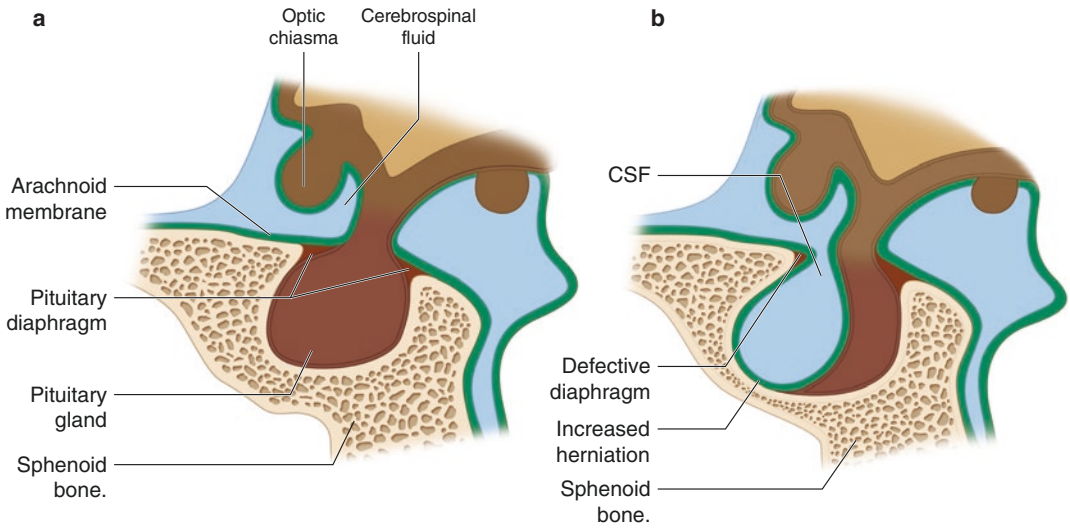


Fig. 14.1 Empty Sella Syndrome. (**a**) Normal pituitary and sella (color hatching green). (**b**) Partial Empty Sella with arachnoid membrane herniation and flattening of normal pituitary

severe, positional headache on standing and experience clear, salty fluid draining from the nares (usually unilaterally) with bending forward (Schlosser and Bolger 2003). Visual field deficits are an uncommon presentation. More severe forms of PES are associated with debilitating headache, increased intracranial pressure, possibly projectile vomiting, papilledema on fundal exam, and rarely seizures. ES can be confirmed by MRI or CT of the sella and suprasellar region (Tyrrell et al. 1994).

14.2.4 Assessment and Testing

The presence of hypopituitarism is controversial, but some studies indicate one or more pituitary axis dysfunctions may be present in up to 53% of cases (Auer et al. 2018; Li et al. 2017). Panhypopituitarism may be present in around 4% of cases (Tyrrell et al. 1994; Carmichael 2017). Pituitary functions testing is warranted even in asymptomatic patients (Auer et al. 2018). Ophthalmology evaluation is indicated to assess for any visual field deficits.

MRI is recommended for diagnosis and CT if MRI is otherwise contraindicated. Characteristic findings of ES on imaging include a fluid density filling the sella indicative of CSF, thinning of the pituitary stalk, and semilunar flattening of the pituitary against the sella floor. The stalk may be distorted to one side if unilateral ES is present (Chiloiro et al. 2017).

14.2.5 Treatment

Treatment is based on the etiology of ES. Replacement of pituitary hormonal deficiencies is warranted, particularly glucocorticoids, in the event of hypothalamic pituitary adrenal (HPA) axis dysfunction and adrenal insufficiency. Hydrocortisone is recommended as first replacement if needed followed by thyroxine. Sex hormones can be introduced when the patient is stable. However, growth hormone (GH) is not recommended in patients with intracranial hypertension (Tyrrell et al. 1994).

14.2.6 Summary

Overall, obese females 30–40 years with a history of pregnancy, headaches, hypertension, and sleep apnea may be at increased risk for PES. Assessment of these risk factors may be

helpful in guiding clinical decisions. Despite an asymptomatic presentation, pituitary function testing is recommended. Diagnostic MRI is recommended along with ophthalmology review for any involvement of the optic apparatus or visual field changes.

14.2.6.1 Intracranial Hypertension (Pseudotumor Cerebri)

14.2.6.1.1 Definition

Idiopathic intracranial hypertension or pseudotumor cerebri (IIH) is a disorder usually presenting with high CSF pressure when brain parenchyma is normal. This is not associated with a cerebral tumor, enlarged ventricles, or malignancy (Friedman et al. 2013). The mechanism of increased intracranial pressure in intracranial hypertension is unknown. Risk factors are as described above for PES. Although the course is mostly benign, there is a risk of vision loss in one or both eyes in 8–10% of cases and vision compromise in an estimated 50% of cases (Ball et al. 2011). Both steroid withdrawal and hyperparathyroidism have been linked to the development of IIH (Wall 2010).

14.2.6.1.2 Epidemiology

The incidence worldwide is reported as 0.5–2/100,000 people per year in the general population (Chatziralli et al. 2018). However, the prevalence increases to 3.5–19/100,000 in young overweight women (usually >20% overweight) (Wall 2010; Chatziralli et al. 2018). In pediatric populations, although there is no gender difference in prevalence, there is a trend toward a higher prevalence with age. There is also a higher prevalence in boys at a younger age than girls and in young adolescents with a higher in body mass index (BMI) (Sheldon et al. 2016). From 53.2 to 77.7% of pediatric cases are thought to be secondary to other known systemic changes, such as endocrine disorders, drugs, infections and/or trauma and, as such, may occur in children with average BMI (Per et al. 2013). The disorder is rare in children younger than 3 years and adults more than 60 years of age (Friedman et al. 2013).

14.2.6.1.3 Presenting Symptoms

Patients will usually present with bilateral headache behind the eyes that may be pulsatile and/or associated with tinnitus (pulse-synchronous tinnitus) (Wall 2010; Chatziralli et al. 2018). They may also report photophobia, nausea and dizziness, plus transient visual blurring of 30 seconds or less (Wall 2010). Headaches may be daily and pulsatile and become worse with coughing, straining, lying down, bending over or with other Valsalva maneuvers (Wall 2010; Chatziralli et al. 2018). Some features may be transient, but headaches most often last more than 1 h. Patients may report intermittent diplopia, that may be worse when looking toward the affected side and is associated with cranial nerve V1 involvement (Chatziralli et al. 2018). If cranial nerve V11 is involved, a slower blink reflex, difficulty in tightly closing the eye on the affected side, and/or sensory changes around and behind the ear may be found (González-Andrades et al. 2016). Children (females <7 years, males <8.5) may be asymptomatic (Sheldon et al. 2016).

14.2.6.1.4 Assessment and Testing

Papilledema is usually found on fundal exam in most patients and is an indication for further evaluation. Referral to neuro-ophthalmology and MRI are warranted. Emerging technologies now recommended include: Ophthalmic echography (ultrasound) and Optical Coherence Tomography (OCT); infrared reflectance imaging; computerized visual field exam; and visual evoked potential exams. These can be used as both diagnostic and follow-up testing to evaluate IIH. They evaluate the morphology of the optic nerve to determine the presence of vascular or CSF flow anomalies or neoplasms (Tyrrell et al. 1994; Chatziralli et al. 2018).

Although neurologic exam is invariably normal, other testing is recommended. Brain imaging with MRI/CT is essential to rule out other lesions. There are usually no cerebral ventricular abnormalities, but empty sella is found in up to 94% of patients with IIH (Tyrrell et al. 1994; Friedman et al. 2013). MRI is often followed by a lumbar puncture (spinal tap), to measure opening pressure of CSF, which has been a diagnostic

standard. However, this is currently controversial as CSF pressure changes during the day. Therefore, repeat testing is discouraged in favor of new optical diagnostics. The diagnosis criteria that have been used in adults and children were derived from the Dandy criteria with some modifications over the years (Friedman et al. 2013; Wall 2010; Rangwala and Liu 2007) (Table 14.1). The CSF opening pressure on spinal tap is largely considered diagnostic of IIH when pressures are >250 mm H_2O in obese adults and > 200 mm H_2O in non-obese adults (Friedman et al. 2013; Wall 2010). In children, particularly over 8 years of age, the opening pressure may be normal up to 250–280 mm H_2O, with lower pressures for younger children (Friedman et al. 2013; Rangwala and Liu 2007). A CSF sample is often collected for analysis to look for potential causes of IIH. Lumbar puncture may also cause a temporary reduction in CSF pressure and symptoms (Wall 2010; Idiopathic Intracranial Hypertension 2014).

Table 14.1 Recommended diagnostic criteria for pediatric IIH

1.	Patient is pre-pubertal
2.	If symptoms or signs present, they may only reflect those of generalized intracranial hypertension of papilledema. Normal mental status
3.	Documented elevated intracranial pressure (age appropriate) measured in the lateral decubitus position *Neonates: >76 mm H_2O *Age less than 8 with papilledema: >180 mm H_2O *Age 8 or above or less than 8 without papilledema: >250 mm H_2O
4.	Normal CSF composition except in neonates who may have up to 32 WBC/mm^3 and protein as high as 150 mg/dL
5.	No evidence of hydrocephalus, mass, structural, or vascular lesion on MRI, with and without contrast, and MR venography. Narrowing of the transverse sinuses is allowed
6.	Cranial nerve palsies allowed if they are of no other identifiable etiology and improve with reduction in cerebrospinal fluid pressure or resolution of other signs and symptoms of intracranial hypertension
7.	No other identified cause of intracranial hypertension

Reference and permission: Rangwala and Liu (2007)

Accurate weight measurement is important. The risk and prevalence of IIH rises concomitantly with BMI in children and in adults (Friedman et al. 2013; Sheldon et al. 2016; Rangwala and Liu 2007). In children, the risk is higher with adolescent weight gain and obesity by early adolescence (Sheldon et al. 2016; Rangwala and Liu 2007). This was also positively correlated with the onset of puberty as defined by tanner criteria and not by age (Sheldon et al. 2016). Girls with IIH may also be taller than boys using standardized anthropometrics. In a random controlled study, the risk of developing IIH in adults was also shown to be progressively higher with higher classes of obesity (Daniels et al. 2007).

Pituitary dysfunction in IIH is usually associated with a high prevalence of ES syndrome and should be evaluated in this context. Elevated prolactin and/or deficiencies in one or more axes functions or panhypopituitarism can occur (Table 14.1) (Chiloiro et al. 2017).

14.2.6.1.5 Treatment and Long-Term Management

There are no guidelines for the management of IIH. The main goals are to reduce ICP, preserve vision, and reduce disability (Chatziralli et al. 2018). Weight loss remains a principle goal in treatment and bariatric surgery may be indicated. A weight loss of 5–10 lbs (2–4.5 kg) has been shown to significantly reduce ICP and papilledema (Tyrrell et al. 1994; Chatziralli et al. 2018).

Medical therapies with diuretics (Acetazolamide and Furosemide) and the antiepileptic, topiramate have been shown to improve symptoms over placebo treatments in clinical trials (Chatziralli et al. 2018). Surgical intervention with CSF diversion (ventriculoperitoneal shunt) may be required to control ICP for intractable headaches if medical therapy fails. Although effective in some cases, up to 50% of patients may subsequently need a shunt revision (Wall 2010). Optic nerve fenestration or cutting window or slits in the fibrous strands that form the optic sheath behind the globe of the eye has been reported as improving or relieving headaches in 50% or more of patients so treated (Wall 2010).

Recurrence may occur many years after initial diagnosis and treatment. This is apparent after weight gain, particularly in children, and reported

from long-term medical follow-up well into adulthood (Friedman et al. 2013). Corticosteroids may be useful, but a slow taper is recommended to avoid recurrent papilledema (Wall 2010).

14.2.6.1.6 Quality of Life (QoL)

Although few studies have focused on QoL, changes in both visual and general QoL have been reported (Ball and Clarke 2006). In one report, no difference was found in patients with IIH with respect to anxiety and depression on QoL short form SF-36 and the hospital anxiety and depression scale (HADS) questionnaires versus a standardized population (Ball and Clarke 2006). Measures for pain and change in health status were higher than in the general population. In another study comparing women with and without IIH with age and weight matched women and normal weight subjects, the patient group was found to have significantly increased anxiety, depression, and hardship related to health issues than other women (Kleinschmidt et al. 2000). Assessment of visual QoL using a standardized instrument at diagnosis of IIH revealed an association between visual acuity in the worst eye, visual symptoms, and pain symptoms (headache, neck pain) with decreased QoL. Obesity was not found to be associated (Digre et al. 2015). More QoL studies are needed, particularly regarding pre- and post-treatment effects.

14.2.6.1.7 Nursing Care

Assess the patients in the context of the impact of their symptoms on current functioning and lifestyle to develop a patient-centered management plan. Evaluate the lifestyle factors that may precipitate symptoms and discuss alternate strategies to avoid increased ICP. These should include: monitor fluid intake and balance intake of electrolyte containing solutions and water; monitor and avoid activities that may precipitate a Valsalva maneuver that increases intrathoracic pressure and subsequently ICP (i.e., breath holding, heavy lifting, straining with defecation, and coughing) (Perry et al. 2014). Encourage the patient to keep a headache diary for long-term assessment of features and pain level throughout treatment.

Weight loss and medication adherence are major foci of treatment. Discuss and implement weight loss strategies, particularly if the patient's BMI is >30 and offer nutritional counseling. If appropriate, refer the patient for consultation with a bariatric surgeon. Stress the need for medication adherence, particularly taking regular doses of antihypertensives and diuretics. If the patient is treated with glucocorticoids, establish a taper schedule in writing for the patient to follow. Review when and how the patient typically takes each medication and discuss alternate strategies and medication reminders as needed.

Regular and long-term monitoring of visual changes is essential to avoid vision loss. Referral for a formal neuro-ophthalmology review and regular follow-up for monitoring to assess papilledema is essential. Provide patient education regarding monitoring symptoms, emphasizing the importance of self-care. Outline an ongoing monitor plan to include symptom review, weight management review, ophthalmology, and MRI as needed.

14.3 Infiltrative Disorders

14.3.1 Definition

Infiltrative disorders occur with the deposition of cells or substances not normally found in the pituitary that originate from distal disease (McDermott 1997). These disorders are often classified as inflammatory, infectious, neoplastic or from other etiologies such as hemochromatosis or cancer immunotherapy (McDermott 1997; Iwama et al. 2014) (Table 14.2).

The impact on the anterior or posterior pituitary may vary by disorder, and some authors report this is influenced by differential vascular supply. The hypothalamus and the anterior pituitary are supplied by the hypophyseal portal circulation from the superior hypophyseal artery, and the posterior pituitary is supplied largely by arterial blood from the inferior hypophyseal artery. This may explain the higher prevalence of some disorders in the anterior versus the posterior pituitary (McDermott 1997).

Table 14.2 Classifications of infiltrative disorders

Inflammatory
Sarcoidosis
Histiocytosis
Hypophysitis
Lymphocytic
Granulomatous
Necrotizing infundibulohypophysitis
Wegener's granulomatosis
Infectious
Tuberculosis
Syphilis
Fungi
Parasites
Viruses
Neoplastic
Metastatic carcinomas
Lymphoma
Leukemia
Other
Hemochromatosis
Cancer immunotherapy

Adapted from McDermott (1997)

These disorders may be asymptomatic and found incidentally on brain imaging for unrelated injuries or for symptoms such as headaches, visual changes, or other pituitary deficiencies.

14.3.2 Hypophysitis

Pituitary hypophysitis (PH) is the result of infiltration into the pituitary of lymphocytes, macrophages, and plasma cells that can lead to temporary or permanent pituitary dysfunction in one or more axes (Glezer and Bronstein 2012). PH is considered a rare disease, with an estimated incidence of one case in nine million individuals per year or approximately 1% of all pituitary adenomas on postoperative histology. PH may be primary or only affecting the pituitary or secondary to other systemic diseases (Glezer and Bronstein 2012). Several types of primary hypophysitis have been identified, including: Lymphocytic (LYH), granulomatous, xanthomatous, mixed forms (lymphogranulomatous, xanthogranulomatous), necrotizing and Immunoglobulin-G4 (IgG4) plasmacytic types or related to immunotherapy or cancer chemotherapy with ipilimumab (Glezer and Bronstein 2012; Shi et al. 2009; Mittal et al. 2012; Faje 2016). Although anti-pituitary or autoantibodies can be measured, the literature reports variable results (Crock 1998; Gellner et al. 2008). Secondary PH is associated with other autoimmune diseases such as thyroiditis, diabetes, hypoparathyroidism, Graves′ disease, Addison′s disease, multiple autoimmune endocrinopathies, or other organ-specific immune diseases (Mittal et al. 2012). Definitive diagnosis and determination of Infiltrative cell types is only found on histopathology.

14.3.2.1 Lymphocytic Hypophysitis (LYH)

LYH can be classified by location within the pituitary, such as lymphocytic adenohypophysitis (focal lesion), lymphocytic infundibuloneurohypophysitis ((LINH) involving the pituitary stalk and posterior pituitary function), and lymphocytic panhypophysitis (generalized) (Glezer and Bronstein 2012).

14.3.2.2 Epidemiology

In LYH, females are more likely to be affected than males 6:1 with an average age of 34.5 and 44.7 respectively years. The highest risk period for the development of PH is during pregnancy or immediately postpartum (usually within 2 months), when approximately 57% of cases are found (Melmed and Kleinberg 2016). Pediatric cases of LYH are extremely rare, but there is a similar preponderance of females, as in adult cases (Gellner et al. 2008). However, in immunotherapy CTLA-4 mediated hypophysitis, males are affected more commonly than females (Faje 2016).

14.3.2.3 Course and Symptoms of LYH

The course of PH in both adults and children may be short and spontaneously resolved but may also be progressive and result in pituitary cell destruction, atrophy and subsequent ES or fibrosis (Gellner et al. 2008; Melmed and Kleinberg 2016). In the Lymphocytic Infundibuloneurohypophysitis (LINH) subtype

that affects the pituitary stalk (or if the posterior pituitary is involved), the patient usually presents with symptoms of diabetes insipidus and elevated prolactin (Mittal et al. 2012; Melmed and Kleinberg 2016). Presenting symptoms are similar in adults and children, and include headache, symptoms of diabetes insipidus (DI) with polyuria and polydipsia DI or compressive symptoms with VF loss (Gellner et al. 2008). Symptoms of pituitary dysfunction may manifest immediately or be delayed as pituitary cells are progressively destroyed as inflammation is replaced by fibrosis (Gellner et al. 2008; Melmed and Kleinberg 2016). Prolactin may be elevated due to stalk involvement or compression, and hypogonadism is estimated to occur in 56% of patients. Hypothyroidism may be a late appearing deficiency. Growth hormone deficiency is also reported in LYH, but is not as common as in other types of PH (Melmed and Kleinberg 2016).

14.3.2.4 Patient Assessment

Assessment of the HPA axis with dynamic testing, along with serum analysis for gonadal functions (Follicle Stimulating Hormone (FSH), Luteinizing hormone (LH), and testosterone), prolactin, Thyroid stimulating hormone (TSH), Thyroxine (FT4), and Insulin-like growth factor 1 (IGF-1) is recommended. In early studies, serum autoantibodies to 49-kDa cytosolic protein were found in 70% of patients with histology-confirmed PH (Crock 1998). Assessment of anti-pituitary antibodies may be helpful in some cases (Glezer and Bronstein 2012; Gellner et al. 2008).

MRI is recommended for diagnosis and management. Characteristic changes found on MRI include: homogenous enlargement of the pituitary, a lesion that is indistinguishable from an adenoma, widening of the pituitary stalk, and loss of the pituitary bright spot in the posterior pituitary. The pituitary gland may appear pear shaped on coronal (frontal) images (Mittal et al. 2012; Melmed and Kleinberg 2016; Laws et al. 2006). As PH resolves, these changes normalize. Although MRI is useful in diagnosis, a definitive diagnosis requires histopathology after a biopsy or removal of the lesion or pituitary tissue.

14.3.2.5 Treatment

Supportive treatment is usually recommended, including the management of pituitary deficiencies (Fleseriu 2017). The need for pituitary hormonal replacement therapy may be prolonged. Glucocorticoids may be needed if adrenal hypofunction is evident. The risk of thyroid dysfunction in cytotoxic T-lymphocyte antigen 4 (CTLA4) mediated hypophysitis is higher and occurs earlier than in lymphocytic hypophysitis, so replacement may be indicated early in the course of the disorder (Dillard et al. 2010).

High dose steroids have been used to treat inflammation and avoid pituitary cell destruction. This remains controversial as results of studies has been equivocal (Faje 2016; Laws et al. 2006). However, high dose glucocorticoids of approximately 1 mg/kg prednisone (or equivalent such as methylprednisolone) with a slow taper may be used. In cases of ipilimumab therapy related PH, steroids the and cessation of the drug may be considered (Faje 2016). Vasopressin replacement with desmopressin may be used to treat symptoms of DI. All pituitary functions should be tested (including testing the HPA axis function) and monitored at regular intervals.

Surgery is usually not indicated if the diagnosis can be made clinically. With clear clinical and biochemical evidence of PH, the patient can be monitored by yearly MRIs for a minimum of 5 years or until stable (Laws et al. 2006). However, surgery is recommended when there is progressive vision loss or there is a need for histology with suspicion or risk of metastatic disease (Faje 2016; Melmed and Kleinberg 2016).

14.3.2.6 Histopathology

Histopathology does provide a definitive diagnosis, and is useful in differentiating the specific infiltrative cells to classify the type of PH (Table 14.3).

14.3.2.7 Immunotherapy-Related Autoimmune Hypophysitis

Hypophysitis associated with the treatment of metastatic cancers with immunotherapies such as Ipilimumab has become more frequent (Dillard et al. 2010). Ipilimumab is a monoclonal antibody that downregulates the immune response by

Table 14.3 Classifications of pituitary hypophysitis

Hypophysitis type	Characteristics
Lymphocytic	Anterior pituitary with diffuse T and B lymphocyte infiltrates (Melmed and Kleinberg 2016)
Granulomatous	Granulomatous areas, multinucleated giant cells (Elgamal et al. 2017)
Xanthomatous	Cholesterol clefts
IgG4	A high ratio of IgG4/IgG-positive cells (>40%) (Bernreuther et al. 2017)
Necrotic	Necrotic tissue, mononuclear cell, and CD8-positive cytotoxic T cells (Gutenberg et al. 2012)

blocking the CTLA4 receptors expressed on pituitary cells, thereby allowing T cell infiltration and triggering an autoimmune response (Faje 2016; Dillard et al. 2010). This may occur preferentially in PRL, TSH, and adrenocorticotropic hormone (ACTH) producing cells (Iwama et al. 2014; Fleseriu 2017). Recent studies indicate that 8–15% of patients treated with ipilimumab may develop PH, men more frequently than women (Faje 2016; Melmed and Kleinberg 2016). Recognition of clinical symptoms is key. Symptoms may appear after 1–2 months of treatment and include headaches, easy fatigability, weakness, anorexia, and nausea. Hyponatremia may develop in some cases. Visual symptoms and DI appear to be rare (Iwama et al. 2014; Faje 2016). Symptoms may be vague and non-specific or severe, particularly when adrenal insufficiency is the presenting symptom. Evidence of pituitary enlargement on MRI may present before other symptoms of pituitary dysfunction (Faje 2016). PH appears to be rare when other immunotherapies are used (Faje 2016).

14.3.2.8 Nursing Care

Patient assessment is centered on symptomatology and long-term management. If treatment with high dose glucocorticoids is initiated, family and patient education regarding side effects and management strategies for mood changes, and increased appetite may be useful to support treatment adherence. A written schedule of taper for patient self-care guidance is helpful. Patients should be aware of the risks of tapering too quickly and the nurse alert for worsening symptoms that may be indicative of recurrent hypophysitis, IIH, or adrenal insufficiency. Dynamic testing of the HPA axis may be indicated before and after glucocorticoid taper. Patient and family members require education regarding the signs and symptoms of adrenal insufficiency. Both symptom evaluation and regular MRIs are used as a means of monitoring treatment efficacy. MRIs may be indicated every 6–12 months until stable or hypophysitis is resolved.

Management of fluids may vary with the patient's climatic environment and is paramount in cases with DI. Provide the patient with the resources to assess under and over treatment of DI as a component of education. Fluid status, hypo- and hypernatremia require close monitoring.

Long-term management of pituitary deficiencies may be required. These needs may change across the lifespan or with changes in accessibility to treatment. The need for replacement may be lifelong and also require a transition plan in the case of patients re-locating or transferring care, particularly to local primary care or general practice services.

14.3.3 Sarcoidosis

Sarcoidosis is an immune disease in which inflammatory cells form abnormal lumps or granulomas. The disease most often begins in the lungs, skin, or lymph system, but may affect any tissue. The hypothalamus and pituitary gland are affected in an estimated 5–10% of cases. Formed of macrophages and T cells during the inflammatory phase, over time, the affected tissue becomes fibrotic (McDermott 1997; Moshkin et al. 2011). Patients present with symptoms of anterior and posterior pituitary insufficiency including DI and adrenal insufficiency. Surgical pathology is needed for definitive diagnosis. Treatment with corticosteroids is the primary therapy (Moshkin et al. 2011). The nursing response is similar to that described for other infiltrative disorders (See above).

14.3.4 Histiocytosis

14.3.4.1 Definition

Langerhans cells are dendritic cells of the immune system that reside in the basal epidermal layers. They process and present antigens to T cells and trigger activation of other lymphocytes to fight disease (Néel et al. 2015). Histiocytes are immature cells. Langerhans cell histiocytosis (LCH) is a rare form of cancer where Langerhans cells proliferate into numerous immature cells in one or in multiple body organs or tissues, forming granulomas (Néel et al. 2015). Mutations of the BRAF, MAP 2 K1, RAS, and ARAF genes have been found to be associated with LCH (PDQ® Pediatric Treatment Editorial Board 2018). Risk factors include: parental exposures to metal, granite, or wood dust in the workplace, parental history of cancer (including LCH) or thyroid disease, Hispanic descent, smoking, newborn infection or lack of inoculations in childhood (PDQ® Pediatric Treatment Editorial Board 2018).

14.3.4.2 Epidemiology

The pituitary is a susceptible site for LCH, but the prevalence is low and estimated at less than one-third of all cases (Néel et al. 2015; PDQ® Pediatric Treatment Editorial Board 2018). Although both adult and childhood cases occur, LCH is more common in children, with a prevalence of 1:200,000 children, with the highest incidence in newborns (Néel et al. 2015; Tillotson and Bhimji 2018). However, some studies indicate that 58% of patients are adults (Néel et al. 2015). Mortality is low if the disease is limited to a single area such as in the pituitary.

14.3.4.3 Symptoms of LCH

Pituitary LCH is often associated with DI as the presenting symptom. In 50% of children, LCH is accompanied by growth hormone deficiency plus DI. When the hypothalamus is involved, children may present with significant weight gain. With anterior pituitary involvement puberty may be early or delayed (Melmed and Kleinberg 2016; PDQ® Pediatric Treatment Editorial Board 2018). Adult onset pituitary LCH also presents with DI and one or more pituitary deficiencies. Hypogonadism is most frequently reported (Catford et al. 2016). The disease may be self-limiting or, in an estimated 6% of cases, progress to panhypopituitarism in both adults and children (Catford et al. 2016).

14.3.4.4 Patient Assessment

Evaluation in all cases includes MRI and assessment of all pituitary functions. Dynamic testing for the evaluation of HPA axis function is critical. Assessment for multisystem disease may be indicated based on the patients' history and physical exam (Catford et al. 2016). A water deprivation test may be needed for diagnosis of DI. Genetic testing is recommended, particularly in cases with a family history of LCH (PDQ® Pediatric Treatment Editorial Board 2018). A history of parental exposures is needed, particularly in pediatric cases. MRI may show enlargement of the pituitary, stalk thickening, and loss of the posterior pituitary bright spot (Melmed and Kleinberg 2016).

14.3.4.5 Treatment

Treatment recommendations vary. Some authors recommend a trial of high dose glucocorticoids prior to surgical biopsy, which may ultimately be necessary for definitive diagnosis (Néel et al. 2015; Catford et al. 2016). High dose glucocorticoids plus cancer chemotherapy are indicated in some cases, particularly in childhood LCH (Melmed and Kleinberg 2016; Carroll et al. 2018). This requires collaboration with pediatric or adult oncology for clinical management. Pituitary replacement therapy with vasopressin for DI control, growth hormone replacement in children, and replacement of gonadal hormones in adults are commonly required. However, all pituitary hormones may require replacement in severe cases (Catford et al. 2016). Chemotherapy and radiation treatments have also been used, but there are no randomized controlled studies that have established the most effective treatment (Carroll et al. 2018).

14.3.4.6 Outcome and Nursing Care

Long-term outcomes depend upon the patient's age and disease severity. Ongoing monitoring

is required with MRI for normalization of the pituitary stalk and gland size, anterior pituitary hormonal functions and electrolytes for control of DI. In children, monitoring growth and diet and for evidence of secondary cancers may be indicated, particularly after early chemotherapy or radiation treatment (Néel et al. 2015). An individual approach to treatment is essential, as some children may suffer neurological deficit and need multidisciplinary approach to care, whereas adults may suffer from issues such as infertility. Childhood survivors may suffer from quality of life issues that need evaluation and intervention appropriate to their life stage needs (PDQ® Pediatric Treatment Editorial Board 2018).

LCH patient and provider support and information available online includes: The Histiocytosis Study Group (GEH) Website http://www.histiocytose.org/geh/ which is described as "An association of health professionals whose purpose is to improve the medical management of patients with histiocytosis as well as the development of medical and scientific research on these pathologies," and the Histiocytosis association https://www.histio.org.

14.3.5 Fungal Infection

Fungal infections of the pituitary associated primarily with sphenoid aspergillus have been reported, but are rare (Sajko et al. 2015). These pituitary lesions show characteristic changes, such as high and low intensity regions on CT or MRI associated with aspergillus proliferation (Sajko et al. 2015). The incidence is reported to be increasing secondary to immunocompromise associated with diabetes mellitus and treatment with immunosuppressive therapies. CNS fungal infections are associated with a mortality of 50–100% and require aggressive treatment with antifungal medications (Iplikcioglu et al. 2004; Dubey et al. 2005).

Patients largely present with headache, vomiting, proptosis, sinus congestion, weakness, and altered sensorium. Although Aspergillus was found in the majority of reported cases, infection with Cryptococcus and Candida has also been found on histopathology (Dubey et al. 2005).

14.3.6 Pituitary Abscess

An abscess in the pituitary is extremely rare, with very few reported cases. These usually present as a pituitary adenoma and the patient reports headaches and visual changes with larger lesions. Pathologic etiology may be fungal, such as in aspergillus abscess, bacterial or sterile (Iplikcioglu et al. 2004). Radiographic findings on MRI or CT are not useful in the diagnosis, and transsphenoidal surgery with biopsy or resection of the lesion is needed for diagnosis and to provide definitive treatment. Antifungal or antibiotic therapy is recommended (Iplikcioglu et al. 2004).

14.3.7 Infectious Disorders

Tuberculosis, syphilis, acquired immune deficiency syndrome (AIDS), hemorrhagic fever, and other viral syndromes may present as pituitary lesions or can result in pituitary dysfunction (Fleseriu 2017). A tuberculin lesion in the pituitary may be indistinguishable on MRI from other pituitary lesion and may present as syndrome of inappropriate antidiuretic hormone (SIADH with hyponatremia), mass effect or may be asymptomatic. These infections may rarely result in a pituitary abscess or fungal infection. ACTH deficiency may be present, in association with AIDS infection or hypogonadism and/or sick thyroid syndrome requiring glucocorticoid replacement. Pituitary atrophy and empty sella syndrome can occur as a result of hemorrhagic fever (Fleseriu 2017). Pituitary deficiencies up to panhypopituitarism may be the end result of infection.

14.3.8 Primary Pituitary and Metastatic Carcinomas

Pituitary carcinomas (PC) are rare but carry a high mortality rate. At 5 years after diagnosis the

estimated mortality is over 66 and 80% of patients by 8 years after diagnosis. However, the estimated prevalence is low, occurring in only 0.1–0.2% of all pituitary tumors (Yoo et al. 2018). Two distinct groups of patients have been described with PC: those with pituitary adenomas having slow progression and recurrence over a number of years from a pituitary adenoma and those with rapid oncogenesis and death. Most PC fall into the former category (Yoo et al. 2018).

Elevation of the histologic proliferative marker Ki67 may be an indicator of tumor aggression but the cutoff percentage of cells required for this to be a sensitive predictor of recurrence or oncogenesis is unclear and not defined by WHO (Yoo et al. 2018). Likewise, the use of tumor suppressor p53 immunopositivity as a malignant marker is also debated. The European Endocrine Society Guidelines recommend the measurement of p53 and a mitotic count if Ki67 is >3% (Raverot et al. 2018).

Once diagnosed with a pituitary tumor, many patients express fears of brain cancer. Based on these statistics, they can be quickly reassured that cancer is most unlikely.

14.3.9 Hemochromatosis

Iron overload associated with high ferritin and total iron binding capacity in hemochromatosis is a hereditary autosomal recessive disorder. The disorder is related to excess absorption of iron from dietary sources (Carmichael 2017). The uptake of iron in the pituitary, preferentially by gonadotroph cells, leads to hypogonadism. Other anterior pituitary hormones may also be affected to a lesser degree (Carmichael 2017). Genetic testing and pituitary function testing are indicated in the presence of hemochromatosis.

14.4 Development and Hypothalamic Tumors

14.4.1 Germ Cell Tumors

Germinomas or germ cell tumors are rare, with reports of prevalence varying by age and country. In children, CNS cases represent 0.5–2.1% of all intracranial tumors reported in western countries but are reported in up to 16% of intracranial tumors in Japan (Moshkin et al. 2011; Guedes et al. 2018). It is very rare that the tumor is focused in the pituitary (Moshkin et al. 2011).

The etiology of germ cell tumors is presumed to be from residual or displaced embryonic cells with tumors most commonly found in the midline suprasellar and pineal regions. Tumors are classified according to stage of embryonic development that the tumor cells most closely resemble such as germinoma, teratoma, choriocarcinoma, or mixed types. The peak incidence occurs in the second decade of life with males more commonly presenting with pineal tumors and females with suprasellar tumors (Moshkin et al. 2011; Guedes et al. 2018). An association with syndromes such as Downs, Klinefelter's, and Cornelia de Lange has also been reported (Moshkin et al. 2011).

Patients with suprasellar lesions usually present with mass effect or compression of the optic chiasm with visual changes, precocious puberty, hypothalamic or pituitary dysfunction (including hypothyroidism, delayed growth hormone deficiency, and/or diabetes insipidus) (Moshkin et al. 2011; Guedes et al. 2018). A biopsy and surgical debulking of the tumor may be needed for diagnosis and for treatment in the event of mass effect. Teratomas may be removed by surgical resection, but germinomas are known to be sensitive to radiation, with an excellent prognosis. However, late effects of radiation therapy need to be considered, including the development of hypopituitarism as the individual ages (Guedes et al. 2018). Some types of germ cell tumors may need the addition of chemotherapies.

14.4.2 Rathke's Cleft Cyst (RCC)

14.4.2.1 Definition

RCCs are thought to form from the remnants of the Rathke's pouch during embryogenesis (Moshkin et al. 2011). They are differentiated from other cysts by their mucoid colloid content (Huo et al. 2018). RCCs are usually small (<5 mm) and asymptomatic, but may grow large

enough to cause compression of the optic apparatus and mass effect symptoms or may be incidentally found on imaging for other purposes. The majority of RCCs are between 10 and 20 mm, but cases up to 50 mm have been reported (Larkin et al. 2014).

14.4.2.2 Epidemiology

Females are affected over males 2:1 with a peak age of 30–40 years (Moshkin et al. 2011). This ratio may be higher in pediatric populations with reports of up to 3.7: 1 female to male case (Larkin et al. 2014).

14.4.2.3 Symptoms

Typical symptoms are headaches that may occur even with small tumors and are a presenting feature in approximately 40% of cases (Larkin et al. 2014; Fleseriu et al. 2009). Visual deficits may begin with increasing mass effect with growth of the cyst. Symptoms of pituitary deficiencies are reported in up to 81% of patients (Larkin et al. 2014). Hypogonadism, menstrual abnormalities, and prolactinemia are most common. Rupture of the cyst can occur resulting in inflammation, headache, and symptoms of aseptic meningitis. Sphenoid sinusitis, syncope, and seizures can also occur (Larkin et al. 2014).

14.4.2.4 Treatment

Treatment varies with the patient's symptoms and size of cyst. Up to one-third of patients may have spontaneous resolution of the cyst but 5.3–31% grow slowly during a watch period and required surgery (Larkin et al. 2014). Transsphenoidal surgical removal of the cyst is the treatment of choice after replacement of glucocorticoids in cases of hypoadrenalism. The use of intraoperative ethanol infusion to remove any residual cell wall has been described, but studies have not shown significant benefit in recurrence rates (Larkin et al. 2014). The need for radiation therapy is rare. Headaches are significantly improved or resolved after cyst removal, and pituitary deficiencies may be resolved (Larkin et al. 2014; Fleseriu et al. 2009). Recurrence usually occurs within the first 5 years postoperatively and can occur in up to 48% of cases. Multiple relapses may occur, but remain rare (Larkin et al. 2014).

14.4.3 Epidermoid and Dermoid Cysts

These are cysts that are formed in early development, either in or around the sella, and are lined with keratinized squamous epithelium. Dermoid cysts contain sebaceous or apocrine glands and/or hair follicles (Moshkin et al. 2011; Huo et al. 2018). Less the 1% of intracranial lesions are epidermoid or dermoid cysts. Similar to other cystic sella and parasellar lesions, the patient usually presents with symptoms of mass effect such as headache and visual disturbances. Males are affected more frequently than females 1.7:1 and with dermoid cysts presenting in early adulthood and epidermoid cyst in mid-40s. Pituitary deficits may also be present and should be evaluated but are not common (Huo et al. 2018).

Surgical resection remains the treatment of choice. However, chemical meningitis may occur if the cyst ruptures and keratinous material is spilled (Moshkin et al. 2011). It is important that the capsule also be removed to avoid recurrence (Huo et al. 2018). Cases of squamous cell carcinoma in the cyst have also been reported (Moshkin et al. 2011).

14.4.3.1 Arachnoid Cyst

Arachnoid cysts are suprasellar cysts that are developmental defects in the arachnoid membrane. Fluid accumulates in the defect and may eventually grow large enough to apply mass effect on the optic apparatus. The patient may present with visual deficits and visual field deficiency, but usually the pituitary is spared and there is no impact to pituitary function (Shin et al. 1999; Gustina et al. 2017). In congenital cases, obstructive hydrocephalus may be found with symptoms of increased intracranial pressure. These patients will often present before the age of 5 years and concomitant ACTH, GH deficiency and/or precocious puberty may be evident (Gustina et al. 2017). In adulthood, arachnoid cysts may be asymptomatic or an incidental finding on a head CT or MRI for other reasons. However, these may grow slowly and present with symptoms of mass effect over time. Pituitary deficiencies are rare in adulthood (Shin et al. 1999). Treatment to remove or fenestrate the cyst

usually resolves the symptoms with very rare recurrence (Shin et al. 1999).

14.5 Meningioma

14.5.1 Definition

An estimated one-fifth of all meningiomas occur in the sella and parasellar regions (Melmed and Kleinberg 2016; Dolecek et al. 2012). These are tumors that arise from the arachnoid and Meningothelial cells. They may invade the pituitary but rarely originate in the pituitary. They normally migrate downwards into the sella and may affect both the optic nerve causing mass effect. Impact on the pituitary stalk can result in elevated prolactin levels.

14.5.2 Epidemiology

Meningiomas represent approximately 30% of all intracerebral tumors (Melmed and Kleinberg 2016; Dolecek et al. 2012). More females are affected than males (2.8:1 in adulthood). However, no gender difference is found for the rare meningiomas found in children and adolescents. The prevalence does increase with age, and most patients present in middle age (40–55 years) (Gustina et al. 2017). Estrogen receptors in meningiomas make these tumors susceptible to growth during pregnancy, during the menstrual cycle, or during the use of estrogen containing birth control or with hormone replacement therapy.

14.5.3 Symptoms

Patient symptoms are dependent on the area affected. In suprasellar tumors, the patient often reports slow vision loss, usually in one eye associated with mass effect (Gustina et al. 2017). Headaches, deterioration in hearing and cognition, short-term memory loss, and confusion are reported in approximately 20% of patients. Up to 40% of patients are obese at the time of presentation (Gustina et al. 2017). Pituitary dysfunction varies but hypogonadism and menstrual disorders are most common (Gustina et al. 2017). On MRI, meningiomas have a characteristic encapsulated appearance and create their own cavity within the brain parenchyma (Gustina et al. 2017).

14.5.4 Treatment

Tumor resection may be achieved in some cases using a transsphenoidal approach. However, meningiomas are very vascular lesions, and may hemorrhage with tumor resection (Melmed and Kleinberg 2016). Craniotomy may to needed and also tumor embolization for safety. Evaluation and monitoring of both visual acuity and visual fields is indicated. Monitoring of pituitary function status pre- and postoperatively is recommended.

14.5.5 Outcome and Recurrence

Short-term outcomes show restoration or improvement of visual deficits in 60% or more of patients. However, recurrence rates are high. Numerous histological variants have been described, and tumors are graded using the World Health Organization (WHO) classification: grade I (benign, 90%), grade II (atypical, 8%), and grade III (anaplastic/malign, 2%) (Shivapathasundram et al. 2018). The higher the grade, the higher the risk of tumor recurrence, with up to 80% recurrence if grade III. However, even WHO grade I meningiomas reoccur in about 20% of patients, particularly when histology indicates a Ki67 index of 3% or higher (Shivapathasundram et al. 2018). Men are more likely to have tumor recurrence than women. Redo surgery and radiation therapy may be necessary for tumor control. Several researchers have found the presence of cancer stem cells in meningiomas that may present a treatment target for the future (Shivapathasundram et al. 2018). Patients require close follow-up and monitoring with MRI every 6–12 months until stable and at least yearly over the first 5 years. Once stable the patient may be able to transition to MRI every 5 years.

14.6 Harmatoma

These are rare benign pedunculated tumors found on the hypothalamus and the floor of the third ventricle that are composed of ganglion cells (Moshkin et al. 2011). Most patients present before the age of 4 years with precocious puberty (90%), "laughing" seizures, behavioral issues, and developmental delay (Gustina et al. 2017). Patients may become obese over time. Harmatomas may also be associated with other inherited autosomal dominant disorders such as Pallister–Hall syndrome (Gustina et al. 2017).

The treatment of precocious puberty is the downregulation of GnRH receptors with long acting GnRH analogues. Surgical options are not usually indicated secondary to increased risk to local structures, but radiation therapy may have a role (Gustina et al. 2017).

14.7 Craniopharyngioma

14.7.1 Definition and Epidemiology

Craniopharyngiomas (CP) are benign, slow growing tumors that account for approximately 3–4.6% of all intracranial tumors (Fahlbusch and Buchfelder 2017; Algahtani et al. 2018). About 9% of all childhood intracranial tumors are CPs, with a peak incidence between 15 and 20 years of age. In adulthood, the peak incidence is between 50 and 74 years (Shin et al. 1999; Gustina et al. 2017). There is no significant difference in prevalence by gender (Fahlbusch and Buchfelder 2017).

14.7.2 Etiology

Pituitary CPs originate from epithelial cells on the surface of the pituitary gland and are thought to arise from the remnants of Rathke's pouch. These often develop along the infundibulohypophysial axis in the region between the sella and hypothalamus, and present treatment challenges associated with tumor growth, associated morbidities and recurrence (Algahtani et al. 2018; Bi et al. 2018). CPs grow to fill the sella and parasellar regions and extend either in front of or behind the optic chiasm, in approximately 4–5.9% of cases (Algahtani et al. 2018).

Two histological subtypes of CP have been identified: adamantinomatous and papillary. Adamantinomatous or cystic CPs are found in most pediatric cases and representing about 60% of all CPs; papillary CPs mostly found in adults in whom 81–95% of which have been found to harbor a *BRAFV600E* mitogenic mutation (Bi et al. 2018). In childhood and adolescent CP, 70% of the adamantinomatous type of CPs bear a mutation of the β-catenin gene (Müller 2016). These may represent a future treatment target (Bi et al. 2018). Tumors are often large and locally aggressive. The majority of children (91%) present with tumors >3 cm.

14.7.3 Symptoms

Patients often present with diabetes insipidus and impaired gonadal function. Hypopituitarism is present in 95% of cases (Shin et al. 1999). The majority of patients present with ophthalmologic complaints, neurological deficits and up to one-third have psychiatric manifestations (Shin et al. 1999). Children often present with intermittent and early morning headache, vomiting (possibly projectile), and changes in visual acuity. Short stature is reported in approximately 43% of children, and sleep disturbances are common (Gustina et al. 2017). Visual changes in acuity and asymmetric visual field deficits are more common in adults (Gustina et al. 2017). Seizures may be a presenting symptom if there is temporal lobe involvement. Ataxia can occur with midbrain involvement (Gustina et al. 2017).

14.7.4 Assessment

On MRI, CPs present with characteristic cystic and solid components or areas of calcification and hemorrhage (Maya and Pressman 2017). Prechiasmic lesions may have symptoms of optic atrophy, and, if the tumor is retrochiasmatic, pap-

illedema may be present on formal ophthalmologic exam. If there is extension of the tumor into the cavernous sinuses, visual exam may show signs of cranial nerve III, IV, and V1 damage with symptoms of diplopia and disconjugate gaze even on a visual confrontational exam (Gustina et al. 2017). Assessment of anterior and posterior pituitary functions and full neurologic examination are recommended.

14.7.5 Treatment

First-line treatment is surgical excision of the tumor and confirmation of histopathology. CPs are described as technically difficult to remove due to adherence of the tumor to local structures. Removal of the tumor can cause further damage to structures such as the optic apparatus, hypothalamus, carotid and basilar arteries, and third ventricle which accounts for some of the associated post-surgical morbidity (Bal et al. 2016; Prieto et al. 2018). Microscopic and endoscopic surgical techniques have improved both mortality and morbidity, but recurrence rates remain at 21–25% (Gustina et al. 2017). Even in the hands of experienced surgeons, historical surgical approaches have resulted in 53–80% of patients requiring postoperative pituitary replacement and management of DI long term (Algahtani et al. 2018). Some surgeons report this can be significantly improved in adults and children using an endonasal endoscopic transsphenoidal surgical approach (Bal et al. 2016). However, higher rates of CSF leak have been reported (Bal et al. 2016; Patel et al. 2017). Radiation may be still indicated for tumor regrowth or large residual lesions.

Postoperative evaluation for persistent or new onset anterior and pituitary deficits is needed. Diabetes insipidus is anticipated postoperatively, given that most tumors are proximate or adherent to the pituitary stalk (Patel et al. 2017). However, this may be transient and resolve postoperatively. Visual acuity and visual field testing postoperatively reveals improved vision in the majority of patients (>60%) (Müller 2016; Patel et al. 2017). Hypothalamic dysfunction and obesity is also apparent in the majority of patients (55–85%) and results in significant morbidity, mortality, and poor quality of life (Müller 2016). Other associated changes include daytime sleepiness, disturbed circadian rhythm, behavioral changes, and imbalances in regulation of thirst, body temperature, heart rate, and/or blood pressure.

14.7.6 Nursing and Long-Term Care

Treatment recommendations include encouraging activity, dietary counseling, and management of hunger, although hypothalamic obesity is usually not responsive to conventional lifestyle modifications. There are few long-term studies to confirm best practice. However, a planned home care environment with respect to diet and exercise has been shown to be somewhat effective (Müller 2016). Antiglycemic medications have been found to be effective for weight reduction in some patients as has lap band bariatric surgery. However, long-term outcomes demonstrated weight gain. Replacement of melatonin to improve sleep, and/or assessment and treatment of sleep apnea and narcolepsy is recommended (Müller 2016). Patients may require long-term replacement of pituitary hormones and associated education and support.

14.8 Conclusions

For all tumors that impact the pituitary, hormonal function, and vision may be compromised. Assessment of all pituitary functions and formal ophthalmology review, both acutely at patient presentation, and with long-term monitoring, is indicated. A comprehensive history and physical including environmental exposures, historical and current medications, symptom review, and a thorough clinical examination are critical in the diagnosis and to guide treatment. MRI may be diagnostic even when clinical findings are negatives.

Surgical treatment may be indicated when vision is threatened or to enable a definitive diagnosis. The need for replacement of pituitary defi-

ciencies and particularly growth hormone in children is common. Likewise, treatment for adrenal insufficiency is indicated in some children and adults and may be required lifelong. When hypothalamic damage is apparent, home management of weight gain is currently the most effective treatment. In the treatment of hypophysitis, the use of high dose glucocorticoids is controversial, but may be useful in some cases.

Nursing care includes attention to a broad spectrum of patient functions. This extends from the time of patient diagnosis through long-term treatment. Patient needs may change across the lifespan necessitating an adaptive treatment plan. Patient and family teaching are tailored to each diagnosis.

References

Algahtani AY, Algahtani HA, Jamjoom AB, Samkari AM, Marzuk YI. De novo craniopharyngioma of the fourth ventricle: case report and review of literature. Asian J Neurosurg. 2018;13(1):62–5. https://doi.org/10.4103/1793-5482.185063.

Auer MK, Stieg MR, Crispin A, Sievers C, Stalla GK, Kopczak A. Primary empty Sella syndrome and the prevalence of hormonal dysregulation—a systematic review. Dtsch Arztebl Int. 2018;115:99–105. https://doi.org/10.3238/arztebl.2018.0099.

Bal E, Öge K, Berker M. Endoscopic endonasal transsphenoidal surgery, a reliable method for treating primary and recurrent/residual craniopharyngiomas: nine years of experience. World Neurosurg. 2016;94:375–85.

Ball AK, Clarke CE. Idiopathic intracranial hypertension. Lancet Neurol. 2006;5:433–42.

Ball AK, Howman A, Wheatley K, Burdon MA, Matthews T, Jacks AS, Lawden M, Sivaguru A, Furmston A, Howell S, Sharrack S, Davies MB, Sinclair AJ, Clarke CE. A randomised controlled trial of treatment for idiopathic intracranial hypertension. J Neurol. 2011;258:874–81. https://doi.org/10.1007/s00415-010-5861-4.

Bernreuther C, Illies C, Flitsch J, Buchfelder M, Buslei R, Glatzel M, Saeger W. IgG4-related hypophysitis is highly prevalent among cases of histologically confirmed hypophysitis. Brain Pathol. 2017;27(6):839–45. https://doi.org/10.1111/bpa.12459. Epub 2017 Jan 11.

Bi WL, Larsen AG, Dunn IF. Genomic alterations in sporadic pituitary tumors. Curr Neurol Neurosci Rep. 2018;18:4. https://doi.org/10.1007/s11910-018-0811-0.

Carmichael JD. Anterior pituitary failure. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2017. p. 329–63.

Carroll KT, Lochte BC, Chen JY, Snyder VS, Carter BS, Chen CC. Intraoperative magnetic resonance imaging-guided biopsy in the diagnosis of suprasellar langerhans cell histiocytosis. World Neurosurg. 2018;112:6–13. https://doi.org/10.1016/j.wneu.2017.12.184. Epub 2018 Jan 6.

Catford S, Wang YY, Wong R. Pituitary stalk lesions: systematic review and clinical guidance. Clin Endocrinol. 2016;85:507–21.

Chatziralli I, Theodossiadis P, Theodossiadis G, Asproudis I. Perspectives on diagnosis and management of adult idiopathic intracranial hypertension. Graefes Arch Clin Exp Ophthalmol. 2018;256(7):1217–24. https://doi.org/10.1007/s00417-018-3970-4. Accessed 26 Mar 2018.

Chiloiro S, Giampietro A, Bianchi A, Tartaglione T, Capobianco A, Anile C, De Marinis L. Diagnosis of endocrine disease: primary empty Sella: a comprehensive review. Eur J Endocrinol. 2017;177(6):R275–85.

Crock PA. Cytosolic autoantigens in lymphocytic hypophysitis. J Clin Endocrinol Metab. 1998;83:609–18.

Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). Am J Opthalmol. 2007;143:635–41.

Digre KB, Bruce BB, McDermott MP, Galetta KM, Balcer LJ, Wall M. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH treatment trial results. Neurology. 2015;84(24):2449–56. https://doi.org/10.1212/WNL.0000000000001687.

Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. Pituitary. 2010;13:29–38.

Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system Tumors diagnosed in the United States in 2005–2009. Neuro-Oncology. 2012;14(Suppl 5):v1–v49. https://doi.org/10.1093/neuonc/nos218.

Dubey A, Patwardhan RV, Sampth S, Santosh V, Kolluri S, Nanda A. Intracranial fungal granuloma: analysis of 40 patients and review of the literature. Surg Neurol. 2005;63:254–60.

Elgamal ME, Mohamed RMH, Fiad T, Elgamal EA. Granulomatous hypophysitis: rare disease with challenging diagnosis. Clin Case Rep. 2017;5(7):1147–51. https://doi.org/10.1002/ccr3.1007.

Fahlbusch R, Buchfelder M. Pituitary surgery. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 671–87.

Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary. 2016;19:82–92. https://doi.org/10.1007/s11102-015-0671-4.

Fleseriu M. Pituitary dysfunction in systemic disorders. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 365–38.

Fleseriu M, Yedinak C, Campbell C, Delashaw JB. Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions.

J Neurosurg. 2009;110(2):354–8. https://doi.org/10.3171/2008.8.JNS08805.

Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013;81(13):1159–65. https://doi.org/10.1212/WNL.0b013e3182a55f1.

Gellner V, Kurschel S, Scarpatetti M, Mokry M. Lymphocytic hypophysitis in the pediatric population. Childs Nerv Syst. 2008;24(7):785–92. https://doi.org/10.1007/s00381-007-0577-1. Epub 2008 Feb 26.

Glezer A, Bronstein MD. Pituitary autoimmune disease: nuances in clinical presentation. Endocrine. 2012;42:74–9. https://doi.org/10.1007/s12020-012-9654-7.

González-Andrades M, García-Serrano JL, Gallardo MCG, Mcalinden C. Multiple cranial nerve involvement with idiopathic intracranial hypertension. QJM. 2016;109(4):265–6. https://doi.org/10.1093/qjmed/hcv217.

Guedes BF, Souza MNP, Barbosa BJAP, et al. Intracranial germinoma causing cerebral haemiatrophy and hypopituitarism. Pract Neurol. 2018;18(4):306–10. https://doi.org/10.1136/practneurol-2017-001771.

Gustina A, Frara S, Spina A, Mortini P. The hypothalamus. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 291–327.

Gutenberg A, Caturegli P, Metz I, et al. Necrotizing infundibulo-hypophysitis: an entity too rare to be true? Pituitary. 2012;15(2):202–8. https://doi.org/10.1007/s11102-011-0307-2.

Huo CW, Caputo C, Wang YY. Suprasellar keratinous cyst: a case report and review on its radiological features and treatment outcome. Surg Neurol Int. 2018;9:15. https://doi.org/10.4103/sni.sni_269_17.

Idiopathic Intracranial Hypertension. National Eye Institute. Last reviewed April 2014. https://nei.nih.gov/health/iih/intracranial.

Iplikcioglu AC, Bek S, Bikmaz K, Ceylan D, Gokduman CA. Aspergillus pituitary abscess. Acta Neurochir. 2004;146:521–4. https://doi.org/10.1007/s00701-004-0256-x.

Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014;6:230ra45.

Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety and quality of life. Neurology. 2000;54:319–24.

Larkin S, Karavitaki N, Ansorg O. Chapter 17: Rathke's cleft cyst. In: Fliers E, Korbonits M, Romijn JA, editors. Handbook of clinical neurology (3rd series), vol. 124. Amsterdam: Elsevier B.V; 2014.

Laws ER, Vance ML, Jane JA Jr. Hypophysitis. Pituitary. 2006;9:331–3.

Li J, Jia HW, Wang CL, Zhang R, Qu MY, Li W, Yuan MH, Cui J, He Q, Wei HY, Zhu TH, Ma ZS, Liu W, Dong ZL, Gao ZG. Primary empty Sella of 123 cases of clinical analysis. Chin J Intern Med. 2017;56(4):268–72. https://doi.org/10.3760/cma.j.issn.0578-1426.2017.04.006.

Maya MM, Pressman BK. Piutitary imaging. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 645–70.

McDermott MT. Infiltrative diseases of the pituitary gland. In: Wierman ME, editor. Diseases of the pituitary. Contemporary endocrinology, vol. 3. New York: Humana Press; 1997. p. 395–6.

Melmed S, Kleinberg D. Chapter 9—pituitary masses and tumors. In: Melmed S, Kenneth S, Polonsky P, Larsen R, Kronenberg HM, editors. Williams textbook of endocrinology. 13th ed. Philadelphia, PA: Elsevier; 2016. p. 232–99.

Mittal R, Kalra P, Dharmalingam M, Verma RG, Kulkarni S, Shetty P. Lymphocytic hypophysitis masquerading as pituitary adenoma. 1. Lymphocytic hypophysitis masquerading as pituitary adenoma. Indian J Endocrinol Metab. 2012;16(8):304–6.

Moshkin O, Albrecht S, Bilboa JM, Kovacs K. Nonpituitary tumors of the sellar region. In: Melmed S, editor. The pituitary. 3rd ed. London: Elsevier; 2011. p. 119–66. https://doi.org/10.1016/B978-0-12-380926-1.10015-X.

Müller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. Curr Opin Endocrinol Diabetes Obes. 2016;23(1):81–9. https://doi.org/10.1097/MED.0000000000000214.

Néel A, Artifoni M, Donadieu J, Lorillon G, Hamidou M, Tazi A. Langerhans cell histiocytosis in adults. Rev Med Interne. 2015;36(10):658–67.

Patel VS, Thamboo A, Quon J, Nayak JV, Hwang PH, Edwards M, Patel ZM. Outcomes after endoscopic endonasal resection of craniopharyngiomas in the pediatric population. World Neurosurg. 2017;108:6–14. https://doi.org/10.1016/j.wneu.2017.08.058.

PDQ® Pediatric Treatment Editorial Board. PDQ Langerhans Cell Histiocytosis Treatment. Bethesda, MD: National Cancer Institute. 2018. https://www.cancer.gov/types/langerhans/patient/langerhans-treatment-pdq. Accessed 28 Apr 2018.

Per H, Canpolat M, Gümüş H, Poyrazoğlu HG, Yıkılmaz A, Karaküçük S, Doğan H, Kumandaş S. Clinical spectrum of the pseudotumor cerebri in children: etiological, clinical features, treatment and prognosis. Brain and Development. 2013;35(6):561–8. https://doi.org/10.1016/j.braindev.2012.08.008. Epub 2012 Sep 13.

Perry BG, Cotter JD, Mejuto G, Mündel T, Lucas SJE. Cerebral hemodynamics during graded Valsalva maneuvers. Front Physiol. 2014;5:349. https://doi.org/10.3389/fphys.2014.00349.

Prieto R, Pascual JM, Rosdolsky M, Barrios L. Preoperative assessment of craniopharyngioma adherence: magnetic resonance imaging findings correlated with the severity of tumor attachment to the hypothalamus. World Neurosurg. 2018;110:e404–26. https://doi.org/10.1016/j.wneu.2017.11.012. Epub 2017 Nov 11.

Rangwala LM, Liu GT. Pediatric idiopathic intracranial hypertension. Surv Ophthalmol. 2007;52(6):597–617.

Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, Trouillas J, Dekkers OM. The European Society of Endocrinology European Society of endocrinology clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol. 2018;178:G1–G24. https://doi.org/10.1530/EJE-17-0796.

Sajko T, Gnjidić Ž, Sesar N, Malenica M. Sphenoid sinus aspergilloma in trans-sphenoidal surgery for pituitary adenomas. Acta Neurochir. 2015;157(8):1345–51 discussion 1351. https://doi.org/10.1007/s00701-015-2485-6.

Schlosser RJ, Bolger WE. Spontaneous nasal cerebrospinal fluid leaks and empty Sella syndrome: a clinical association. Am J Rhinol. 2003;17(2):91–6.

Sheldon CA, Paley GL, Xiao R, Kesler A, Eyal O, Ko MW, Boisvert CJ, Avery RA, Salpietro V, Phillips PH, Heidary G, McCormack SE, Liu GT. Pediatric idiopathic intracranial hypertension: age, gender, and anthropometric features at diagnosis in a large, retrospective multisite cohort. Ophthalmology. 2016;123(11):2424–31. https://doi.org/10.1016/j.ophtha.2016.08.004. Epub 2016 Sep 28.

Shi J, Zhang J, Wu Q, Chen G, Zhang H, Bo W. Granulomatous hypophysitis: two case reports and literature review. J Zhejiang Univ Sci B. 2009;10(7):552–8. https://doi.org/10.1631/jzus.B0820355.

Shin JL, Asa SL, Woodhouse LJ, Smyth HS, Ezzat S. Cystic lesions of the pituitary: clinicopathological features distinguishing craniopharyngioma, Rathke's cleft cyst, and arachnoid cyst. J Clin Endocrinol Metab. 1999;84(11):3972–82.

Shivapathasundram G, Wickremesekera AC, Tan ST, et al. Tumour stem cells in meningioma: a review. J Clin Neurosci. 2018;47:66–71.

Tillotson CV, Bhimji SS. Histiocytosis, Langerhans cell. In: StatPearls [internet]. Treasure Island, FL: StatPearls; 2018. https://www-ncbi-nlm-nih-gov.liboff.ohsu.edu/books/NBK430885.

Tyrrell JB, Finding W, Aron DC. Hypothalamus and pituitary: chapter 2. In: Greenspan FS, Baxter JD, editors. Basic & clinical endorinology. 4th ed. Norwalk, CT: Appelton & Lange; 1994. p. 91.

Wall M. Idiopathic intracranial hypertension. Neurol Clin. 2010;28(3):593–617. https://doi.org/10.1016/j.ncl.2010.03.003.

Yoo F, Kuan EC, Heaney AP, et al. Corticotrophic pituitary carcinoma with cervical metastases: case series and literature review. Pituitary. 2018;21:290. https://doi.org/10.1007/s11102-018-0872-8.

15 Dynamic Investigations and Diagnostic Testing

Christine Yedinak and Kate Davies

Contents

15.1 **Introduction** 280

15.2 **Basal Testing and Random Serum Analysis** 280
15.2.1 Corticotropin Assessment 280
15.2.2 Somatotrophs: Growth Hormone Assessment 281
15.2.3 Gonadotroph Assessment 281
15.2.4 Thyrotroph Assessment 281
15.2.5 Lactotrophs Assessment 281
15.2.6 Posterior Pituitary Assessment 282

15.3 **Hypopituitarism** 284
15.3.1 Combined Pituitary Function Test (ITT/TRH/GnRH) 284

15.4 **Corticotroph Function Testing** 284
15.4.1 Diurnal Curves (Cortisol Day Curve/24 h Cortisol Profile/ Hydrocortisone Day Curve) 284
15.4.2 Hypocortisolism 284
15.4.3 Metyrapone (Metopirone) Dynamic Testing 288

C. Yedinak (✉)
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

K. Davies
Department of Advanced and Integrated Practice, London South Bank University, London, UK
e-mail: kate.davies@lsbu.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_15

15.5 **Hypercortisolism** ... 288
15.5.1 Urinary Free Cortisol: 24 h (UFC) ... 289
15.5.2 Late Night Salivary Cortisol (LNSC) ... 289
15.5.3 Low Dose Dexamethasone Suppression Test (DST) ... 290
15.5.4 Overnight Dexamethasone Suppression Test (O/N DST) ... 291
15.5.5 High Dose Dexamethasone Suppression Test/2 Day DST ... 291
15.5.6 Corticotropin Releasing Hormone (CRH) Test ... 291
15.5.7 Dexamethasone Suppression and CRH Stimulation Test (DST/CRH) ... 292
15.5.8 Insulin Tolerance Test (ITT) ... 292
15.5.9 Central Venous Sampling: Inferior Petrosal and Cavernous Sinus Sampling ... 292

15.6 **Growth Hormone Testing** ... 294
15.6.1 Growth Hormone Stimulation Testing ... 294
15.6.2 Growth Hormone Excess ... 297

15.7 **Gonadotroph Assessment** ... 298
15.7.1 Clomiphene Stimulation Test/Clomiphene Citrate Challenge Test (CCCT) ... 298
15.7.2 Human Chorionic Gonadotropin (HCG) Stimulation Test ... 298
15.7.3 Gonadotropin Releasing Hormone Test (GnRH Test) ... 299

15.8 **Thyrotroph Assessment** ... 299
15.8.1 Thyroid Releasing Hormone (TRH) Test ... 299

15.9 **Conclusions** ... 300

References ... 300

Abstract

The evaluation of pituitary function is complex and critical. Pituitary dysfunction causes a wide range of physical, emotional, social, and potentially spiritual changes, all of which compound the process of evaluation. Patient and family anxieties are heightened given either symptoms of unknown etiology or a new discovery of a "brain tumor," which can influence testing outcomes and requires nursing expertise in management.

Infants and children are affected by pituitary dysfunction that can present with life-threatening symptoms and parents in need of significant support. Both issues pose a challenge to the endocrine nurse involved in the child's evaluation. Most testing is not emergent and appropriate patient and parent preparation with attention to factors that can invalidate testing is vital. Explanations and/or literature provided to the patient and family must be age and language appropriate.

There is a broad range of diagnostic techniques that may be employed in diagnosis and ongoing patient management for patients with pituitary diseases. Knowledge of the testing purpose, procedure, and result interpretation is essential for the endocrine nurse performing testing and advance practice nursing for long-term patient management.

Keywords

Provocative testing · Dynamic testing · Pituitary dysfunction · Patient preparation · Anterior pituitary · Posterior pituitary

Abbreviations

17KG	17-ketogenic steroid
17OHCS	17-hydroxycorticosteroid
17OHP	17-hydroxyprogesterone
ACTH	Adrenocorticotropic hormone
ADA	American Diabetic Association
ADH	Anti-diuretic hormone
AI	Adrenal insufficiency
AVP	Arginine vasopressin
CAH	Congenital adrenal hyperplasia
Cm	Centimeter
CRH	Corticotropin releasing hormone
CSF	Cerebral spinal fluid
CT	Computed tomography
DDAVP	Synthetic desmopressin
DI	Diabetes insipidus
dL	Deciliter
EMR	Electronic Medical Record
FSH	Follicle stimulating hormone
G	Gram
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone releasing hormone
GnRH	Gonadotropin releasing hormone
GST	Glucagon stimulation test
HCG	Human chorionic gonadotropin
HPA	Hypothalamic pituitary adrenal
HPG	Hypothalamic pituitary gonadal
HPT	Hypothalamic–pituitary thyroid
IGF-1	Insulin-like growth factor 1
IPSS	Inferior petrosal sinus sampling
ITT	Insulin tolerance test
IV	Intravenous
IVP	Intravenous push
Kg	Kilogram
LH	Luteinizing hormone
LNSC	Late night salivary cortisol
m^2	Meter squared
mL	Milliliter
mOsm	Milli-osmolarity
MRI	Magnetic resonance imaging
Na	Sodium
Ng	Nanogram
nmol/L	Nanamole/liter
PCOS	Polycystic ovarian syndrome
PET-CT	Positron emission tomography with computerized tomography
rhGH	Recombinant growth hormone
SAI	Secondary adrenal insufficiency
SHBG	Sex hormone binding globulin
SRS	Somatostatin receptor scintigraphy
T3	Triiodothyronine
T4	Thyroxine
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
WDT	Water deprivation test
µg	Microgram

Key Terms

- **Provocative/dynamic/stimulation testing:** is the exposure of the patient to a substance or drug to evaluate their bodies' response. This response is compared to average responses from unaffected individuals.
- **Testing protocol:** describes the standardized method or procedure used to perform a test.
- **Cut-off values:** differentiate normal responses from abnormal or dysfunctional responses.
- **Informed consent:** is a process of explanation to a patient and family, in an understandable language and age-appropriate manner, the proposed procedure, risks and benefits, and anticipated outcome(s) of testing. The patient must be given ample opportunity to ask questions and consider the information provided. This must be provided for all procedures with written consent for any invasive or experimental procedures.

Key Points

- Many pediatric dynamic/provocative function tests are based on adult protocols, with weight-related dosages of medication.
- All patients require age-appropriate preparation for provocative testing. Parents of pediatric patients also require preparation with respect to the developmental medical needs of their child.
- Provocative testing is often time intensive for staff and time consuming for the

patient. Some tests are carried out over a number of days.
- Medical testing is anxiety provoking and some invasive tests may require the patient to be pretreated with anxiolytics or receive sedation, particularly in children. Thoughtful preparation can reduce anxiety and the need for other medications.
- In order to fully prepare a patient for testing, the nurse must have detailed knowledge of why and how the test is performed, and the meaning of the results.

15.1 Introduction

Both random and provocative or dynamic blood tests are the cornerstone of diagnosis in pituitary diseases and dysfunction. However, there is substantial variability in testing protocols between countries and between individual testing sites. Standardization is inhibited in some cases by lack of consensus regarding the timing of blood collections and drug dosages that will reliably arrive at a consistent diagnosis. There is variability in assays used between studies that make results difficult to compare. Likewise, cut-off point variability is apparent between different protocols adding further complexity.

Given these challenges, the information in this chapter attempts to provide some standardized recommendations for patient preparation and testing procedures and highlights some of the significant differences in process and/or interpretation of results. This chapter is meant as a guide and must be interpreted in the context of the reader's clinical site.

15.2 Basal Testing and Random Serum Analysis

15.2.1 Corticotropin Assessment

Corticotropin levels are assessed to determine adequacy of adrenal function or the presence of cortisol excess. Low cortisol levels may be associated with primary or secondary adrenal insufficiency. Likewise, cortisol excess may be associated with pituitary-derived adrenocorticotropic hormone (ACTH) excess or adrenal hypersecretion. Both clinical assessment and biochemical testing are used in diagnosis (Nieman 2003). When cortisol levels are high, it is important that further testing distinguish between Cushing's and pseudo-Cushing's syndrome (Nieman 2018). Prior to a blood draw the patient must be screened for all forms of cortisol suppressive or corticosteroid containing agents both prescribed and over the counter (creams, lotions, sprays, supplements, herbal preparations, tonics, and skin bleaching agents, joint injections, etc.) as well as estrogen use (effects cortisol binding globulin) (Nieman 2018).

Random cortisol levels must be interpreted in the context of the time of day the sample was drawn, as these levels display a variable circadian or 24 h pattern of production (see Anatomy & Physiology). The highest cortisol levels are found in the early morning and lowest at midnight. Random cortisol levels are therefore not diagnostic and further dynamic testing modalities are usually required.

In primary adrenal failure or dysfunction, a morning cortisol of less than 140 nmol/L (5 g/dL) with a concomitant ACTH level that is twofold the upper limit of the reference range is diagnostic for primary adrenal insufficiency. However, a dynamic corticotropin stimulation test to confirm the diagnosis is recommended (Bornstein et al. 2016).

In secondary adrenal insufficiency (SAI), impaired corticotropin releasing hormone (CRH) and/or ACTH secretion lead to low adrenal cortisol production. A baseline cortisol measurement of <3 μg/dL (83 nmol/) is indicative of SAI. Conversely, a cortisol >18 μg/dL (500 nmol/L) excludes a diagnosis of adrenal insufficiency. The cortisol level should be evaluated in the context of factors such as the time of day, specific assay cut-off, the presence of liver dysfunction, and the use of estrogen in women. However, many cases of SAI may not be quite so overt. Therefore, dynamic corticotropin testing is recommended (Nieman 2003; Bornstein et al. 2016).

In addition, the mineralocorticoid axis remains intact in untreated SAI, resulting in a subsequent increase in arginine vasopressin (AVP)/antidiuretic hormone (ADH) level, water retention, and hypervolemic hyponatremia (Wallace et al. 2009).

In cases of cortisol excess, random elevated ACTH and/or cortisol requires further evaluation, as described below.

15.2.2 Somatotrophs: Growth Hormone Assessment

Growth hormone (GH) levels may be measured using a random GH level plus an insulin growth hormone-1 (IGF-1) measurement from a single draw blood sample. The diagnostic use of random GH measurement is limited by its short half-life, which is estimated at a mean of 13.6 min (range 11.9–19.4) (Mullis et al. 1992). A mean of 5 time point draws at 30 min intervals has shown to be effective in measuring GH excess in patient with active or treated acromegaly (Roelfsema et al. 2016). Growth hormone measurement in children explores implications for growth (see Chap. 2), and stimulation testing is necessary.

GH excreted from the pituitary attaches to receptor sites on liver cells. This stimulates the liver to produce IGF-1 which can be measured at any time of day (Schilbach et al. 2017). IGF-1 levels are adjusted for gender and age. Both low and elevated levels require further evaluation for GH deficiency and excess (Roelfsema et al. 2016).

15.2.3 Gonadotroph Assessment

The measurement of follicle stimulating hormone (FSH) and luteinizing hormone (LH), testosterone and estrogen levels assess pituitary production along with ovarian and testicular function. In women, the estrogen level rises to inhibit the production of FSH. LH then rises with the inhibition of FSH, matures the ovum, and results in ovulation. The empty ovum produces progesterone to support a pregnancy but falls again if pregnancy does not occur. The levels of FSH and LH will vary according to the woman's age and the timing of the blood draw with respect to the menstrual cycle (Ben-Schomo and Melmed 2011). Reference ranges are usually provided by the laboratory according to the woman's age and time of cycle. Testosterone levels may also be measured in woman suspected of having polycystic ovarian syndrome (PCOS). The performing laboratory publishes reference levels.

In males, FSH and LH stimulate the production of testosterone from the Leydig cells in the testes. When the secretions of FSH and LH from the pituitary are impaired, there is resultant hypogonadotropic hypogonadism (Kaiser 2016). Testosterone production is diurnal with the highest surges in the morning, particularly in young men. Measurement, therefore, is best attempted in the morning. For a full evaluation of gonadal function, total testosterone and a testosterone profile can be ordered which includes a total and free testosterone plus a sex hormone binding globulin (SHBG) (Kaiser 2016).

15.2.4 Thyrotroph Assessment

Hypothalamic thyrotropin stimulating hormone (TRH) stimulates the production of pituitary thyroid stimulating hormone (TSH). In turn, TSH binds to receptors on the cell surface in the thyroid gland and results in the production and release of thyroid hormones triiodothyronine (T3) and thyroxine (T4). TSH is often measured as an indicator of thyroid function and is usually a reliable facsimile, except in the context of pituitary dysfunction. Measurement of free T4 is recommended as the most sensitive indicator of central hypothyroidism in the context of pituitary disease (Carmichael 2016).

15.2.5 Lactotrophs Assessment

Prolactin level is measured in non-pregnant females or with concomitant pregnancy testing in sexually active females. Avoidance of breast stimulation or stressful venipuncture is recommended prior to measurement of prolactin. A

number of medications may elevate the prolactin level and need to be discontinued, when possible, prior to level assessment. Levels above normal range when patients demonstrate symptoms, need further evaluation for the presence of a prolactinoma (see Chap. 19) (Melmed et al. 2011).

15.2.6 Posterior Pituitary Assessment

The neurohypophysis releases AVP, which influences the anterior pituitary ACTH secretion, as well as responding to osmotic changes, hemorrhage, or the concentration of sodium (Na) in cerebrospinal fluid (CSF). AVP release is increased to reabsorb water from the kidneys when Na levels are high and decreases in order to allow diuresis when Na levels are low (Bichet 2016). Serum sodium levels, urine and serum osmolality, and AVP levels are useful in the management of dysfunction. Full evaluation of the posterior pituitary function requires a water deprivation test.

15.2.6.1 Water Deprivation Test (WDT)

A WDT needs to be undertaken when diagnosis of diabetes insipidus (DI) is suspected. DI occurs when insufficient anti-diuretic hormone (ADH) is produced by the posterior pituitary gland or when the target organs (kidneys), do not respond by adequately concentrating urine. The former is known as central diabetes insipidus and the latter nephrogenic DI (Davies and Collin 2015). Patients with both diagnoses will present with polydipsia and polyuria.

Initial investigations would include a full screening of blood and urine tests. Plasma sodium, potassium, bicarbonate, chloride, urea, creatinine, phosphate, calcium, glucose, liver function tests, and full blood count are usually performed. Both a serum and urine will also be investigated for osmolality. Plasma copeptin (a stable peptide stoichiometrically co-secreted with AVP) is a promising new marker for the diagnosis of AVP-dependent fluid disorders (Timper et al. 2015).

If indicated, a WDT is performed. The goal of this test is to determine if the patient's posterior pituitary is able to excrete adequate amounts of AVP/ADH and/or if the renal tubules in the kidneys are able to concentrate urine (Davies and Collin 2015).

15.2.6.1.1 Patient Preparation

Adults are asked to take all regular medications and eat the morning of testing, avoid alcohol for 48-h, and caffeine for 12–24 h prior to testing. Smoking is also discouraged. Many centers allow fluids and normal diet until the time of admission. All fluids are restricted at the time of admission and throughout the test. The test must be done under medical supervision as it can potentially cause dehydration with elevated sodium.

Children may be admitted, in some centers, for a 24 h fluid balance assessment, to confirm polyuria and polydipsia and also to rule out psychogenic or habitual, excessive drinking (Cheetham and Baylis 2002; Raine et al. 2011). Usually during this time, children should be restricted to solids and water only, omitting flavored or sugary drinks. If flavored drinks are withheld and the child refuses water, if the posterior pituitary and renal function is normal, the polyuria will cease. However, if the symptoms continue, the investigation should progress to the water deprivation test. Children are usually permitted to eat and drink until they arrive at the testing center (Cheetham and Baylis 2002).

Clear, age-appropriate, explanation of the testing purpose and procedure is essential, particularly as water intake during testing will invalidate the test.

15.2.6.1.2 Procedure

The WDT is a standardized 6–7 h test in adults and children, during which the patient is able to eat foods such as toast, biscuits but no water. The patient is closely observed during testing to avoid inadvertent fluid intake. Children may need to be accompanied to the lavatory.

(a) Baseline measurement of weight is done on admission to the testing unit and 97% of this weight is calculated and recorded.

(b) Baseline vital signs (blood pressure and heart rate) are taken and recorded on admission.
(c) The patient voids and discards first void.
(d) An intravenous catheter (cannula) is placed in the patients arm.
(e) A sample of blood for serum sodium and osmolality is collected at the beginning of the study (usually around 9 a.m.) and sent to the laboratory for STAT analysis.
(f) Urine samples are collected and measured hourly (volume, specific gravity, osmolality).
(g) Blood samples are collected hourly for STAT analysis.
(h) Vital signs are assessed hourly.
(i) The patients are weighed hourly and weight is compared to baseline. (See Table 15.1) (Cheetham and Baylis 2002; Raine et al. 2011).

The test is discontinued if:

– The first urine osmolality is >600 mOsmol/kg and subsequent sample is >750 mOsmol/kg the test can be aborted as results are normal.
– The child or adult has more than a 3% loss in body weight indicating moderate dehydration.
– Plasma osmolality >295 mOsm/kg (where normal values are 285–295) and sodium (Na) >145 mmol/L–confirms central (cranial) DI.
– Urine osmolality >800 mOsm/kg*—this would exclude DI, and the urine will be concentrated (normal values are 500–800: lower values would indicate dilute urine) or if the thirst is intolerable (Wong and Man 2012). * In some reports urine osmolality >700 mOsm/kg.
– The urine output has not decreased, and the urine: plasma ratio is less than two, but plasma osmolality remains below 295, continue the test (Wong and Man 2012).
– Urine osmolarity is greater than 800 mOsmol/kg after fluid deprivation, and greater than 800 mOsmol/kg after desmopressin suggests primary polydipsia.

15.2.6.1.3 Additional Procedure/Step 2

If 3–5% of body weight is lost, the patient has continued to have urine output which is not decreasing, urine has not concentrated and plasma osmolality has risen to >300 mOsmol/kg, desmopressin is administered by subcutaneous or intramuscular injection.

Patients with central/cranial DI (vasopressin deficiency or insufficiency) will respond to desmopressin administration by concentrating urine output. The urine osmolality will rise to >700 mOsm/kg. In patients with nephrogenic DI who have renal resistance to vasopressin, the urine continues to have a low osmolality of less than 700 mOsm/kg (Moore et al. 2003; Dashe et al. 1963).

DDAVP (desmopressin) can be administered, usually 0.4 μg (under 2 years of age) to 1 μg (over 2 years of age), to assess the renal desmopressin response (Cheetham and Baylis 2002; Raine et al. 2011). Samples for plasma and urine osmolality, and plasma sodium need to be measured for a further 4 h, and the child or adult can eat and

Table 15.1 Water Deprivation Test sampling (adapted from Butler and Kirk 2011)

	Time	Weight (kg)[a]	HR (bpm)	BP (mmHg)	Urine volume (mL)	Specific gravity	Samples
$T = 0$	0830						*, **
$T = 1$ h	0930						**
$T = 2$ h	1030						*, **
$T = 3$ h	1130						**
$T = 4$ h	1230						*, **
$T = 5$ h	1330						*, **
$T = 6$ h	1430						**
$T = \mathbf{7}$ **h**	1530						*, **

*Blood and **urine specimens to be sent for Na + and osmolality
Plasma osmolality: 0830, 1030, 1230, 1330, 1530 h
Urine osmolality: 0830, 0930, 1030, 1130, 1230, 1330, 1430, 1530, 1630, 1730 h
[a]Notify Doctor if body weight drops by 5% or more of the weight at the start of the test

drink normally. This part of the test can sometimes be performed at a later date if need be.

15.3 Hypopituitarism

15.3.1 Combined Pituitary Function Test (ITT/TRH/GnRH)

Pituitary reserve is completely assessed by using a combined pituitary function test. Some studies have combined an insulin tolerance test (ITT), TRH and GnRH tests, CRH, GRH, TRH, LH-RH, and lysine vasopressin. However, reports of efficacy vary (Burke 1992; Hashimoto et al. 1990). In practice, the TRH and GnRH tests are criticized for providing little clinically useful data beyond the basal hormone measurements: TFTs and prolactin; gonadal steroids; and gonadotropins. There have been reports that TRH and GnRH may be associated with a risk of pituitary apoplexy (Burke 1992). Additionally, others suggest that random basal samples should be drawn prior to doing provocative or dynamic testing in order to avoid unnecessary testing (Howlett 1997).

15.4 Corticotroph Function Testing

15.4.1 Diurnal Curves (Cortisol Day Curve/24 h Cortisol Profile/ Hydrocortisone Day Curve)

1. *A cortisol day curve* is used to determine the individual's endogenous cortisol production over a defined period during the day or for up to 24 h. This allows closer examination of adrenal response to endogenous ACTH production. The patient may be monitored as frequently as hourly with serum cortisol/ACTH levels (after the placement of an intravenous access), or at 3 or more time points during the day using salivary cortisol sampling (Selmaoui and Touitou 2003; Charles et al. 2016).
2. *The hydrocortisone day curve* is a means of assessing the adequacy of hydrocortisone replacement therapy over an average 24-h period. The goal is to determine appropriate dosing and dose intervals based on cortisol levels drawn in the morning, mid-day, and in the evening prior to bedtime. The patient is administered their usual replacement doses of hydrocortisone during testing (Howlett 1997). Similarly, salivary cortisol levels collected have also been shown to be an effective means of assessment (Ross et al. 2013).
3. *A single morning plasma cortisol level* of <3 μg/dL (83 nmol/L) is considered indicative of AI and a plasma cortisol level > 19 μg/dL (524 nmol/L) excludes adrenal insufficiency (Nieman 2003). Dynamic testing is recommended for values in between.

15.4.2 Hypocortisolism

15.4.2.1 Insulin Tolerance Test (ITT)

The insulin tolerance test (ITT) is the "gold standard" for cortisol stimulation testing. Testing with ITT is used in the assessment of ACTH and cortisol reserve, growth hormone deficiency in adults and children, and to differentiate Cushing's syndrome from depression or pseudo-Cushing's (Nieman 2003; Carmichael 2016).

The ITT involves precipitating hypoglycemia with subcutaneous insulin injection, inducing a rise in cortisol and GH in normal individuals. However, it is contraindicated in patients with ischemic heart disease, epilepsy, type 2 diabetes mellitus, untreated hypothyroidism, patients over the age of 60 and should be used with caution for patients over the age of 55 years. ITT is not recommended when a random morning cortisol is <100 nmol/L (3 μg/dL) (Carmichael 2016).

Alternatives are the glucagon stimulation test, which is a central test of GH and cortisol reserve, and thus comparable to the ITT, or the short Synacthen test. The latter is disadvantaged by of only testing adrenal reserve and may give a false-positive result if performed soon after pituitary surgery/damage (Burke 1992).

ITT can be performed in children over the age of 10 years when the diagnosis of panhypopituitarism is suspected, such as after radiotherapy of a brain tumor (see Sect. 10 Chaps. 58–60). It can-

not be performed following an HCG stimulation test, or after priming with sex steroids (Butler and Kirk 2011). ITT is recognized as the gold standard test for growth hormone deficiency diagnosis in children by the BSPED (British Society of Paediatric Endocrinology and Diabetes). Some centers in the UK advocate varying the procedure protocol by excluding the 120-min sample and also administering IV 10% dextrose after the 20-min sample has been taken. There is no proven benefit to these practices (Lone et al. 2011).

ITT should only be administered by trained/experienced, licensed medical professionals due to the risks associated to hypoglycemia. Hypoglycemic rescue must be available at the bedside in case of a severe hypoglycemic crisis.

Patient Preparation: Patients are asked to fast for 8–10 h prior to testing and should hold their morning medications prior to arrival but bring these medications with them to the testing center. All usual medications can be taken following the end of testing. Continued intake of water is recommended to allow better venous access. To allow IV placement, comfortable attire should allow access to both the right and left arm. In some centers, patients may be asked to bring a sandwich or a meal to be consumed at the completion of testing. Patients should not drive for 2 h after testing. It is recommended that patients receive written instructions at the time of appointment scheduling.

Children: Sex steroid priming remains controversial in the literature but guidelines by the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society do recommend sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years. This is proposed as a means of addressing age-related deficiencies to allow comparison with established norms. Estrogen is administered to girls 2 days prior to testing and testosterone to boys 1 week prior to testing.

Girls: 2 mg (1 mg for body weight <20 kg) of β-estradiol (not ethinyl estradiol) orally for 2 evenings prior to testing.

Boys: Intramuscular testosterone 50–100 mg of a depot formulation administered 1 week before the test.

Procedure: On admission to the testing unit, patients will be weighed to allow calculation of the appropriate insulin dosage. Vital signs will also be taken and recorded at this time. If the unit is using electronic medical records, the data is entered directly. However, templates of testing records are often practical to use at the bedside to record data such as glucose measurements, signs and symptoms, or other notes during testing.

Regular insulin is used in testing. The dose is weight based and is administered to the patient via intravenous push (IVP) to induce hypoglycemia. The dose required ranges from 0.05 to 0.15 IU/kg. There is some variability between centers. The dose of 0.1 IU/kg (maximum 0.015 IU/kg) is standard in children, particularly if panhypopituitarism is suspected or the patient has low morning cortisol (Butler and Kirk 2011).

Baseline and fasting labs will be drawn prior to the insulin administration. Venous samples for glucose and GH are collected at 0, +15, +30, +60, +90, and +120. Bedside monitoring of blood glucose with a glucometer is advised, particularly in response to patient symptoms. Vital signs and patient symptoms are also measured and all information is recorded at each time point.

To be a valid test, the patient's glucose must drop to either 40 mg/dL or below OR 50% of their baseline fasting glucose (Carmichael 2016). If the post-dosing glucoses do not meet this criterion, another dose of insulin can be administered under the supervision of the licensed medical professional's discretion. If glucoses still do not drop to either of these levels, the test should be terminated and rescheduled for another time.

Upon completion of the test, the patient should have a meal prior to discharge and their glucose should be back to baseline. In children, parents are advised to observe their children at home for signs of rebound hypoglycemia, treat with orange juice and protein snack, and contact the testing unit as needed. All contact phone numbers should be given to the parents at patient discharge.

Hypoglycemic Symptoms: Patients need to be closely monitored throughout the testing with venous sampling and/or bedside blood glucose finger stick monitoring to prevent serious hypoglycemia. Symptoms of hypoglycemia

include sweating, heart palpitations, clammy skin, fatigue, headache, thirst, confusion, pallor, and dizziness. If not monitored closely, severe hypoglycemia can lead to seizures, coma, or, in extreme cases, death. Therefore, patients must be able to communicate during this test and must be kept awake (Butler and Kirk 2011). Pediatric nurses should fully understand hypoglycemic symptoms, as children may not be able to verbalize their symptoms.

Hypoglycemic Rescue: If blood glucose is <40 mg/dL (≤2.2 mmol/L) with symptoms a glucose drink of at least 30 mL is given orally. If blood glucose does not rise within 15–30 min, decreases further or if oral glucose is not tolerated then IV glucose is administered. Dextrose-50 (or 10% glucose in the UK) must be at the bedside in case of a severe hypoglycemic emergency. For management of hypoglycemia in children, a rescue dose of 200 mg/kg of 10% dextrose (2 mL/kg) administered IVP slowly over about 3 min if the blood glucose falls below <40 mg/dL (2.2 mmol) although some authors recommend treatment at <4 mmol/L. (Butler and Kirk 2011) Overzealous management of hypoglycemia has been proven to be complex and sometimes fatal (Shah et al. 1992). This underscores the importance of experienced medical management of ITT in children. In children, if hypopituitarism is suspected, 100 mg hydrocortisone should also be prepared for IV administration.

Test Interpretation: There continues to be debate regarding lower cut-off levels indicative of GHD, particularly as levels are currently not BMI adjusted. Peak levels of <3.1 μg/L or <5.0 μg/L indicate pituitary dysfunction and the presence of growth hormone deficiency syndrome in adults and children, respectively (Grimberg et al. 2016).

15.4.2.2 ACTH Stimulation Testing

ACTH stimulation test is performed to measure the adrenal stress response to ACTH. These tests are used to diagnose or exclude primary and secondary adrenal insufficiency, Addison's disease, and other related conditions. The tests are also used distinguish whether the cause is from the adrenal glands (low cortisol and aldosterone production) or the pituitary gland (low ACTH production). Significant variability has been reported in a UK regarding patient preparation, laboratory reported normal ranges, and procedure protocols (Chatha et al. 2010).

There continues to be debate regarding the optimal testing to determine adrenal hypofunction or insufficiency. No current test is safe, economic, convenient, and has a high sensitivity and specificity (Nieman 2003). Some centers use a low dose or a 1 μg dose of Synacthen while others only use 250 μg testing (Nieman 2003). In the evaluation of primary adrenal insufficiency, the Endocrine Society guidelines recommend the 1 μg test as a screening test but favor the 250 μg (standard dose) test when available (Bornstein et al. 2016).

15.4.2.2.1 Short ACTH (Synacthen/Cosyntropin)/Low Dose (1 μg)

Although advocated, as a sensitive test there is some debate about false-positive results (Nieman 2003; Dickstein and Saiegh 2008; Fleseriu et al. 2010). Additionally, there is no commercially available 1 μg preparation necessitating dilution of 250 μg doses introducing a risk of dilutional error. This test is used to identify secondary adrenal insufficiency or to test the HPA axis function following prolonged steroid treatment (Carmichael 2016; Butler and Kirk 2011; Moloney et al. 2015; Broersen et al. 2015). In children, the short Synacthen test is also used for the investigation and diagnosis of congenital adrenal hyperplasia (Trapp et al. 2011). (See Chap. 35).

Patient Preparation: This is minimal, with instructions to hold all glucocorticoid medications and treatments (including steroid creams and sprays) the morning of testing. In some countries, children may be admitted the evening before the test for safety. Anesthetic cream can be applied to both arms in the antecubital space and the back of both hands an hour prior to arrival in the testing unit.

Procedure: An intravenous cannula (IV) is placed in a vein, typically in the inside of the elbow or in the back of the hand on admission to the testing unit. If there is concern regarding

the viability of an IV for subsequent blood draws, a second cannula may be placed, particularly in children where the access may not be maintained after several draws. This also allows blood draws to be obtained without the potential for drug contamination. As this procedure is stressful, particularly in children, and ACTH and cortisol may rise, the patient is allowed to rest for 30–60 min prior to initiating testing. Blood is drawn for baseline measurement of blood cortisol and ACTH levels. Beginning the procedure by 9 a.m. is recommended in children (Butler and Kirk 2011).

Drug Preparation and Administration: A dose of 1 μg of ACTH (Synacthen/Cosyntropin/Synacthen = **SYN**thetic **ACTH**) is prepared by:

(a) Inject a 250 μg of drug into a solution of 249 mL of normal saline and mix well. The solution is prepared and 1 mL (1 μg) is withdrawn for administration immediately prior to testing to avoid adherence of the medication to the syringe walls or tubing.
(b) Dilute 250 μg of drug in 50 mL of normal saline giving a solution of 250 μg in 50 mL. Take 1 mL of this solution and dilute with 9 mL of saline giving 5 μg in 10 mL. Withdraw 2 mL (1 μg) for administration.
   - This test requires accuracy in dilution and administration technique for best results.
   - *Adult and Pediatric dose:* One μg of drug (milliliters as per dilution) is withdrawn and administered to the patient via IVP (Carmichael 2016).
   - The IV catheter is flushed with 3–4 mL of normal saline after drug administration. After 2–4 mL of saline is withdrawn and from the catheter and discarded, a second cortisol level is drawn at 30 min after drug administration. This test is usually well tolerated and without side effects (Chitale et al. 2013).
   - *Interpretation*: Peak serum levels above 18 μg/dL (500 nmol/L) indicated and adequate adrenal response in adults or 19 μg/dL > 550 nmol/L in children (Nieman 2003; Bornstein et al. 2016; Carmichael 2016; Butler and Kirk 2011).

15.4.2.2.2 Standard Dose ACTH Test/High Dose (25 mg/250 μg)

A supraphysiologic dose of 250 μg ACTH (1000 times higher than normal peak production) is effective in identify primary adrenal insufficiency (AI), but although used to identify secondary AI may have limited ability to detect secondary adrenal hypofunction unless the adrenal glands have atrophied over time from lack of pituitary ACTH stimulation (Nieman 2003; Bornstein et al. 2016; Carmichael 2016). In pediatrics a newborn baby with ambiguous genitalia will need immediate testing (see Chaps. 3 and 35) or when the child's levels of 17-hydroxyprogesterone (17OHP) are elevated above 30 nmol/L and is indicative of CAH (Butler and Kirk 2011).

Patient Preparation: The test can be performed at any time of the day (Carmichael 2016). However, the patient is instructed to hold any glucocorticoid replacement the day of testing which may risk symptomatic adrenal insufficiency, such as after long-term glucocorticoid use. Performance of the test early in the day may avoid this. This is especially pertinent in children. Patients should be instructed to bring their normal dose of glucocorticoid to clinic for administration at the completion of the test. In children, anesthetic cream can be applied to both antecubital spaces and the backs of both hands about an hour prior to arrival at the testing unit. This test is usually well tolerated.

Procedure: An angio-catheter (IV) is usually placed in a vein, typically in the inside of the elbow or in the back of the hand. In children two sites may need to be cannulated. Blood is drawn for baseline measurement of blood cortisol and ACTH levels.

Adult Dose: A solution of 250 μg/2 mL of sterile saline is prepared and administered IVP. Note: Synachten may be supplied in a 250 μg lyophilized vial or as 1 mL solution. The drug must be prepared according to package instructions.

Dose for Children: The dose of Synacthen should be 500 ng(0.5 μg)/1.73 m^2 body surface area/(BSA). (To calculate BSA, = [height(cm) × weight (kg)/3600]m^2). Therefore, it is imperative that the child's weight

AND height is recorded upon admission. This may be administered IV or IM (Butler and Kirk 2011).

Usual doses:

0–6 months	62.5 μg
6 months–2 years	125 μg
>2 years	250 μg

Dilution: The dose and dilution of Synacthen may be different in each country or testing center. Most preparations require dilution. Check the package insert for dilution instructions. The dosage must be calculated according to the dilution. The solution also needs to be well mixed prior to drawing up the required dosage.

Recommended start time for testing in children is 9 a.m. At this time, baseline samples for cortisol and ACTH and 17OHP are drawn. A second baseline cortisol level is drawn 1 h later at some facilities. Synacthen is then administered, and sampling for cortisol continues at 30 and 60 min (Carmichael 2016; Butler and Kirk 2011). The test is well tolerated with very rare hypersensitivity reaction.

Interpretation: Peak serum levels above 18 μg/dL (500 nmol/L) indicated and adequate adrenal response (Nieman 2003; Bornstein et al. 2016; Carmichael 2016).

15.4.3 Metyrapone (Metopirone) Dynamic Testing

Metyrapone stimulation test is used to assess pituitary function. The drug blocks the conversion of 11-deoxycortisol to biologically active cortisol. In normal subjects, this stimulates the production of CRH and ACTH by negative feedback. Therefore, this test is useful to evaluate adrenal hypo- or hyperfunction. A failure to increase ACTH indicates either ACTH deficiency or primary adrenal disease and excludes a diagnosis of Cushing's disease (Newell-Price JDC 2016).

This drug can be used in two different ways, including an overnight single-dose test (OMT) or a multiple-dose test (STD). These tests are contraindicated in patients who are hypersensitive to metyrapone or its components. Common to both tests, the procedure is performed under medical supervision (Fiad et al. 1994; Berneis et al. 2002).

Common side effects for either test can include hypotension, nausea, vomiting, abdominal discomfort, headache, dizziness, and allergic rash. As with all clinical testing, check with the patient's health insurance to ensure testing is covered (Fiad et al. 1994; Berneis et al. 2002).

OMT Procedure: Metyrapone is a 250 mg oral capsule taken with milk. Adults are dosed at 30 mg/kg at midnight with a maximum of 3 g given. A single blood sample is taken between 0730 and 0800 for 11-deoxycortisol (11-DOC) and/or adrenocorticotropic hormone (ACTH) levels.

Interpretation: A normal response is indicated in a rise of plasma ACTH levels of 44 pmol/L or 200 ng/L or an increase in 11-DOC to over 0.2 μmol/L or μg/L. (Fiad et al. 1994; Berneis et al. 2002)

STD Procedure: Patients are hospitalized for 24 h and administered six divided doses of 750 mg every 4 h over 24 h for a cumulative dose of 4.5 g. Patients collect a total of three 24 h urine specimens (the day prior to dosing, the day of dosing, and the day after dosing). Samples are measured for 17-hydroxycorticosteroids (17-OHCS) and/or 17 ketogenic steroids (17-KGS) levels.

Interpretation: A doubling of 17-KGS or a two- or fourfold increase in 17-OHCS indicates a normal response. Abnormal responses are indicative of partial or full panhypopituitarism, Cushing's syndrome, and/or adrenal hyperplasia.

These tests are limited by the availability of metyrapone and clinical laboratories able to perform the analysis (Newell-Price JDC 2016; Fiad et al. 1994; Berneis et al. 2002).

15.5 Hypercortisolism

The protocol for investigating Cushing's syndrome in children is the same in adults. Cushing's syndrome, especially Cushing's disease, is very rare in children. Close contact between adult and pediatric endocrine teams during pediatric investigations is vital (Savage et al. 2008).

15.5.1 Urinary Free Cortisol: 24 h (UFC)

Urinary cortisol excretion over a 24 h period has been considered the gold standard of adrenocortical activity for the diagnosis of Cushing's syndrome. There is currently some debate about this status and the cut-off values used for the upper limit of normal, based on new assay methods (Raff et al. 2015). Regardless, it remains a highly sensitive marker of cortisol production and useful in the diagnosis of both low and excess cortisol (Newell-Price JDC 2016; Nieman et al. 2008). However, cortisol only appears in the urine when it exceeds the binding capacity in plasma (Raff et al. 2015).

The purpose of this test is to assess how much free (unbound) cortisol is in urine. This level is correlated with blood levels of free cortisol over the previous 24 h period (Newell-Price JDC 2016). Two collections are recommended (Nieman et al. 2008).

Patient preparation: includes avoidance of medications including all steroid creams, oral or injected glucocorticoids (including intraarticular injections), ketoconazole, estrogens, carbamazepine, fenofibrate, and mitotane that interfere with the assay and provide false cortisol levels (Nieman et al. 2008). When the glomerular filtration rate less than 30 mL/min or if the patient is drinking more than 3–5 L of fluid daily, the testing results may be inaccurate (Nieman 2018).

Procedure: The patient is instructed to void on awakening and discard the first morning urine. However, the time of this void is recorded and initiates the 24 h of the collection. All urine is collected in jugs provided by the laboratory or large clean containers for exactly 24 h from the start time. This includes the first morning void on the following day. All urine collected must be kept refrigerated or on ice during the collection and until deposited at the laboratory (Nieman 2018). Check with the laboratory that will perform the assay regarding what type of urine preservative may be required.

Interpretation: The results are interpreted in the context of the urine volume and creatinine and in children, corrected for body surface area. Cut-off values are published by the lab performing the test based on the specific assay used.

15.5.2 Late Night Salivary Cortisol (LNSC)

In people with normal cortisol production, cortisol nadir or the lowest level, is immediately before sleep with a circadian rise in the early morning. The loss of this circadian pattern is the hallmark of Cushing's syndrome (Yaneva et al. 2004). However, in shift workers with a variable schedule, LNSC may not be reliable (Nieman 2018).

Patient Preparation: Patient should not be taking glucocorticoids and women are instructed to discontinue estrogen about 2 weeks prior to testing. The patient must not take anything by mouth for an hour prior to collecting the salivary sample. This includes glucocorticoid medications or creams, food, fluids, gum, toothpaste, and cigarettes. Gentle teeth cleaning is recommended in order to avoid blood contamination of saliva.

Appropriate selection of saliva collection device for use in children takes into account the age and cooperation level of the child (e.g. whole saliva sampling, passive drool or spitting in tube, braided cotton dental rope, polymer rolls, mucous extractors, or modified eye sponges) (Keil 2011). Typically for children, an assistant using disposable gloves can place the pledget under the tongue and assist to replace the pledget inside the collection tube. There are a number of styles of collection devices and new devices and apps are available for some smartphones (Fig. 15.1).

Patients should receive clear written instructions regarding sample collection (Hodgson and Granger 2013): Emphasis should be placed on labeling all tubes with collection times, name, birthdate, and date of collection. The pledget or swab should not be touched but tipped directly into saliva pooled on the floor of the mouth. This should be saturated before it is returned to the storage tube. The specimen does not require refrigeration and can be delivered to laboratory at room temperature (Hodgson and Granger 2013). Check with the laboratory performing the assay if refrigeration is required for other types of spec-

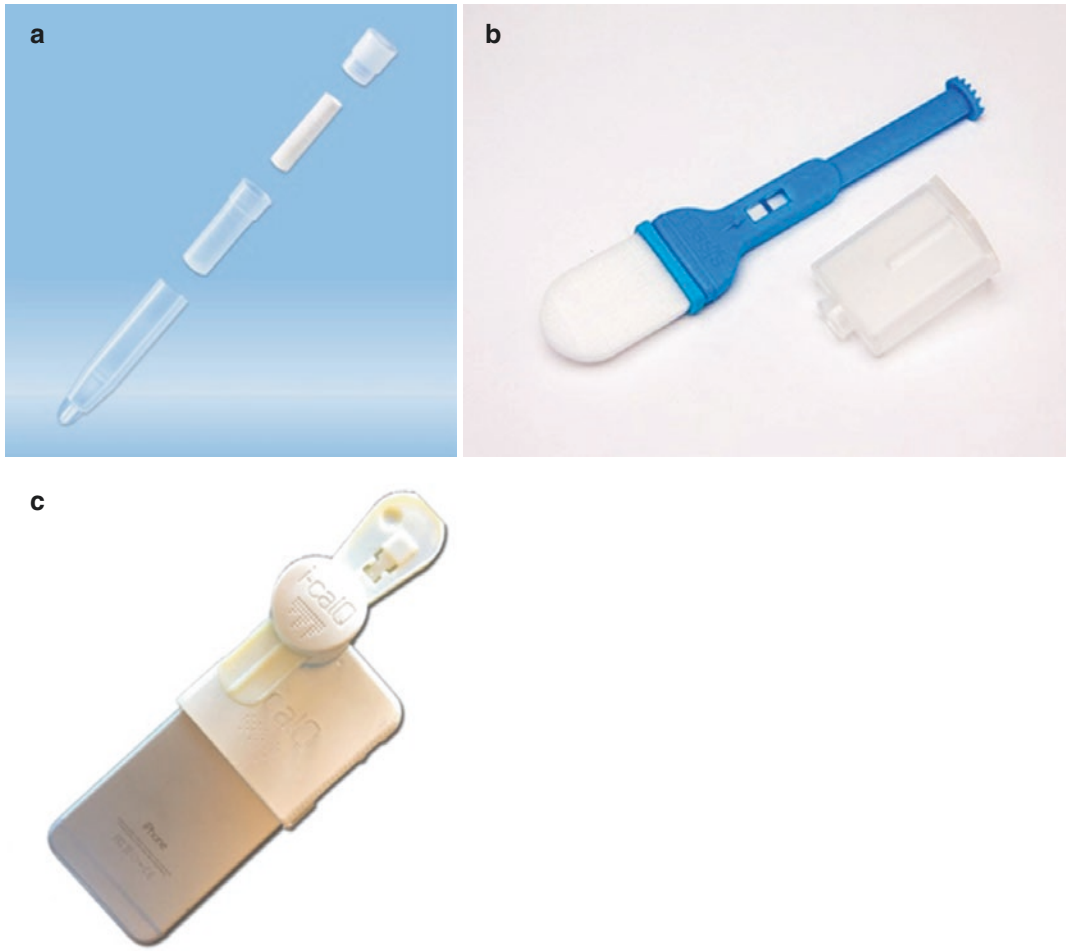


Fig. 15.1 Salivary cortisol testing devices (**a**, **b**) cotton pledgets (**c**) Smart phone based cortisol measuring systems. From: Choi S, et al. Real-time measurement of human salivary cortisol for the assessment of psychological stress using a smartphone. Sens BioSens Res. 2014;2:8–11

imens. Any required health insurance/authorization forms to accompany the samples should be fully completed.

Result interpretation: An LNSC level > than 145 ng/dL (4 nmol/L) is indicative of Cushing's syndrome (Nieman et al. 2008; Papanicolaou et al. 1998). Two specimens are recommended for diagnosis (Nieman et al. 2008).

15.5.3 Low Dose Dexamethasone Suppression Test (DST)

This test is used to assess hypercortisolism, differentiating between those patients with, and without, Cushing's syndrome (Newell-Price JDC 2016). In normal subjects, a dose of 0.5 mg of dexamethasone every 6 h for 8 doses has been shown to suppress urinary 17 hydroxycorticosteroid excretion by the second day of administration in patients without Cushing's disease. This suppression is not evident in patients with Cushing's syndrome (Newell-Price JDC 2016; Liddle 1960).

Patient Preparation and Procedure: The patient is given a clear written schedule to time dose administration every 6 h for 8 doses. Usually recommended beginning at 9:00 a.m. day 1. Following this schedule, patients are instructed to present to a laboratory at 9 a.m. day 3, 6 h

after the last dose of dexamethasone. A cortisol level is drawn on presentation. A salivary cortisol collection at precisely 2 h after the last dose of dexamethasone may also be used (Newell-Price JDC 2016).

Dose adjustment in children: 2 mg/day per 1.73 m^2. Body surface area in children less than 40 kg or 30 μg/kg/day in divided doses. The dose required in adults or in pediatric patients is the same when the patient's weight is over 40 kg (88.2 lb) (Butler and Kirk 2011; Newell-Price JDC 2016).

Interpretation: A morning serum cortisol level is normal if less than 1.8 μg/dL (50 nmol/L) ruling out Cushing's syndrome (Nieman et al. 2008).

15.5.4 Overnight Dexamethasone Suppression Test (O/N DST)

As for DST, the overnight test is based on the suppression of urinary 17 hydroxycorticosteroid excretion. It is advocated as a practical alternative screening test for Cushing's syndrome, but does not differentiate the sources of cortisol. The patient is administered 1 mg of dexamethasone between 11:00 and 12:00 p.m. and serum cortisol is measured by venipuncture the next morning between 8:00 and 9:00 a.m. (Newell-Price JDC 2016)

Interpretation: Cut-off for normal levels remains less than 1.8 μg/dL (50 nmol/L) although there is some ongoing debate. The specificity of ON/DST is low (Newell-Price JDC 2016; Nieman et al. 2008).

15.5.5 High Dose Dexamethasone Suppression Test/2 Day DST

A high dose of dexamethasone is used to differentiate pituitary-dependent Cushing's for adrenal sources of hypercortisolism. It is also useful but not conclusive in excluding ectopic Cushing's. This test is useful only after Cushing's syndrome has been diagnosed (Newell-Price JDC 2016).

Procedure: A baseline 24 h urine free cortisol (UFC) or morning serum cortisol level is drawn. A morning serum cortisol is recommended as more accurate and convenient (Nieman et al. 2008). Dexamethasone 2 mg is administered orally every 6 h for 2 days (for a total of 8 mg). A second 24 h UFC is collected or a serum cortisol level is after the last dose of dexamethasone. Two protocols have been described; initiation of dexamethasone at 9 a.m. with cortisol level drawn at 9 a.m. or 6 h after the last dose; or the first dose of dexamethasone at 12 noon with the cortisol level drawn at 8 a.m., exactly 2 h after the last dose (Hashimoto et al. 1990; Yanovski et al. 1998).

Interpretation: If the level of cortisol suppresses to less than 50% of the baseline levels in either test, or if cortisol level is >1.8 μg/dL (50 nmol/L) pituitary-dependent Cushing's disease is confirmed (Newell-Price JDC 2016; Nieman et al. 2008).

15.5.6 Corticotropin Releasing Hormone (CRH) Test

CRH is the releasing factor for pituitary ACTH. CRH testing is used to confirm ACTH-dependent source of excess ACTH, establishing a diagnosis of Cushing's disease. Pituitary ACTH producing tumors, but not ectopic ACTH tumors respond to CRH stimulation. It can also be used to diagnose and to differentiate the source of adrenal insufficiency as primary or suprapituitary to diagnose hypercortisolism or to evaluate adrenal function post-pituitary surgery. In patients with ACTH deficiency causing adrenal insufficiency, ACTH does not rise in response to CRH. In Cushing's disease, there is a significant rise in ACTH (Trainer et al. 1995).

Although both ovine and human forms of CRH are available, only ovine CRH such as Corticorelin Ovine Triflutate/Acthrel is FDA approved for use in the USA. Ovine CRH is about five times more potent, mainly because it has a longer effect on ACTH and subsequent cortisol secretion (Trainer et al. 1995).

Patient Preparation: Patients should not be taking glucocorticoids or estrogen as in all testing for hypercortisolism. Anticipated side effects of drug administration including facial, neck, and upper body flushing and an increase in heart rate are described to the patient prior to testing. Patients also report sensing the need to take a

deep breath immediately after drug administration. Side effects are minimized by slow bolus over 30 s or more. The procedure is the same for adults and children.

Procedure:

- Schedule a start time preferably at 8–9 a.m.
- Encourage children to void prior to the start of the procedure.
- Establish IV access and secure cannula, particularly in young children.
- Draw baseline ACTH and cortisol level at −15 min. Place ACTH specimen on ice.
- Administer Ovine* (or human) CRH. 1.0 μg/kg body weight is injected intravenously as a bolus over 30 s for adults and children. Maximum dose is 100 μg or one vial reconstituted with 2 m of sterile saline for 50 μg/mL dilution.
- Saline flush IV cannula with 5–10 mL.
- Serum ACTH and cortisol are measured at 5 time points: baseline, 15, 30, 45, and 60 min after drug administration.

Result interpretation: A 35% rise in ACTH and a 20% rise in cortisol compared to baseline at 15–30 min after administration is diagnostic of Cushing's disease and excludes pseudo-Cushing's syndrome (Chitale et al. 2013; Batista et al. 2007).

The response is increased in persons with hypothyroidism, ethanol withdrawal, and some acute and chronic illnesses. Pregnancy and renal failure may decrease the response.

There is no apparent difference in ACTH response between children and adults (Newell-Price JDC 2016; Batista et al. 2007).

15.5.7 Dexamethasone Suppression and CRH Stimulation Test (DST/CRH)

A combination of dexamethasone and CRH testing has been advocated to improve diagnostic accuracy for Cushing's syndrome and exclude pseudo-Cushing's. Reason for testing is as described previously. This test may also be useful in discriminating mild or cyclical cases of Cushing's disease (Erickson et al. 2007; Moro et al. 2000).

Patient Preparation: Evidence indicates improved test accuracy when medication use, particularly antidepressant medications and some cardioactive drugs are used at the time of testing (Valassi et al. 2009). When possible, estrogen and antidepressant medications should be held during testing. The patient is given written instructions with the dexamethasone prescription with medication start time and subsequent dose times.

Procedure: Eight doses of oral dexamethasone 0.5 mg every 6 h for 48 h. The patient presents to the testing unit and has an IV cannula placed within 1.5 h of the last dose of dexamethasone. An IV infusion of 100 mg of CRH is administered as per CRH protocol described previously.

Interpretation: A serum cortisol threshold of 1.4 μg/dL (38 nmol/L) 15 min after CRH is diagnostic for Cushing's syndrome. Simultaneous baseline measurement of dexamethasone, cortisol, and ACTH is recommended to assess dexamethasone metabolism and improve the diagnostic accuracy of testing. Dexamethasone level must be adequate to suppress ACTH/cortisol prior to CRH administration (Raff et al. 2015). An adequate dexamethasone level is considered to be >5.6 nmol/L (160 ng/dL) (Nieman et al. 2008).

15.5.8 Insulin Tolerance Test (ITT)

This test is used to assess cortisol respone for both hypo and hypercortisol states. (See Sect. 15.4.2.1) for a detailed description.

15.5.9 Central Venous Sampling: Inferior Petrosal and Cavernous Sinus Sampling

Central venous sampling is used to determine a pituitary ACTH-dependent source of hypercortisolism or Cushing's syndrome. In some patients, it may also help to determine the lateralization or the location (right or left) of the hypersecret-

ing tumor in the pituitary. There are two methods of venous sampling: Inferior petrosal sinus sampling and cavernous sinus sampling.

15.5.9.1 Inferior Petrosal Sinus Sampling (IPSS)

Bilateral inferior petrosal sinus sampling (IPSS) is considered the single most accurate test for the differentiation of ACTH-dependent Cushing's syndrome in adults and children. IPSS is recommended in cases where less invasive biochemical testing has confirmed hypercortisolism or has been equivocal and when the MRI of the pituitary is normal or contains a small mass less than 6 mm. This procedure is best performed by an experienced neuroradiologist (Newell-Price JDC 2016).

This is an invasive procedure involving the direct catheterization of both right and left petrosal sinuses to measure ACTH in the blood draining from vessels each side of the pituitary. Central ACTH levels are compared with ACTH levels from peripheral vein samples, which are drawn simultaneously (Sharma and Nieman 2011; Lindsay and Nieman 2005). This helps to determine the side with the highest production of ACTH.

Patient Preparation: This includes an explanation of risks and benefits and requires the patients' written informed consent. The procedure is usually well tolerated with mild discomfort with bilateral catheter placement. Rare serious side effects have been reported and include vascular damage and venous thromboembolism, sixth nerve palsy, venous subarachnoid hemorrhage, brain stem infarction, and acute renal insufficiency due to contrast dye (Newell-Price JDC 2016; Lindsay and Nieman 2005; Miller and Doppman 1991). Preparation with an age-appropriate explanation of the procedure is particularly important for children and the procedure is typically performed with sedation for safety.

Procedure: A peripheral IV catheter is placed on admission to the interventional radiation center and conscious sedation is usually administered prior to and during the procedure. The use of local anesthetic creams applied to the antecubital spaces bilaterally and the back of both hands about an hour prior to admission to the procedure center is recommended for children.

The patient is placed in supine position and under fluoroscopy; catheters are placed in the femoral veins bilaterally at the groin and advanced to the right and left petrosal sinus. ACTH sample are drawn from the peripheral IV cannula along with simultaneous samples drawn from both the right and left petrosal sinuses catheters. Blood samples are drawn for baseline measurement at −3 min and 0 time points. CRH is administered peripherally and serial samples are taken at 3–5 min intervals for 2–3 measures. Desmopressin can also be used to stimulate the release of ACTH during IPSS (Machado et al. 2007; Oldfield et al. 1985).

Interpretation: For the diagnosis of Cushing's disease, a basal central to peripheral ACTH gradient (comparison of ACTH from petrosal vein to peripheral source) of more than 2:1 or more than 3:1 after administration of CRH is required. The absence of a gradient indicates an ectopic source of Cushing's syndrome outside of the pituitary gland (Sharma and Nieman 2011). When performed by a skilled and experienced radiologist; accuracy can be as high as 99%. However, false negatives and false positives can occur due to unsuccessful catheterization, inappropriate catheter placement, performance during normocortisolemic periods, and in the case of CRH secreting tumors. In order to increase accuracy, concurrent sampling of prolactin can be used to normalize ACTH ratios. While still highly accurate as a differential diagnostic tool, the use of IPSS to lateralize a tumor within the pituitary gland is still a matter of controversy, with its accuracy somewhere between 50 and 100%.

Post-procedure, pressure is applied to both venous access sites, typically the groin, to prevent bleeding (Miller and Doppman 1991). The most common complication of IPSS is a groin hematoma, seen in 3–4% of patients (Fig. 15.2).

15.5.9.2 Cavernous Sinus Sampling (CSS)

Cavernous sinus sampling (CSS) is recommended as an alternative to IPSS as the cavernous sinuses are closer to the pituitary gland and may provide a higher central to peripheral gradient without the use of CRH. However, no studies have concluded

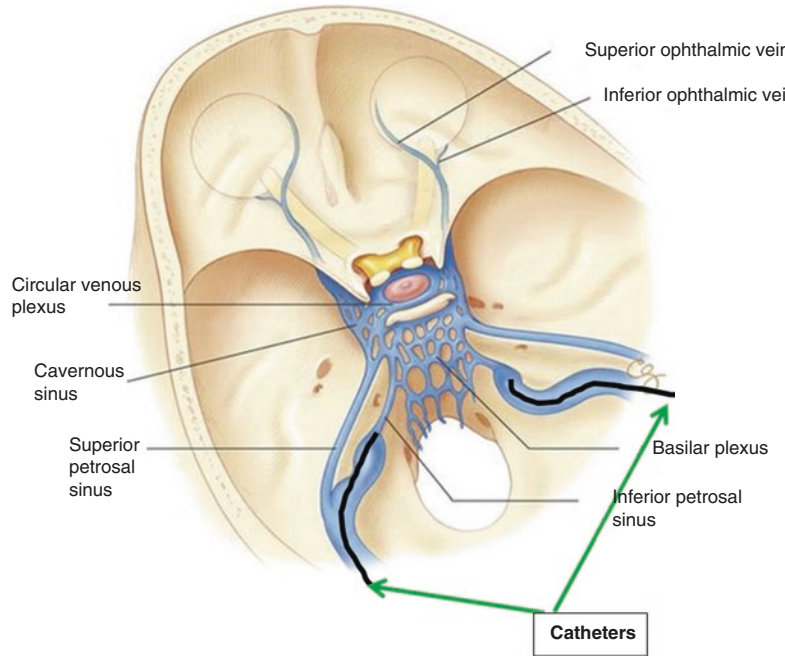


Fig. 15.2 Catheter placement for bilateral simultaneous blood sampling of the inferior petrosal sinuses

that it offers any additional advantages. There is additional risk of complications from entering the cavernous sinus as compared to the petrosal sinuses, as well as increased cost (Lindsay and Nieman 2005).

Other alternative methods of venous sampling may be used due to the risk of complications and technical difficulty of performing IPSS. Some centers have suggested the use of jugular venous sampling (JVS) with the administration as it is safer and requires less expertise. However, accuracy is lower than that of IPSS (Ilias et al. 2004).

15.6 Growth Hormone Testing

Dynamic/provocative testing is used to evaluate both growth hormone deficiency (stimulation testing) and growth hormone excess (suppression testing).

15.6.1 Growth Hormone Stimulation Testing

Although initially associated with children with idiopathic short stature, growth hormone deficiency (GHD) is now recognized in both adults and children (Gupta 2011). More recently GHD has been associated with a history of traumatic brain injury (TBI). Stimulation testing determines the presence of GHD. Several tests may be used for this evaluation including IGF-1 generation test or stimulation with: glucagon, arginine, GHRH (semorelin acetate), ITT, L-Dopa, or clonidine. Two tests may be required to demonstrate GHD.

Children with a bone age of >10 years who are not yet in puberty may not show an optimal response to GH stimulation. Hence, they may be "primed" with sex steroids, such as estrogen, testosterone, or stilbestrol (Butler and Kirk 2011). Priming has been used to increase the GH peak response in testing in prepubertal children to levels equivalent of children already in puberty and remains controversial (Strich et al. 2009). Accurate pubertal staging is required prior to this test. Some advocates of priming before GH testing indicate that the timing of "priming" is important with respect to puberty. They observe that this method should be used only within 5 years before normal pubertal onset (Rosenbloom 2011). Others believe priming is unnecessary and simply reduces the number of "non-responders" by artificially raising the GH peak level (Soliman et al. 2014; Lazar and Phillip 2010).

Nevertheless, priming protocols include:

- Ethinyl estradiol 10 μg orally once a day for 5 days prior to the test for girls
- Testosterone esters 100 mg IM 1 week before the test for boys
- Oral stilbestrol 1 mg daily for 3 days before the test, or twice daily for 2 days before the test
- If priming is taking place, steps should be taken to ensure test continuity with GH testing at the appropriate testing center. Either ITT, glucagon, or GHRH testing is used after "priming."

15.6.1.1 Insulin Tolerance Testing (ITT)

This has been previously described in (See Sect. 15.4.2.1).

15.6.1.2 IGF-1 Generation Test

Dysfunction in the GH-IGF-1 axis is apparent in children with idiopathic short stature related to growth hormone insensitivity. This test measures circulating IGF1 levels generated in response to subcutaneous injections of recombinant human GH (rhGH) administration. Growth hormone insensitivity (GHIS) is apparent when growth hormone levels are high, but baseline IGF-1 remains low (Cotterill et al. 1998). Some authors suggest that the IGF-1 generation test is less sensitive for diagnosing mild GHIS, yet it is still widely used to confirm a diagnosis of GHD (Coutant et al. 2012).

Procedure. There are a number of protocols described for this test. The most common is performed over 5 days and requires four rhGH injections (33 mg/kg per day; total dose of 132 mg/kg) (Coutant et al. 2012). The patient presents on day 1 for a serum IGF-1 level. After returning home, the child can eat and drink as normal. On the following 4 days, a dose of GH is administered to the child, usually by a visiting nurse. Twelve hours after the administration of the last dose of GH, the child returns to the testing clinic for another serum IGF-1 level to be drawn.

Interpretation: Failure to increase IGF-1 levels on growth hormone administration and/or IGF-1 increment of <15 ng/mL is indicative of GHIS and is discussed in more detail in the Chap. 2. In the case of GHD, the IGF-1 is increased (Blair et al. 2004). Although used frequently as a diagnostic tool in Europe, this test has been criticized for its inability to identify mild and some more severe cases of GHD in children (Coutant et al. 2012).

15.6.1.3 Glucagon Stimulation Test (GST)

The glucagon test is commonly used in adults and in children under the age of 12 years of age, whereas the insulin tolerance test is commonly used for children over this age. The GST is used as an alternative in adult patients where ITT is contraindicated. The GST is a very effective and safe way to measure pituitary function with fewer side effects than ITT, as hyperglycemia and not hypoglycemia is induced (Yuen et al. 2013).

Patient preparation: This is a 3–4 h test. Adults and children are fasted for at least 12–24 h and present to the testing site early morning (8 a.m.). Intake of water is encouraged. Patients are asked to hold morning medications but can take medications at the completion of testing. Common side effects can include headache, sweating, nausea, and vomiting. Children are particularly susceptible to vomiting. Rebound hypoglycemia may occur later in the day if the child does not eat or drink after testing. Most centers keep the children long enough to ensure tolerance of a normal diet has resumed (Butler and Kirk 2011).

Procedure: An IV cannula is inserted and sampling commences with samples of glucose and growth hormone at 0, 60, 90, 120, 150, and 180 min in children (25, 2011). In some centers, more frequent samples are obtained at time 0, +15, +30, +45, +60, +90, + 120, +180, +210, and + 240 min. However, standard draws in adults are every 20 min for 4 h (Bonert 2016). Cortisol levels may also be measured.

A dose of glucagon is administered via an intramuscular (IM) injection, usually in the buttock after baseline (0) serum samples are drawn. This drug is contraindicated in the presence of pheochromocytoma or insulinoma. There are two ways of determining the dose of glucagon needed: the fixed dose and the weight-based dose.

Patients are dosed with 1 mg (10 μg) of glucagon IM for weights under 90 kg and 1.5 mg (15 μg) of glucagon for weights above 90 kg in a fixed dose GST. For the weight-based dosing GST, patients are dosed at 0.03 mg/kg of glucagon. This dose is used in children to a maximum of 1 mg and can be administered subcutaneously (Carmichael 2016).

Interpretation: Patients whose response peaks >3 ng/mL have a normal test and their pituitary is functioning appropriately. Results under 3 ng/mL (3 μg/L) demonstrate pituitary dysfunction and pharmacologic treatment could be required. In children, 3–6 μg/L is considered partial growth hormone deficiency. Consider a cut-off of 1 ng/mL for obese patients (Yuen et al. 2013; Bonert 2016; Hamrahian et al. 2016).

15.6.1.4 Arginine Stimulation Testing

Arginine is seldom used as a single agent for the diagnosis of growth hormone deficiency secondarily to efficacy; it is often used in combination testing. In some countries, the availability of arginine also limits its use. Arginine is also not as commonly used in children. Most frequent combination use is with either L-DOPA or GHRH. Arginine is an intravenous stimulant to the pituitary for the release of HGH in patients where the measurement of pituitary reserve for HGH can be diagnostic for GHD.

Patient Preparation: The patient is usually fasted overnight or for 8–10 h. Infants may eat up to 4 h prior to the procedure. Consumption of water is encouraged. Morning medications are usually held. The most common side effects are nausea, headache, and complaints of a metallic taste in the mouth or polyuria. Children are encouraged to bring a favorite activity, DVD, or comfort toy. Application of anesthetic cream to antecubital areas or forearms for IV placement can be done by parents prior to arrival at the testing site. Arginine may exacerbate acidosis in patients with renal failure and may be hazardous in patients with liver disease; other stimulatory agents should be used in persons with these disorders (R-Gene 2016). This drug is also contraindicated in persons having highly allergic tendencies.

Procedure: After arrival in clinic, an IV cannula is placed and baseline levels of IGF-1 and GH are drawn. An arginine dose of 0.5 g/kg (maximum 30 g) is infused via IV infusion over 30 min (Carmichael 2016). Dose must be double checked, as arginine overdose in children can be fatal. Excessive rates of infusion may result in local irritation and in flushing, nausea, or vomiting. Inadequate dosing may diminish the stimulus to the pituitary and nullify the test (R-Gene 2016).

If this is to be a combined test with glucagon, the lyophilized glucagon must be reconstituted and a dose of 30 μg/kg (maximum 1 mg) of body weight is administered IM (thigh or buttocks). GH, glucose (and cortisol levels if needed) blood samples are drawn every 30 min for 2 h (Glucagon 2017).

Similar to the arginine/L-DOPA test, the arginine/GHRH test also takes place over 120 min. Baseline labs, including GH, are drawn prior to the GHRH 1 μg/kg via IVP for patients weighing over 60 kg (consult the package insert for patients weighing less than 60 kg). Arginine dosing of 30 g is then infused over 30 min with GH blood draws thereafter every 30 min for 2 h (GNRH Ferring 2012).

Interpretation: A peak value under 3 ng/mL is considered abnormal and could warrant a second confirmation test. Some authors define levels <3 ng/mL as severe GHD and < 5 ng/mL as GHD (Hamrahian et al. 2016).

- A normal response is a peak >5 ng/mL or increase of 5 ng/mL over basal level.
- A blunted response occurs in hypothalamic-pituitary dwarfism.
- Lack of response also is found in persons with hypothyroidism.
- Response is inversely proportional to basal GH; no response may be seen if basal level is >5 ng/mL.
- GH levels may be decreased in hyperglycemia, obesity, and during treatment with cimetidine. GH levels may increase if the patient is treated with diethylstilbestrol, propranolol, indomethacin, glucocorticoids.

15.6.1.5 Growth Hormone Releasing Hormone Stimulation Testing (GHRH)

Growth hormone releasing hormone is often combined with other tests such as arginine stimulation to evaluate GHD. The purpose is to confirm new or persistent GHD in adulthood or adolescence, particularly after final height is achieved, or to diagnose GHD when ITT is contraindicated (GNRH Ferring 2012; Molitch et al. 2011).

Preparation: The patient is instructed to fast overnight or for 8–12 h. Continued intake of water is encouraged. GH treatment should be held for 1 month prior to testing. Side effects may include Facial flushing, rare paresthesia, nausea, and abnormal taste sensation after GHRH administration.

Procedure:

- An IV cannula is placed on admission and the patient allowed to rest for 45 min.
- Baseline GH and IGF-1 measurement are drawn (−15 mins), and GH at 0 min.
- GHRH (Somatorelin, Ferring, Geref) 1 μg/kg (maximum dose 100 μg) is injected through IV as a bolus injection (GNRH Ferring 2012).
- If a combined test, infuse 0.5 g/kg L-arginine monohydrochloride (maximum dose 30 g) as a 10% solution (30 g/300 mL) in normal saline over 30 min.
- Blood samples for further GH estimation are drawn at 30, (45), 60, 90, 120, and 150 min after the start of the arginine infusion.
- Patient is able to eat lunch at +150 min or after the last blood test.
- Pulse and BP are monitored and recorded during the procedure.

Interpretation: Cut-offs for diagnosis of GH deficiency remain unclear, but may depend on peak GH, age, and BMI and waist circumference (Colao et al. 2009). Using GHRH-arginine test is most sensitivity and specific to GHD, at a GH cut-off of <4.1 μg/L and has been shown to be comparable to ITT (Molitch et al. 2011). Higher cut-off of ≤8.0 μg/L have been recommended for patients with BMI ≥25 and <30 (Carmichael 2016).

15.6.1.6 L-DOPA Stimulation Test

Similar to the test listed above, the L-DOPA stimulation test can be used as an independent test of GHD but results are inferior to ITT or combination testing. It is administered over 2 h with fasting GH levels taken at baseline and every 30 min thereafter via an IV line. After baseline samples are obtained, patients are dosed with 125 mg of oral L-DOPA if weighing <10 kg, 250 mg if 10–30 kg and 500 mg orally if >30 kg. The most common side effect is nausea. L-DOPA is contraindicated in patients with a history of cardiac arrhythmia. The maximum GH secretion occurs after 60–90 min (Bonert 2016).

15.6.1.7 Clonidine Test

Clonidine was found to stimulate a profound rise in GH levels in oral, and subsequently intravenous doses (Gil-Ad et al. 1979). This is used more frequently in children (Coutant et al. 2012).

Procedure: The child is placed in the supine position for venous cannulation. After rest, a sample of whole blood is collected for baseline GH. After obtaining the baseline sample, a dose of 0.10–0.15 mg/m^2. Clonidine is administered orally and subsequent blood samples for GH are collected after 30, 60, 90, and 120 min (Gil-Ad et al. 1979). Side effects are reported as mild including fatigue and somnolence and mild postural hypotension (Bonert 2016).

Interpretation: A cut-off level of >3.0 ng/mL is reported as indicating normal GH levels (De Fátima Borges et al. 2016).

15.6.2 Growth Hormone Excess

Growth hormone (GH) is secreted in bursts with higher amplitude burst during sleep. The half-life of GH is short, around 11–19 min, making a random single sample unreliable to diagnose acromegaly (Faria et al. 1989). Two tests are typically used for this diagnosis: A growth hormone profile and an oral glucose tolerance test (OGTT) which will suppress normal but not excess GH secretions and thereby confirm growth hormone excess or acromegaly.

15.6.2.1 Growth Hormone Profile

This test is typically done after an 8–12 h fast. A growth hormone 5-point profile is an average of serum GH levels collected at intervals of 30 min, usually over a 2 h time period. Baseline IGF-1 and GH levels are collected. A mean GH >2.5 μg/L (6.9 nmol/L) is indicative of acromegaly.

15.6.2.1.1 Oral Glucose Tolerance Test (OGTT) for Growth Hormone Suppression

This test is rarely done in children, as growth hormone excess is rare in children. However, the protocol is the same as that for adults.

Patient preparation: The patient is fasted for 8–12 h, usually from midnight prior to the test. On admission to the testing area, an IV cannula is placed for peripheral access, and baseline serum glucose and growth hormone levels are drawn. Side effects are usually mild and include nausea, vomiting, abdominal bloating, and/or headache.

Procedure: Baseline levels of serum glucose, growth hormone, and IGF-1 are drawn prior to glucose administration and at 30, 60, 90, and 120 min following ingestion of glucose. The patient is given 75 g of glucose to drink. In children, the oral glucose solution is calculated at 1.75 g/kg, up to the maximum 75 g (Butler and Kirk 2011). This is usually flavored orange, fruit punch or lemon lime, and most contain corn-derived dextrose, citric acid, flavoring, sodium benzoate, yellow #6, and purified water.

Interpretation: A lack of suppression to <1 μg/L occurs in pituitary tumors secreting GH or in ectopic GHRH production (Melmed 2016). Lack of suppression also is common in patients with Cushing's syndrome, affective disorders, and anorexia nervosa. In acute illness, acromegaly, or chronic renal failure, a paradoxic rise in GH may occur.

15.6.2.1.2 Glucose Tolerance Test (GTT) for Insulin Resistance

Insulin resistance and type 2 diabetes is common in the general population but is often a hallmark of pituitary disease. This test also performed frequently in children, with the rise in pediatric obesity and type 2 diabetes (Conwell and Batch 2004). The testing protocol is the same as for adults.

Patient preparation and procedure as per OGTT for GH suppression.

Patients are encouraged to withhold drugs that will increase or decrease glucose levels.

Oral contraceptives, estrogens, glucocorticoids, thiazides, phenytoin, lithium, ranitidine, propranolol, and tetrahydrocannabinol can increase glucose levels and guanethidine, clofibrate, and salicylates can decrease glucose levels.

Interpretation as per American Diabetic Association (ADA) criteria (American Diabetes Association 2015):

Diabetes: Peak glucose level over 2 h > 200 mg/dL.

Impaired glucose tolerance: Peak glucose level over 2 h > 140–200 mg/dL

15.7 Gonadotroph Assessment

15.7.1 Clomiphene Stimulation Test/ Clomiphene Citrate Challenge Test (CCCT)

The purpose of the CCCT is to predict ovarian reserve and the prognosis for future pregnancy. Clomiphene has an antiestrogenic effect, stimulating GnRH and LH and FSH production from the pituitary (Kaiser 2016).

Procedure: Baseline FSH and LH and estrogen are measured on cycle day 3. Patients are administered 100 mg Clomiphene orally daily for 1–4 weeks or two pills per day cycle days 5–9. FSH and LH are drawn on day 10.

Interpretation: A doubling of LH and a 20–50% rise in FSH indicates normal pituitary response. Failure to increase may indicate decreased ovarian reserve or fewer remaining quality eggs (Carmichael 2016).

15.7.2 Human Chorionic Gonadotropin (HCG) Stimulation Test

In adult males, the HCG stimulation test is used to assess Leydig cell function and their capacity to produce testosterone. This is particularly pertinent in the evaluation of infertility (Kaiser 2016; Carmichael 2016).

Procedure: A baseline total testosterone level is drawn, followed by an injection of 5000 IU

hCG (Pregnyl) in the gluteal muscle. A follow-up blood sample is taken 72 h later.

Interpretation: A rise of >7.5 nmol/L indicates normal Leydig cell function (Bang et al. 2017).

In pediatics: The HCG stimulation test is widely considered the gold standard for investigating children with ambiguous genitalia (Grant et al. 1976). The 4-day test is discussed in more detail in the Chap. 3. A prolonged HCG stimulation test is performed when primary hypogonadism is suspected, or when exploring the causes for delayed puberty (Butler and Kirk 2011). This test takes over 3 weeks and requires frequent IM injections of HCG. Liaison with the local general or primary care practitioner or community nursing team will decrease the family's burden of travel for injections.

Procedure: Baseline plasma total testosterone, LH and FSH are drawn on day 1 prior to administration of 2000 IU HCG IM twice weekly for 3 weeks. Testosterone levels are drawn 24 h after the last injection (Butler and Kirk 2011). The dose may vary from 1000 to 5000 IU administered every day for 3–5 days. Testosterone levels may be sampled at 0, 48, and 72 h.

Interpretation: A flat response to HCG indicates testicular agenesis or hypogonadotropic hypogonadism. A rise in the testosterone levels >5 nmol/L (or 8 nmol/L in some studies) indicates adequate Leydig cell function or constitutional delay in puberty in adolescents (Butler and Kirk 2011; Carmichael 2016).

15.7.3 Gonadotropin Releasing Hormone Test (GnRH Test)

The GnRH test assesses the child for precocious puberty (see Chap. 4) and is a simple and most accurate way to assess the hypothalamic pituitary gonadal axis (Davies and Collin 2015). This test confirms a diagnosis of central gonadotropin-dependent precocious puberty (Eckert et al. 1996). It is not useful in determining pubertal signs such as premature thelarche (Bizzarri et al. 2014).

Procedure: The test takes 1 h to perform. Samples for LH, FSH, and estrogen or testosterone are drawn at 0, 20, and 60 min. GnRH is administered intravenously after the 0 sample is drawn. A dose of 2.5 μg/kg, with a maximum dose of 100 μg, is administered (Butler and Kirk 2011). The test can be performed at any time of the day and does not require fasting.

Table 15.2 Responses to GnRH stimulation

Diagnosis	Response
Normal child	FSH and LH both rise at 20, decreases at 60 min
Central precocious puberty	Pubertal response
Gonadotropin-independent precocious puberty	LH and FSH levels are suppressed
Gonadal failure	Basal LH and FSH values are increased, and the response to the GnRH is vastly increased
Delayed puberty	Response is either poor or absent
Hypogonadotropic hypogonadism	Response is either poor or absent

Adapted from Davies and Collin (2015)

Interpretation: Central precocious puberty is diagnosed if the LH level rises and gives a "pubertal response" in response to GnRH. The differences in the LH and FSH responses indicate the cause, as seen in the Table 15.2 (Davies and Collin 2015).

15.8 Thyrotroph Assessment

15.8.1 Thyroid Releasing Hormone (TRH) Test

The TRH test is rarely used in adults or children, given the availability of sensitive TSH assays. TRH testing was used to assess hyperthyroidism and suppression of TSH, TSH resistance, or a TSH secreting tumor (Butler and Kirk 2011). The test involves measuring baseline TSH levels via an IV cannula, administration of TRH, and subsequent draws for serum TSH after 15 and 30 min. In children, measurement at 60 and 120 min is also required. There is some associated discomfort including nausea, vomiting, bitter taste in the mouth, flushing and an urge to urinate, which is especially difficult for children (Table 15.3) (Mehta et al. 2003).

Table 15.3 Interpretation of TRH testing

Dysfunction	TSH after TRH administration
Primary hyperthyroidism	No change in TSH levels
Low TSH: end organ failure	Immediate increase in TSH
Secondary hypothyroidism (pituitary disease)	No increase in TSH
Tertiary hypothyroidism (hyperthalamic disease)	Delayed response (60–120 min)

Moncayo et al. (2007)

15.9 Conclusions

Testing for hypothalamic and pituitary dysfunction is complex and often requires multiple modalities to confirm a diagnosis. Random blood testing is not always diagnostic and dynamic or provocative testing may be required for a definitive diagnosis. Some provocative tests require complex patient preparation and are anxiety provoking. It is recommended that detailed written instructions be provided to the patient in order for testing to provide accurate, useful information in diagnosis.

In pediatric patient, preparation for testing is directed at both the child and the parent, and should be age-appropriate. Topical, light, or conscious sedation may be used for some testing modalities.

To instill confidence in patients during the critical, and emotion laden, diagnostic period the nurse must be knowledgeable in all facets of testing preparation, performance, and interpretation according to their role.

References

American Diabetes Association. Classifications and diagnosis of diabetes. Diabetes Care. 2015;38(Supplement 1):S8–S16. https://doi.org/10.2337/dc15-S005. Accessed 20 Jun 2018.

Bang AK, Nordkap L, Almstrup K, Priskorn L, Petersen JH, Rajpert-De Meyts E, Andersson AM, Juul A, Jørgensen N. Dynamic GnRH and hCG testing: establishment of new diagnostic reference levels. Eur J Endocrinol. 2017;176(4):379–91. https://doi.org/10.1530/EJE-16-0912.

Batista DL, Riar JR, Keil M, Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. Pediatrics. 2007;120(3):575–86.

Ben-Schomo A, Melmed S. Hypothalamic regulation of anterior pituitary function. In: Melmed S, editor. The pituitary. 3rd ed. London: Elsevier; 2011. p. 261–99. https://doi.org/10.1016/B978-0-12-380926-1.10015-X.

Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Müller B. Combined stimulation of adrenocorticotropin and compound-S by single dose Metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. J Clin Endocrinol Metab. 2002;87(12):5470–5. https://doi.org/10.1210/jc.2001-011959.

Bichet DG. The posterior pituitary. In: Melmed S, editor. The pituitary. 3rd ed. London: Elsevier; 2016. p. 251–88.

Bizzarri C, Spadoni GL, Bottaro G, Montanari G, Giannone G, Cappa M, Cianfarani S. The response to gonadotropin releasing hormone (GnRH) stimulation test does not predict the progression to true precocious puberty in girls with onset of premature thelarche in the first three years of life. J Clin Endocrinol Metab. 2014;99(2):433–9.

Blair JC, Camacho-Hubner C, Miraki-Moud F, Rosberg S, Burren CP, Lim S, Clayton PE, Bjarnason R, Albertsson-Wikland K, Savage MO. Standard and low-dose IGF-I generation tests and spontaneous growth hormone secretion in children with idiopathic short stature. Clin Endocrinol. 2004;60:163–8.

Bonert VS, Melmed S. Growth hormone. In Melmed S Pituitary 4th. London. Elsevier 2016:85–127.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2016;101(2):364–89. https://doi.org/10.1210/jc.2015-1710.

Broersen LH, Pereira AM, Jorgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(6):2171–80.

Burke CW. The pituitary megatest: outdated? Clin Endocrinol. 1992;36:133–4.

Butler G, Kirk J. Paediatric endocrinology and diabetes. Oxford: OUP Press; 2011.

Carmichael J. Anterior pituitary failure pituitary. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2016. p. 329–64.

Charles LE, Fekedulegn D, Burchfiel CM, et al. Shiftwork and diurnal salivary cortisol patterns among police officers. J Occup Environ Med. 2016;58(6):542–9. https://doi.org/10.1097/JOM.0000000000000729.

Chatha KK, Middle JG, Kilpatrick ES. National UK audit of the short synacthen test. Ann Clin Biochem. 2010;47(Pt 2):158–64. https://doi.org/10.1258/acb.2009.009209.

Cheetham T, Baylis PH. Diabetes insipidus in children. Pediatr Drugs. 2002;4(12):785–96.

Chitale A, Musonda P, McGregor AM, Dhatariya KK. Determining the utility of the 60 min cortisol measurement in the short synacthen test. Clin Endocrinol. 2013;79(1):14–9.

Colao A, Di Somma C, Savastano S, Rota F, Savanelli MC, Aimaretti G, Lombardi G. A reappraisal of diagnosing GH deficiency in adults: role of gender, age, waist circumference, and body mass index. J Clin Endocrinol Metab. 2009;94:4414–22.

Conwell LS, Batch JA. Oral glucose tolerance test in children and adolescents: Postives and pitfalls. J Paediatr Child Health. 2004;40:620–6.

Cotterill A, Camacho-Hubner C, Savage MO. Changes in serum IGF-1 and IGFBP3 concentrations during the IGF-1 generation test performed prospectively in children with short stature. Clin Endocrinol. 1998;48:719–24.

Coutant R, Dorr HG, Gleeson H, Argente J. Diagnosis of endocrine disease: limitations of the IGF1 generation test in children with short stature. Eur J Endocrinol. 2012;166(3):351–7.

Dashe AM, Cramm RE, Crist CA, Habener JF, Solomon DH. A water deprivation test for the differential diagnosis of polyuria. JAMA. 1963;185:699–703.

Davies K, Collin J. Understanding clinical investigations in children's endocrinology. Nursing children and young people. 2015;27(8):26–36.

De Fátima Borges M, Teixeira FCC, Feltrin AK, et al. Clonidine-stimulated growth hormone concentrations (cut-off values) measured by immunochemiluminescent assay (ICMA) in children and adolescents with short stature. Clinics. 2016;71(4):226–31. https://doi.org/10.6061/clinics/2016(04)09.

Dickstein G, Saiegh L. Low-dose and high-dose adrenocorticotropinvtesting: indications and shortcomings. Curr Opin Endocrinol Diabetes Obes. 2008;15:244–9.

Eckert KL, Wilson DM, Bachrach LK, Anhalt H, Habiby RL, Olney RC, Hintz RL, Neely EK. A single sample, subcutaneous gonadotropin releasing hormone test for central precocious puberty. Pediatrics. 1996;97(4):517–9.

Erickson D, Natt N, Nippoldt T, Young WF Jr, Carpenter PC, Petterson T, Christianson T. Dexamethasone-suppressed corticotropin-releasing hormone stimulation test for diagnosis of mild hypercortisolism. J Clin Endocrinol Metab. 2007;92(8):2972–6. Epub 2007 May 8.

Faria AC, Veldhuis JD, Thorner MO, Vance ML. Half-time of endogenous growth hormone (GH) disappearance in normal man after stimulation of GH secretion by GH-releasing hormone and suppression with somatostatin. J Clin Endocrinol Metab. 1989;68(3):535–41.

Fiad TM, Kirby JM, Cunningham SK, McKenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol. 1994;40:603–9. https://doi.org/10.1111/j.1365-2265.1994.tb03011.x.

Fleseriu M, Gassner M, Yedinak C, Chicea L, Delashaw JB Jr, Loriaux DL. Normal hypothalamic-pituitary-adrenal axis by high-dose cosyntropin testing in patients with abnormal response to low-dose cosyntropin stimulation: a retrospective review. Endocr Pract. 2010;16(1):64–70. https://doi.org/10.4158/EP09153.OR.

Gil-Ad I, Topper E, Laron Z. Oral clonidine as a growth hormone stimulation test. Lancet. 1979;2(8137):278–9.

Glucagon. Glucagon [package insert]. New York: Eli Lilly and Company; 2017.

GNRH Ferring. GNRH Ferring (Somatorelin) [package insert]. Saint Prex: Ferring Pharmaceuticals; 2012.

Grant DB, Laurance BM, Atherden SM, Ryness J. HCG stimulation test in children with abnormal sexual development. Arch Dis Child. 1976;51:596–601.

Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, Murad MH. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86:361–97.

Gupta V. Adult growth hormone deficiency. Indian J Endocrinol Metab. 2011;15(Suppl 3):197. https://doi.org/10.4103/2230-8210.84865.

Hamrahian AH, et al. Revised GH and cortisol cut-points for the glucagon stimulation test in the evaluation of GH and hypothalamic-pituitary-adrenal axes in adults: results from a prospective randomized multicenter study. Pituitary. 2016;19:332–41.

Hashimoto K, Makino S, Hirasawa R, Takao T, Kageyama J, Ogasa T, Ota Z. Combined anterior pituitary function test using CRH, GRH, LH-RH, TRH and vasopressin in patients with non-functioning pituitary tumors. Acta Med Okayama. 1990;44(3):141–7.

Hodgson NA, Granger DA. Collecting saliva and measuring salivary cortisol and alpha-amylase in frail community residing older adults via family caregivers. J Vis Exp. 2013;82:50815. https://doi.org/10.3791/50815.

Howlett TA. An assessment of optimal hydrocortisone replacement therapy. Clin Endocrinol. 1997;46(3):263–8.

Ilias I, Chang RE, Pacak K, et al. Jugular venous sampling: an alternative to petrosal sinus sampling for the diagnostic evaluation of adrenocorticotropic hormone-dependent Cushing's syndrome. J Clin Endocrinol Metab. 2004;89:3795.

Kaiser S. Conadotropin hormones. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2016. p. 205–50.

Keil MF. Salivary cortisol: a tool for biobehavioural research in children. J Ped Nurs. 2011;27(3):287–9.

Lazar L, Phillip M. Is sex hormone priming in peripubertal children prior to growth hormone stimulation tests still appropriate? Horm Res Paediatr. 2010;73(4):299–302.

Liddle GW. Tests of pituitary-adrenal supressibility in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1960;20:1539–60.

Lindsay JR, Nieman LK. Differential diagnosis and imaging in Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34(2):403–21.

Lone SW, Khan YN, Qamar F, Atta I, Ibrahim MN, Raza J. Safety of insulin tolerance test for the assessment of growth of growth hormone deficiency in children. J Pak Med Assoc. 2011;61(2):153–7.

Machado MC, de Sa SV, Domenice S, et al. The role of desmopressin in bilateral and simultaneous inferior petrosal sinus sampling for differential diagnosis of ACTH-dependent Cushing's syndrome. Clin Endocrinol. 2007;66:136–42.

Mehta A, Hindmarsh PC, Stanhope R, Brain CE, Preece M, Dattani MT. Is the thyrotropin releasing hormone test necessary in the diagnosis of central hypothyroidism in children. J Clin Endocrinol Metab. 2003;88(12):5696–703.

Melmed S. Acromegaly. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2016. p. 423–66.

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JAH. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2011;96(2):273–88. https://doi.org/10.1210/jc.2010-1692.

Miller D, Doppman J. Petrosal sinus sampling: technique and rationale. Radiology. 1991;178:37–47.

Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Mary Lee Vance M. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2011;96(6):1587–609. https://doi.org/10.1210/jc.2011-0179.

Moloney S, Murphy N, Collin J. An overview of the nursing issues involved in caring for a child with adrenal insufficiency. Nurs Child Young People. 2015;27(7):28–36.

Moncayo H, Dapunt O, Moncayo R. Diagnostic accuracy of basal TSH determinations based on the intravenous TRH stimulation test: an evaluation of 2570 tests and comparison with the literature. BMC Endocr Disord. 2007;7:5. https://doi.org/10.1186/1472-6823-7-5.

Moore K, Thompson CJ, Trainer P. Disorders of water balance. Clin Med. 2003;3:28–33.

Moro M, Putignano P, Losa M, Invitti C, Maraschini C, Francesco Cavagnini F. The desmopressin test in the differential diagnosis between Cushing's disease and Pseudo-Cushing states. J Clin Endocrinol Metabol. 2000;85(10):3569–74. https://doi.org/10.1210/jcem.85.10.6862.

Mullis PE, Pal BR, Matthews DR, Hindmarsh PC, Phillips PE, Dunger DB. Half-life of exogenous growth hormone following suppression of endogenous growth hormone secretion with somatostatin in type I (insulin-dependent) diabetes mellitus. Clin Endocrinol. 1992;36(3):255–63.

Newell-Price JDC. Cushing's disease. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2016. p. 515–71.

Nieman LK. Dynamic evaluation of adrenal hypofunction. J Endocrinol Investig. 2003;26(7 Suppl):74–82.

Nieman LK. Diagnosis of Cushing's syndrome in the modern era. Endocrinol Metab Clin N Am. 2018;47(2):259–73. Review. PMID: 29754631. https://doi.org/10.1016/j.ecl.2018.02.001.

Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40. https://doi.org/10.1210/jc.2008-0125.

Oldfield E, Chrousos G, Schulte H, et al. Preoperative lateralization of ACTH-secreting microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. N Engl J Med. 1985;312:100–3.

Papanicolaou DA, Yanovski JA, Cutler GB, Chrousos GB, Nieman LK. A single sleeping midnight serum cortisol measurement distinguishes Cushing's syndrome from pseudo-Cushing's states. J Clin Endocrinol Metab. 1998;83:1163–7.

Raff H, Auchus RJ, Findling JW, Nieman LK. Urine free cortisol in the diagnosis of Cushing's syndrome: is it worth doing and, if so, how? J Clin Endocrinol Metabol. 2015;100(2):395–7. https://doi.org/10.1210/jc.2014-3766.

Raine JE, Donaldson MDC, Gregory JW, van Vliet G, editors. Practical endocrinology and diabetes in children. Chichester: Wiley-Blackwell; 2011.

R-Gene. R-Gene (Arginine) [package insert]. New York: Pharmacia & Upjohn; 2016.

Roelfsema F, Biermasz NR, Pereira AM, Veldhuis JD. Optimizing blood sampling protocols in patients with acromegaly for the estimation of growth hormone secretion. J Clin Endocrinol Metab. 2016;101(7):2675–82. https://doi.org/10.1210/jc.2016-1142.

Rosenbloom AL. Sex hormone priming for growth hormone stimulation testing in pre- and early adolescent children is evidence based. Horm Res Paediatr. 2011;75(1):78–80.

Ross IL, Levitt NS, Van der Walt JS, Schatz DA, Johannsson G, Haarburger DH, Pillay TS. Salivary cortisol day curves in Addison's disease in patients on hydrocortisone replacement. Horm Metab Res. 2013;45(1):62–8. https://doi.org/10.1055/s-0032-1321855. Epub 2012 Aug 14.

Savage MO, Chan LF, Afshar F, Plowman PN, Grossman AB, Storr HL. Advances in the management of paediatric Cushing's disease. Horm Res. 2008;69:327–33.

Schilbach K, Strasburger CJ, Bidlingmaier M. Biochemical investigations in diagnosis and follow up of acromegaly. Pituitary. 2017;20(1):33–45. Review. PMID: 28168377. https://doi.org/10.1007/s11102-017-0792-z.

Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. Life Sci. 2003;73:3339–49.

Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. Br Med J. 1992;304:173–4.

Sharma ST, Nieman LK. Cushing's syndrome: all variants, detection, and treatment. Endocrinol Metab Clin N Am. 2011;40(2):379–91.

Soliman A, Adel A, Sabt A, Elbukhari E, Ahmed H, De Sanctis V. Does priming with sex steroids improve the diagnosis of normal growth hormone secretion in short children? Indian J Endocrinol Metab. 2014;18(Suppl 1):S80–3.

Strich D, Terespolsky N, Gillis D. Glucagon stimulation test for childhood growth hormone defi-

ciency: timing of the peak is important. J Pediatr. 2009;154:415–9.
Timper T, Fenske W, Kuhn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Muller B, Katan M, Christ-Crain M. J Clin Endocrinol Metab. 2015;100(6):2268–74.
Trainer PJ, Faria M, Newell-Price J, Browne P, Kopelman P, Coy DH, Besser GM, Grossman AB. A comparison of the effects of human and ovine corticotropin-releasing hormone on the pituitary-adrenal axis. J Clin Endocrinol Metab. 1995;80(2):412–7.
Trapp CM, Speiser PW, Oberfield SE. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 2011;18(3):166–70.
Valassi E, Swearingen B, Lee H, et al. Concomitant medication use can confound interpretation of the combined dexamethasone-corticotropin releasing hormone test in Cushing's syndrome. J Clin Endocrinol Metab. 2009;94(12):4851–9. https://doi.org/10.1210/jc.2009-1500.
Wallace I, Cunningham S, Lindsay J. The diagnosis and investigation of adrenal insufficiency in adults. Ann Clin Biochem. 2009;46(5):351–67. https://doi.org/10.1258/acb.2009.009101.
Wong LM, Man SS. Water deprivation test in children with polyuria. J Pediatr Endocrinol Metab. 2012;25(9–10):869–74.
Yaneva M, Mosnier-Pudar H, Dugue M-A, Grabar S, Fulla Y, Bertagna X. Midnight salivary cortisol for the initial diagnosis of Cushing's syndrome of various causes. J Clin Endocrinol Metab. 2004;89(7):3345–51.
Yanovski JA, Cutler GB Jr, Chrousos GP, Nieman LK. The dexamethasone-suppressed corticotropin-releasing hormone stimulation test differentiates mild Cushing's disease from normal physiology. J Clin Endocrinol Metab. 1998;83(2):348–52.
Yuen KC, et al. Clinical characteristics, timing of peak responses and safety aspects of two dosing regimens of the glucagon stimulation test in evaluating growth hormone and cortisol secretion in adults. Pituitary. 2013;16:220–30.

Key Reading

1. Dashe AM, Cramm RE, Crist CA, Habener JF, Soloman DH. A water deprivation test for the differential diagnosis of polyuria. JAMA. 1963;185(9):699–703.
2. Lienhardt A, Grossman AB, Dacie JE, Evanson J, Huebner A, Afshar F, Plowman PN, Besser GM, Savage MO. Relative contributions of inferior petrosal sinus sampling and pituitary imaging in the investigation of children and adolescents with ACTH dependent Cushing's syndrome. J Clin Endocrinol Metab. 2001;86(12):5711–4.
3. Pavord SR, Girach A, Price DE, Absalom SR, Falconer-Smith J, Hewlett TA. A retrospective audit of the combined pituitary function test, using the insulin stress test, TRH and GnRH in a district laboratory. Clin Endocrinol (Oxf). 1992;36(2):135–9.
4. Jenkins RC, Ross RJM. Protocols for common endocrine tests. In: Grossman A, editor. Clinical endocrinology. 2nd ed. Oxford: Blackwell Science; 1998. p. 1117–34.
5. Nieman LK. Dynamic evaluation of adrenal hypofunction. J Endocrinol Invest. 2003;26(7 Suppl):74–82.
6. Nieman LK. Diagnosis of Cushing's syndrome in the modern era. Endocrinol Metab Clin North Am. 2018;47(2):259–73. https://doi.org/10.1016/j.ecl.2018.02.001. Review. PMID: 29754631
7. Carmichael J. Anterior pituitary failure pituitary. In: Melmed S, editor. Pituitary. 4th ed. London: Elsevier; 2016. p. 329–64.
8. Miller D, Doppman J. Petrosal sinus sampling: technique and rationale. Radiology. 1991;178:37–47.
9. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Mary Lee Vance M. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2011;96(6):1587–609. https://doi.org/10.1210/jc.2011-0179.
10. Wong LM, Man SS. Water deprivation test in children with polyuria. J Pediatr Endocrinol Metab. 2012;25(9–10):869–74.

Diagnostic Imaging

16

Christine Yedinak

Contents

16.1 **Introduction** 306
16.2 **CT Scan vs MRI** 307
16.3 **MRI** 307
16.3.1 Sella Imaging 310
16.4 **Octreotide Scan** 316
16.5 **DOTA-Peptide PET-CT Scanning** 317
16.6 **Conclusions** 318
References 318

Keywords
Pituitary · Imaging · Suprasella · Sella
Tumours · Ectopic hormone secretion

Abbreviations

CSF	Cerebrospinal fluid
CT	Computed tomography
DWI	Diffusion weighted images
FLAIR	Fluid attenuated inversion recovery
Gy	Grey
MRI	Magnetic resonance imaging
T	Tesla
T1	Longitudinal (parallel to the magnetic field)
T2	Transverse (perpendicular to the magfield)
TE	Echo time
TR	Repetition time (TR)

Key Terms

- **Dynamic sequencing:** a rapid sequences of imaging obtained after contrast administration
- **Imaging planes:** planes that divide up the body directionally. By convention the divided body is facing the observer.
- **Paramagnetic contrast:** a contrast agent used to enhance delineation of tumors on imaging.
- **Ectopic tumors:** the production of peptides by neuroendocrine tumors outside the pituitary.

C. Yedinak (✉)
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_16

- **Ionizing radiation:** X-rays, or gamma rays with sufficient energy to cause ionization in the medium through which it passes.
- **Non-iodizing radiation:** does not have sufficient energy to remove atoms but can create heat.
- **Diffusion weighted images:** detect the movement of water particles in tissue and help to identify ischemic characteristics of tumors.

Key Points

- Although CT and MRI are both used to image the sella and suprasella region, MRI is the preferred modality to delineate a pituitary tumour.
- Anyone entering an MRI suite, or preparing patients for MRI, must be trained and adhere to MRI safety precautions.
- Paramagnetic contrast agents and dynamic sequenced imaging are used to highlight small tumours and other structures.
- Current concerns regarding the use of gadolinium as a contrast media have resulted in the development and use of alternate solutions.
- Localizing ectopic tumours may require the administration of sophisticated nuclear tagged agents and scintigraphy techniques. These require special patient education and preparation.

16.1 Introduction

Both Computed tomography (CT) and Magnetic resonance imaging (MRI) are used in the diagnosis of hypothalamic/pituitary tumours and have replaced plain radiography and pneumoencephalograms for imaging of the sella region. Angiography continues to be useful, and is often combined with MRI for visualization of the sella and masses and for vessel anatomy and pathology. The advent of tomography allowed for multidirectional thin anatomic section analysis and, along with the development of computer assisted tomography (CAT scans) and magnetic resonance imaging (MRI), (particularly when combined with angiography), allows significant resolution of pathology in the pituitary region. MRI is now the imaging of choice when evaluating space occupying lesions in the hypothalamic and pituitary sella regions (Maya and Pressman 2011; Basics, neuroradiology 2018).

Imaging is captured in several planes: (Fig. 16.1)

- Axial plane: Transverse images represent 'slices' of the body perpendicular to the spine that divides the body into superior and inferior sections.
- Sagittal plane: Images taken perpendicular to the axial plane which separate the left and right sides (lateral view).

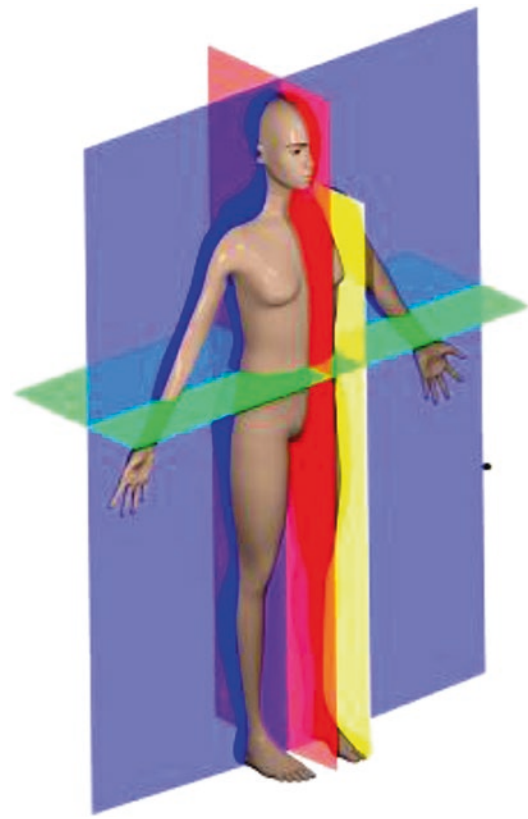


Fig. 16.1 Anatomical imaging planes. Blue: Coronal plane. Red: Sagittal (medial). Green: Axial or transverse plane. Yellow: Sagittal (lateral) plane

- Coronal plane: Images taken perpendicular to the sagittal plane, which separate the front from the back (frontal view).

16.2 CT Scan vs MRI

Both CT and MRI are used in imaging the hypothalamus and sella region. However, there are differences in these imaging modalities. Generally, contrast enhanced MRI is considered a superior modality for the assessment and monitoring of sella and suprasellar tumours (Basics, neuroradiology 2018; Weidman et al. 2015).

CT images are only acquired in the axial plane. This data is then used to reconstruct images in other planes. When reading CT images, air is displayed as black (such as in the sinuses), and brain parenchyma is Grey (Gy), while bone of the skull is seen as bright white (Basics, neuroradiology 2018).

MRI can be acquired in any plane. Each MR image is captured as a sequence. The primary MR sequences include: T2, T1, T1 with contrast, Diffusion and FLAIR. Because of the number of sequences, each being separately acquired, an MRI takes much longer to complete than a CT (Basics, neuroradiology 2018; Weidman et al. 2015; Radue et al. 2016).

The colour of the same structure in MRI may be light or dark according to the type of sequence. Fluid, such as CSF and blood, appears bright on T2 and dark on T1. White structures are subcutaneous fat (Basics, neuroradiology 2018; Weidman et al. 2015; Radue et al. 2016).

No ionizing radiation is used in MRI. A powerful magnet creates a magnetic field around the patient. Magnet strengths range from 0.3 to 3 T (1.5 and 3 T most common) which re-align the protons in cell nuclei of water molecules in the body (Basics, neuroradiology 2018; Weidman et al. 2015; Yousem and Grossman 2010). Pulsed radio waves (radiofrequency) are then directed at the patient. These are absorbed by, and disturb, the proton alignment. Subsequently, the magnet 'relaxes' and the protons return to their original state emitting the radiofrequency energy (echo signal). This *relaxation time* is the time it takes for the protons to regain their original equilibrium state. After repeated pulses to the same slice, the energy is converted to a digital image, based on the intensity of the echo signal, the relaxation time, and the density of the proton. Two types of relaxation time differentiate the direction of the images displayed:T1—Longitudinal (parallel to the magnetic field) and T2—transverse (perpendicular to the magfield) (Weidman et al. 2015; Yousem and Grossman 2010).

The contrast in the image is referred to as '*weighting*' and is determined by:

1. Repetition Time (TR)—the time between successive RF pulses
2. Echo Time (TE)—time between the arrival of the RF pulse that excites and the arrival of the return signal at the detector.

Therefore, T1 weighted images show CSF as dark versus T2 images in which CSF appears bright (Basics, neuroradiology 2018; Yousem and Grossman 2010).

Fluid Attenuated Inversion Recovery (FLAIR) refers to images with a long TR and TE time. This accentuates pathology with abnormalities remaining bright in FLAIR images (Basics, neuroradiology 2018) (Fig. 16.2).

Diffusion weighted images (DWI) on the other hand are a sensitive means of detecting stroke and random movement of water protons. Water in the brain moves freely in the extracellular spaces, but is restricted within intracellular spaces. During ischemia, the sodium-potassium pump fails and sodium accumulates prompting water to move into the cell due to the osmotic gradient. This is seen as on DWI as an extremely bright signal (area) (Radue et al. 2016; Yousem and Grossman 2010).

16.3 MRI

Identification of specific types of lesions or masses of the sella and suprasellar region on MRI is made based on key features. Masses are described by the location and extension of the mass (such as above the sella or to one or both

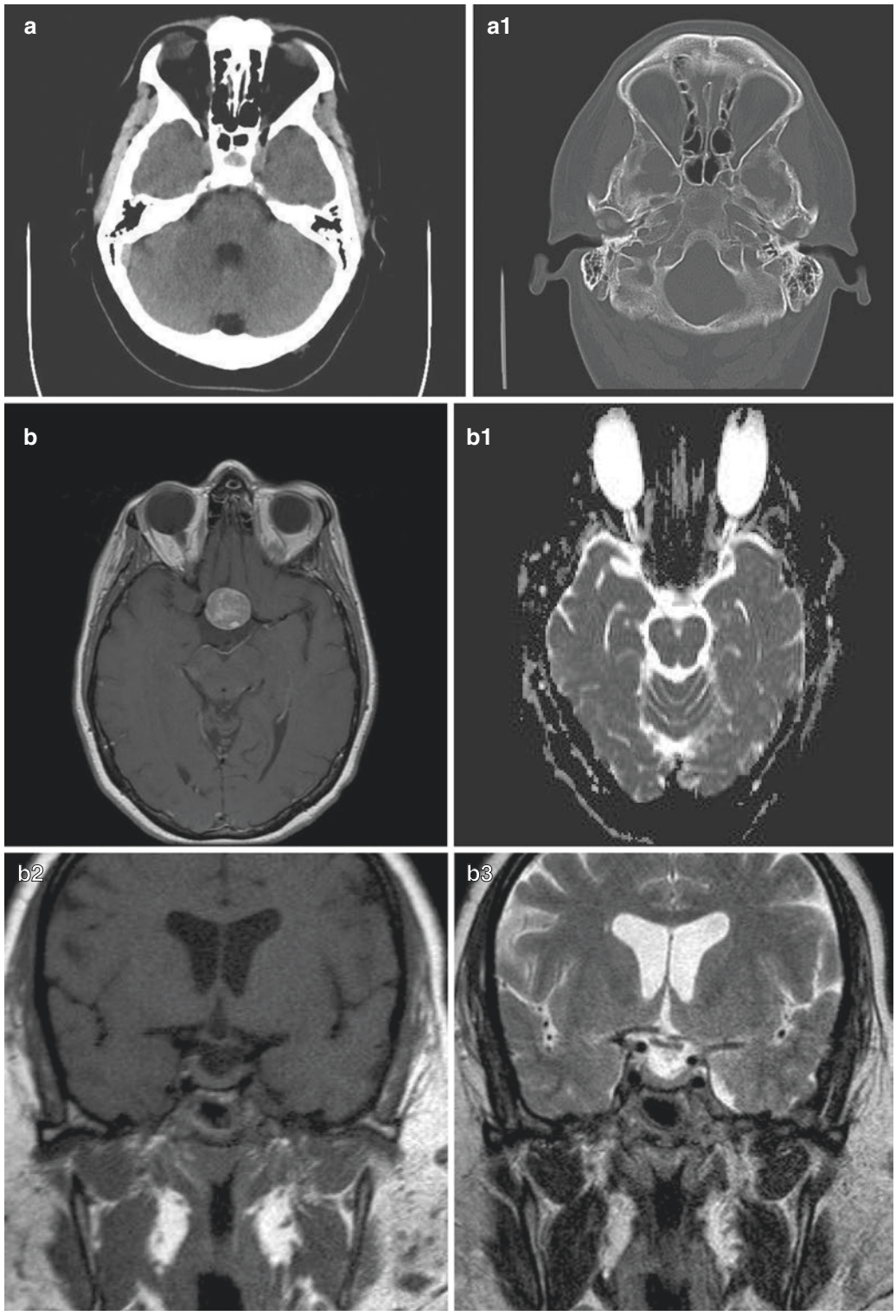


Fig. 16.2 (**a** and **a1**). CT and (**b**) MRI Images. (**b**) Axial Flair post contrast. (**b1**) DWI. (**b2**) Coronal T1 pre contrast (fluid/dark, tissue/white, brain parenchyma/grey). (**b3**) Coronal T2 pre contrast (fluid/white, air/dark, tissue/light, brain parenchyma/grey). (**b4**) Coronal T1 post contrast (fluid/dark, enchanced pituitary and tissue white)

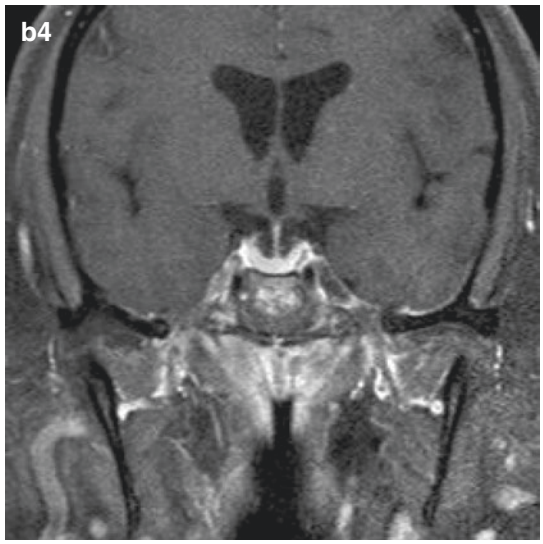


Fig. 16.2 (continued)

cavernous sinuses beside the pituitary gland), the uniformity of the image (the pattern of contrast enhancement described as the intrinsic signal), and other distinguishing features such as cystic areas and calcifications (See burg et al. 2017).

Procedure: The use of MRI may be limited when the patient has implanted metals and other magnetizable materials. Therefore, all patients must be assessed prior to MRI. MRI *incompatible* implants include non-titanium joint replacements, orthodontic braces, surgical aneurysm clips, cochlear implants, some artificial heart valves, implanted cardiac pacemakers, cerebral shunts, etc. Some cobalt-chromium and stainless steel implantable products *are* MR compatible (Koch et al. 2010). Concern for intraocular metals or the potential for metal shrapnel may need to be assessed prior to MRI with x-ray images in patients with an occupational exposure risk. Metals can cause local distortion and degrade the MRI image. The magnet can also cause motion in magnetizable materials with potential for tissue damage and burns (Koch et al. 2010). Implantable devices can also be damaged. Some reprogrammable CSF shunts will require resetting after MRI. Patients are advised to remove medication patches to avoid burns and are usually asked to disrobe and dress in a hospital gown to avoid skin contact with snaps, zippers or other metal in clothing (Weidman et al. 2015). The use of handheld ferrous detectors has also been recommended, particularly for use with children (See burg et al. 2017).

An intravenous paramagnetic contrast enhancement agent is used to help improve the quality of images and enhance visualization of pathology such as microadenomas. Likewise, it improves the visibility of inflammation, blood supply and vessels in the sella and suprasella region. Gadolinium contrast is used to assess brain lesions due to its ability to cross the blood brain barrier. However, iodinated IV contrast can also be used to assess the pituitary gland, which is outside the blood brain barrier (Maya and Pressman 2011). It contains a gadolinium molecule bonded to a chelating agent to prevent toxicity. However, there remains some concern regarding accumulation of gadolinium in the brain and in 2017, the European Medicines Agency (EMA) restricted it use (EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans 2017). The use of Dotarem (gadoteric acid/gadoterate meglumine) has been maintained. To date, the FDA in the USA has not followed suit but studies are ongoing. Many US imaging centres have adopted Dotarem as an alternative to gadolinium. Although gadolinium is usually reported as well tolerated it is contraindicated in pregnancy, in cases of sensitivity to the drug and in renal impairment. A creatinine is usually drawn prior to contrast administration to ensure administration is safe (Yousem and Grossman 2010).

Side effects are rare and most patients feel no effects. Some patients report a sensation of cold in the arm during injection, which takes about 30 s. Up to 4/100 patients report mild nausea or headache and vomiting occurs for less than 1/100 patients after injection. Mild itching occurs in 1/1000 patients (Ramalho et al. 2016). Some patients will also require treatment with an oral anxiolytic agent prior to MRI to avoid a sense of panic associated with being confined within the MRI unit (claustrophobia). In severe cases, or in paediatrics, IV conscious sedation or anaesthesia may be required (See burg et al. 2017).

Additionally, motion artefact degrades the quality of MR images. In some cases, the use of an 'open' MRI may be useful.

Special Considerations: Although MRI can be performed during pregnancy, it is only performed with an urgent indication. Gadolinium is known to cross the placenta and may be retained in amniotic fluid during pregnancy. Given the unknown impact on the foetus, administration of contrast is not recommended during pregnancy (Bulas and Egloff 2013). Gadolinium is water soluble and very little is reported to cross into breast milk during 24 h after MRI. Guidelines from the American College of Obstetricians and Gynaecologists recommend continuing breastfeeding after MRI (Copel et al. 2017).

An imaging study is usually composed of coronal and sagittal images and in some centres dynamic scanning techniques are used to enhance or differentiate small pituitary masses from normal tissue. Dynamic sequencing involves the rapid acquisition of images immediately after the administration of contrast (Maya and Pressman 2011). Standard MR imaging of the sella and perisellar region are captured in thin slices of 2–3 mm.

Paediatric patients may require sedation. However, for infants, sleeping images may be obtained by feeding and swaddling the infant prior to imaging. Videos and stories delivered via earphones may also be useful. A clear description of the reason and process of imaging that is appropriate to the child's age is recommended (Raschle et al. 2012).

The choice of wording is important in early childhood. MRI may be described as a 'brain camera' that takes pictures of the brain and scanner noise as 'camera clicks' (Raschle et al. 2012). In preparation, showing the child 'photographs' depicting MRI images and allowing them to walk around the imaging room and scanner to familiarize them with the equipment may help to allay anxiety and promote cooperation. Incorporating verbal games into the process such as counting 'clicks' and 'de-medicalizing' the event is useful (Raschle et al. 2012). The parent must also be prepared in advance and can be directed to vetted web-sites to understand why and how the images are obtained.

16.3.1 Sella Imaging

16.3.1.1 Normal Imaging

High resolution 1.5 or 3 T imaging is preferred for imaging the sella to improve the diagnostic capacity. Coronal and sagittal views are usually obtained with contrast enhancement and dynamic sequences.

The normal anterior pituitary tissue usually enhances homogeneously or in a uniform colour (signal). The intensity of the colour should be approximately the same as that of the brain tissue (i.e. it is isointense). After contrast administration, the signal in the anterior pituitary is much lighter (hyperintense). The colour of the cavernous sinuses lateral to the pituitary is darker relative to the rest of the brain (hypointense). The carotid arteries (flow or signal voids) are seen clearly as dark areas and can be tracked through each image slice. The optic chiasm and the optic nerves can be seen clearly on T1 weighted images, and do not enhance with contrast administration because of their blood brain barrier. The pituitary stalk (infundibulum) does enhance similarly to the anterior pituitary (Maya and Pressman 2011; Weidman et al. 2015; Yousem and Grossman 2010). The normal pituitary size reaches about 7–8 mm (less than 9 mm) in an adult male and the infundibulum measures 2 mm at the point of insertion into the gland. The gland in children and women of childbearing years may be more superiorly convex (Maya and Pressman 2011; Yousem and Grossman 2010; Buchfelder and Schlaffer 2014). This size increases in pregnant females and returns to normal size around 6 months post-partum (Buchfelder and Schlaffer 2014). All pituitary dimensions may decrease in the elderly (Maya and Pressman 2011).

The posterior pituitary is usually hyperintense on T1 weighted images and is often described as the pituitary bright spot. After contrast administration, this distinction between the anterior and posterior pituitary is not as apparent (Maya and Pressman 2011) (Fig. 16.3).

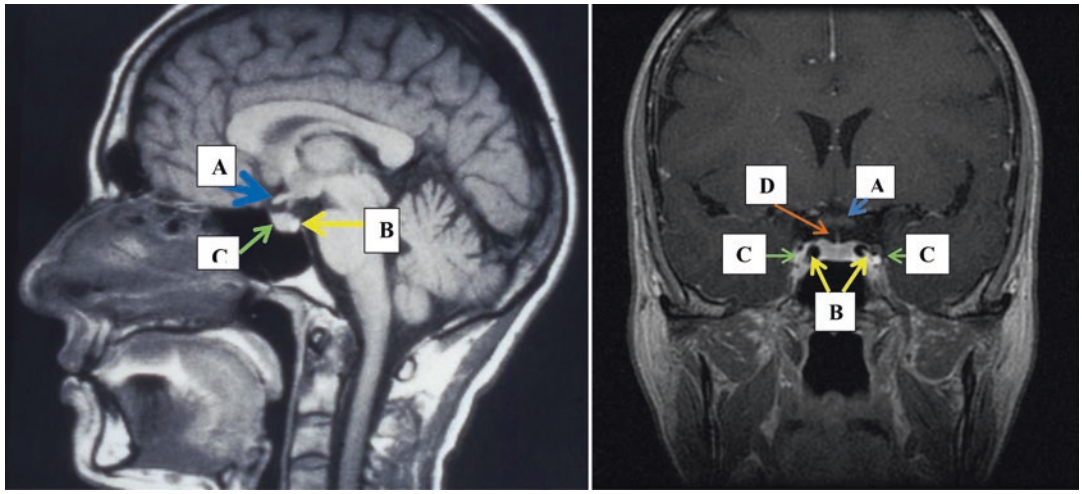


Fig. 16.3 Normal pituitary: sagittal view. A: Optic apparatus/nerves. B: Posterior 'bright spot'. C: Anterior pituitary. T1 normal pituitary gland: coronal view. A: Optic chiasm. B: Flow voids, internal carotid arteries. C: Cavernous sinuses. D: Pituitary stalk (infundibulum)

16.3.1.2 Non-functioning Microadenoma

Microadenomas have been reported as a common finding in the general population with an incidence up to 27% (Maya and Pressman 2011). They are often an incidental finding on imaging for other purposes, such as after a head injury, and are frequently asymptomatic.

A paramagnetic contrasted MRI with multiple views through the pituitary may be needed to identify a small microadenoma. Microadenomas, by definition, are <10 mm in any dimension. It is usually easier to identify those >4 mm so smaller lesions may go undetected (Buchfelder and Schlaffer 2014). They are usually round ovoid or flattened and are *hypo*intense in T1 images compared to the surrounding pituitary tissue. They usually have minimal effect on the infundibulum (pituitary stalk) but when this is no longer midline and is deviated to one side, then closer examination is indicated for a lesion on the opposite side to the deviation (Maya and Pressman 2011). The lesion itself is often uniform in intensity and may cause bulging in the affected side of the pituitary. Dynamic images may be especially useful in locating small tumours not visible on other images (Buchfelder and Schlaffer 2014). Other imaging techniques may also be applied to identify small tumours such as in Cushing's disease.

When a convex gland is seen on MRI in females of childbearing age, without areas of hypoenhancement, checking for pregnancy is recommended. When no tumour is found and the patient's biochemical testing indicates Cushing's syndrome, the presence of ectopic sources of ACTH production may need to be evaluated (Maya and Pressman 2011) (Fig. 16.4).

16.3.1.3 Non-functioning Macroadenoma

By definition, a macroadenoma is mass that is greater than 10 mm (1 cm). Non-contrasted MRI usually demonstrates the enlargement of the sella turcica in the presence of a large mass but contrasted views further differentiate the tumour from surrounding structures. There may be some changes to the sella floor with erosion into the bone. The infundibulum may be significantly deviated or not distinguishable from the tumour. The gland itself may be convex and also not distinguishable from the mass. This may impinge on, compress or elevate the optic chiasm (apparatus). This may be seen best in coronal views, and is a most important assessment (Maya and Pressman 2011; Buchfelder and Schlaffer 2014). There may be invasion of the cavernous sinuses either on one side or both sides of the pituitary, which becomes most obvious when the internal

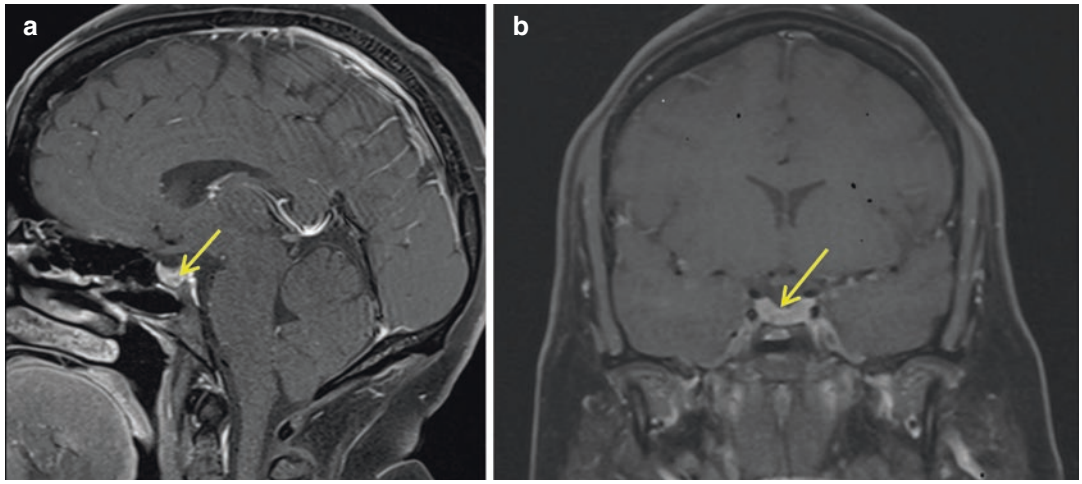


Fig. 16.4 Non-functioning microadenoma. T1 images (**a**) sagittal, (**b**) coronal view

carotid artery (arteries) are completely surrounded. The tumour mass may also extend inferiorly down into the sphenoid sinus (Maya and Pressman 2011; Buchfelder and Schlaffer 2014).

Benign adenomas are differentiated from carcinoma by associated bony changes and irregular shaped infiltrative features of the latter (Maya and Pressman 2011). They may also have some darker areas contained within the boundaries of the tumour that may represent cysts, necrosis or areas of haemorrhage. Macroadenomas usually appear uniformly solid or homogenously enhance with contrast. If they extend to the suprasella region they give a characteristic 'snowman' appearance (Gupta et al. 2018) (Fig. 16.5).

16.3.1.4 Empty Sella

In empty sella syndrome, the pituitary appears as a half-moon with thin enhancing tissue. This appears squashed against the floor of the sella (Ranganathan et al. 2013). The sella fills with CSF fluid, appearing dark on imaging. Empty sella can be partial or complete, and pituitary function testing is indicated (Fig. 16.6).

16.3.1.5 Prolactin Producing Adenoma

Prolactinomas represent about 41% of all microadenomas. A lesion or mass found on MR imaging is confirmed as prolactin secreting based on elevated serum prolactin. Lactotrophs are usually located in the lateral areas of the anterior pituitary; therefore, prolactinomas are often seen in the posterolateral aspects of the gland (Maya and Pressman 2011) (Fig. 16.7).

16.3.1.6 ACTH Producing Adenoma

Typically, ACTH tumours are microadenomas and may be difficult to distinguish from the normal gland. MR images are usually captured in 2–3 mm slices, particularly through the anterior pituitary, where most ACTH secreting tumours are found (Sahdev et al. 2007). Some clinicians feel dynamic images are more sensitive in identifying small ACTH producing tumours (Friedman et al. 2007). An estimated 40–50% of these tumours are not found on imaging (Fig. 16.8).

16.3.1.7 Growth Hormone (GH) Producing Adenoma

Often GH producing tumours are found as macroadenomas. Assessment of the extent of tumour invasion into the cavernous sinuses and supra sella is helpful in determining post-surgical prognosis for disease remission and clinical management. In several studies, a characteristic tumour hypointensity in T2 images is seen in patients with high insulin-like growth factor 1 (IGF-1), and has been found in up to 50% of patients with GH secreting adenomas (Hagiwara et al. 2003; Potorac et al. 2015) (Fig. 16.9).

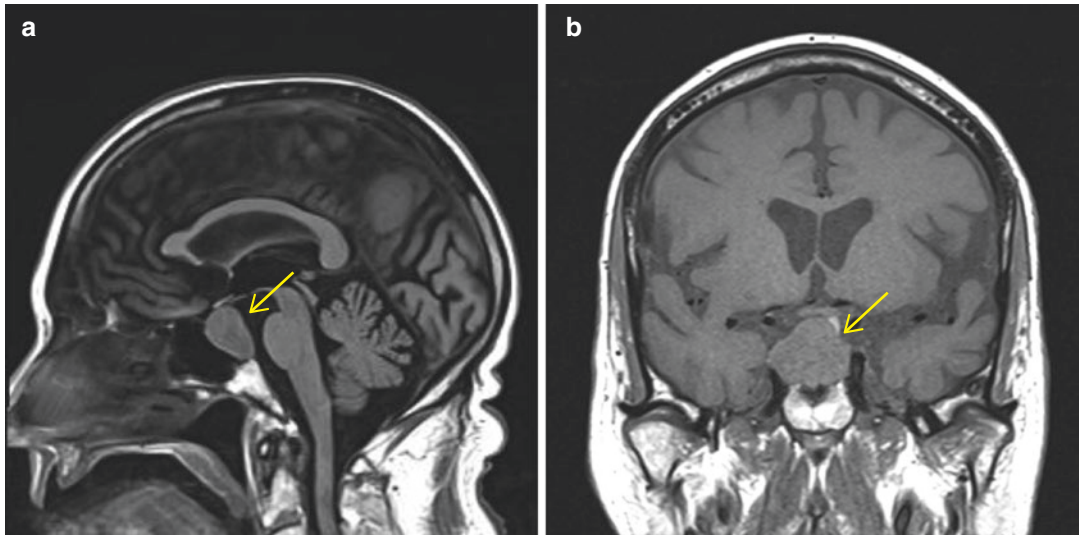


Fig. 16.5 Non-functional macroadenoma. (**a**) FLAIR sagittal image. (**b**) T1 coronal image

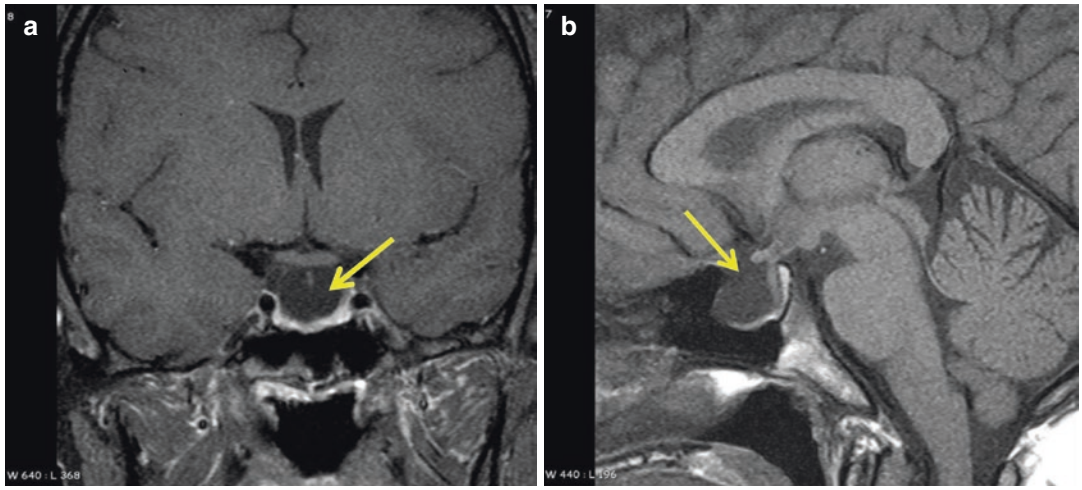


Fig. 16.6 Empty sella syndrome (arrow indicates CSF fluid). (**a**) T1 coronal view. (**b**) T1 sagittal view. Case courtesy of Dr. Sandeep Bhuta, Radiopaedia.org, rID: 5484

16.3.1.8 Rathke's Cleft Cyst

Rathke's cleft or pouch is formed from the invagination of the roof of the mouth during embryonic development. This eventually forms the anterior and the intermediate lobes of the pituitary gland. Cysts forming in this region are referred to as pars intermedia cysts or Rathke's cleft cysts. Lined with epithelial cells, they contain mucoid and serous material (Maya and Pressman 2011).

Bounded by a cyst wall, they are clearly defined and typically in front of the infundibulum (pituitary stalk) (Maya and Pressman 2011). They usually appear uniform in intensity, but this may vary from hypointense to hyperintense depending on the fluid content. Characteristic features on imaging include intracystic nodules with low to iso signal intensity (Byun et al. 2000).

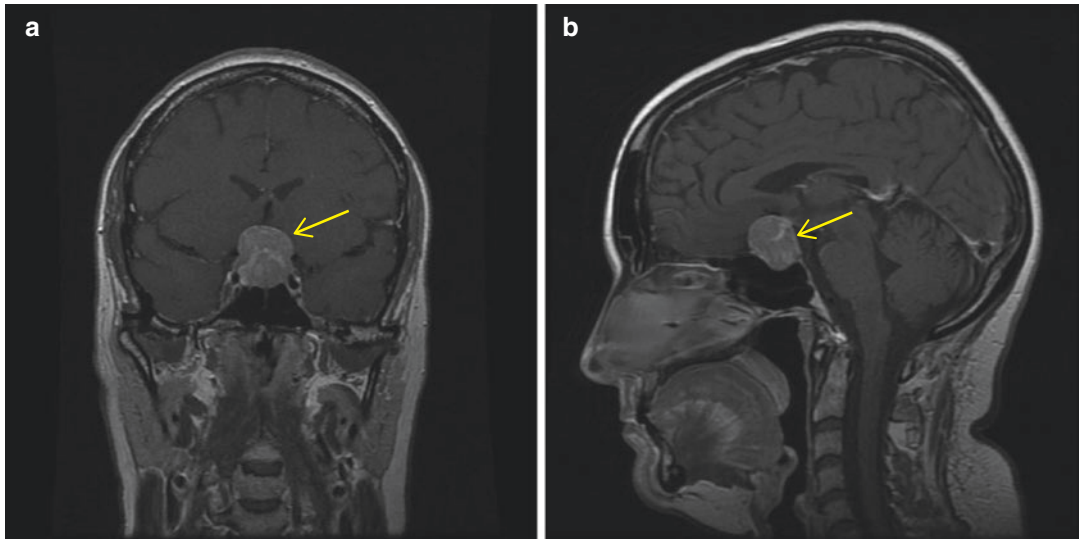


Fig. 16.7 Prolactinoma. (**a**) T1 coronal image. (**b**) T1 sagittal image

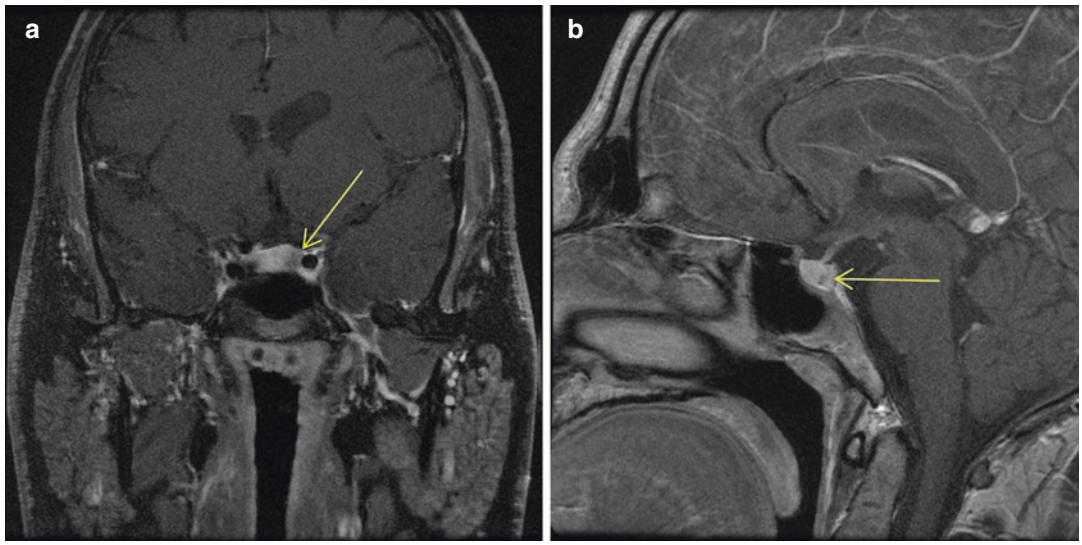


Fig. 16.8 ACTH producing adenoma (arrow indicates tumour). (**a**) T1 coronal view. (**b**) T1 sagittal view

Pars media (pituitary intermediate or middle lobe) cysts are a frequent finding and are usually seen best on sagittal T1 views (Fig. 16.10).

16.3.1.9 Hypophysitis

Hypophysitis is frequently misdiagnosed as a macroadenoma. With clear identification of features on diagnostic imaging, the patient may be treated medically and avoid the need for surgical intervention (Gutenberg et al. 2009). Two clear distinguishing features found on imaging are symmetric enlargement of the pituitary gland and a thickened non-tapering pituitary stalk. Comparatively, macroadenomas are usually irregular in shape and the pituitary stalk is deviated. In addition, a homogeneous appearance, both on pre- and post-gadolinium images, and an intense gadolinium enhancement were

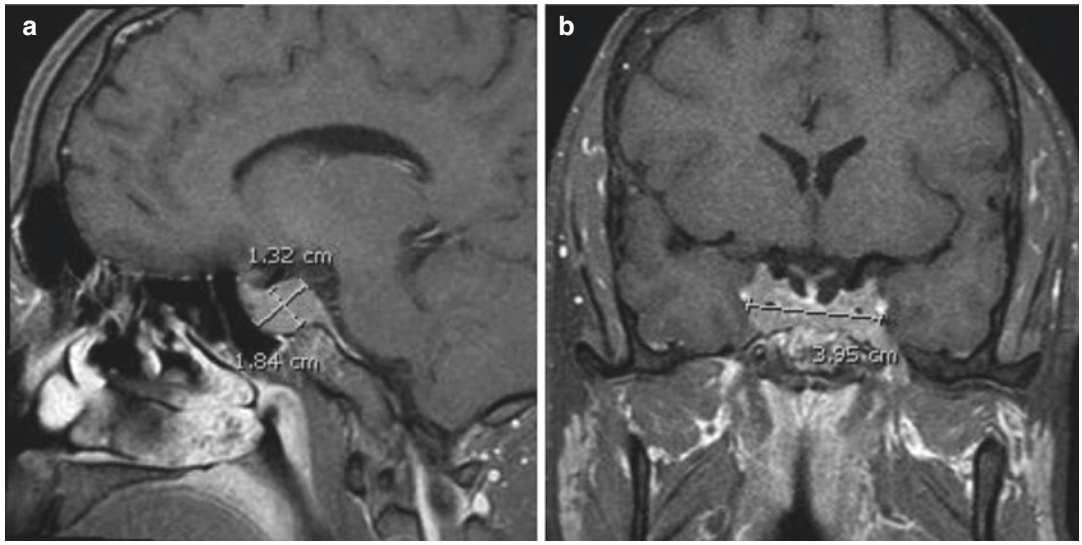


Fig. 16.9 Growth hormone producing adenoma. (**a**) T1 sagittal view. (**b**) T1 coronal view

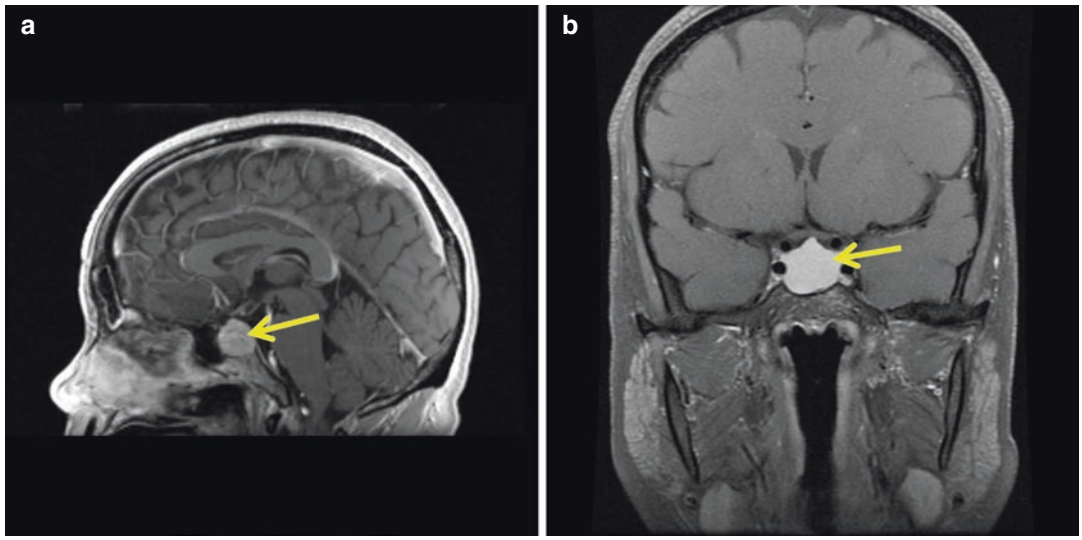


Fig. 16.10 Rathke's cleft cyst (arrow indicates cyst). (**a**) T1 sagittal view. (**b**) T1 coronal view

found to be characteristic of hypophysitis (Gutenberg et al. 2009). The pituitary bright spot may be absent. Dynamic images may be helpful in differentiating hypophysitis from other infective aetiologies (Fig. 16.11).

16.3.1.10 Craniopharyngioma

These tumours also arise from remnants of Rathke's pouch, but may originate anywhere along the infundibulum and midline up to the floor of the third ventricle (Maya and Pressman 2011; Buchfelder and Schlaffer 2014). They are differentiated from Rathke's cleft cysts by the incorporation of solid and cystic regions. Areas of calcifications and haemorrhage are more commonly found on MR images in paediatric populations than in adults (Maya and Pressman 2011) (Fig. 16.12).

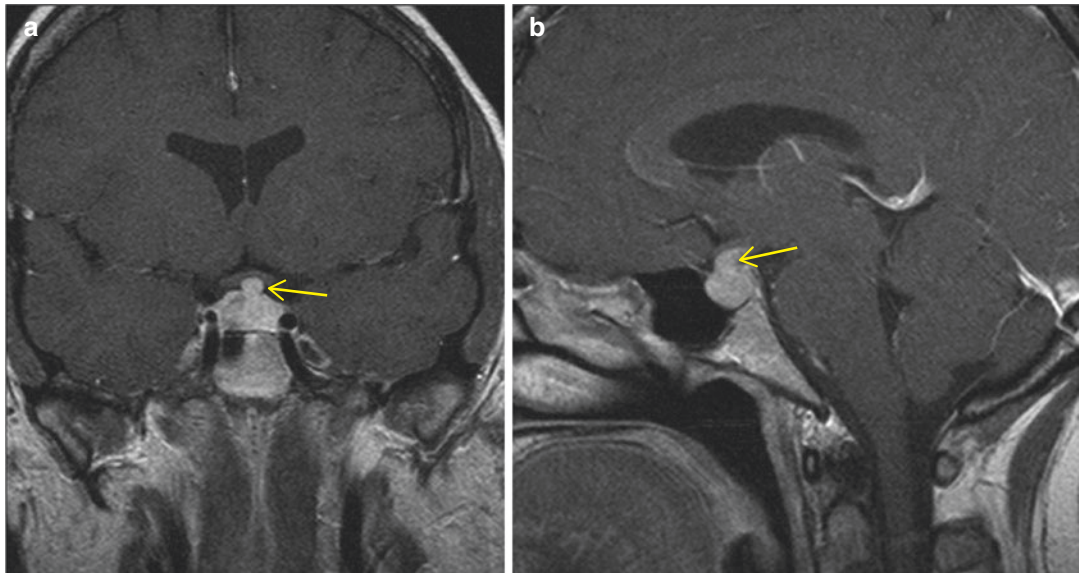


Fig. 16.11 Hypophysitis. (**a**) T1 coronal view. (**b**) T1 sagittal view

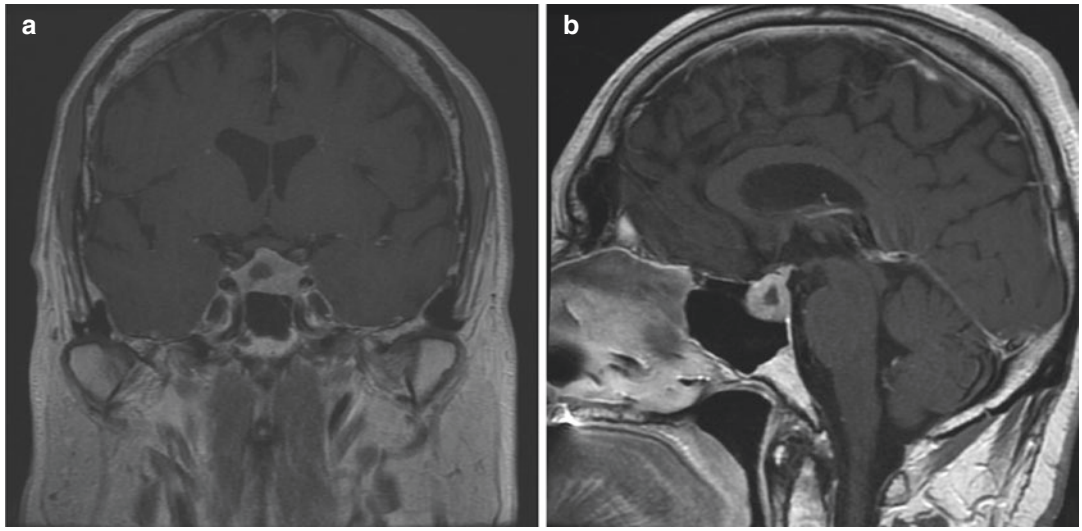


Fig. 16.12 Craniopharyngioma. (**a**) T1 coronal image. (**b**) T1 sagittal view

16.3.1.11 Meningioma

Arising from above the pituitary (suprasella), meningiomas are more likely to invade the pituitary. On imaging, both T1 and T2 images are isointense with the brain parenchyma (Maya and Pressman 2011). Post contrast administration, meningiomas enhance evenly (homogeneously) and intensely. A tail of enhancing tissues may be seen projecting from the tumour. The pituitary itself can usually be identified as separate from the tumour (Fig. 16.13).

16.4 Octreotide Scan

In ACTH-dependent Cushing's syndrome, there is an ectopic source of ACTH in 10–20% of cases (Ilias et al. 2005). An octreotide scan is a nuclear

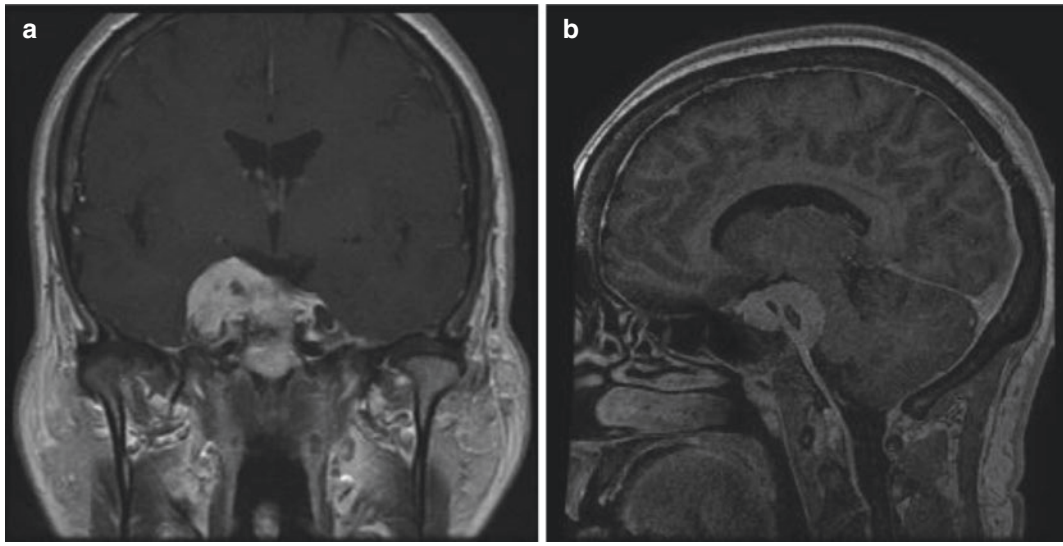


Fig. 16.13 Meningioma. (**a**) T1 coronal view. (**b**) T1 sagittal view

medicine test used to isolate a neuroendocrine tumour. Somatostatin receptor scintigraphy (SRS) using radiolabeled ^{111}In-DTPA octreotide is the conventional imaging methodology for identifying neuroendocrine tumours, ectopic ACTH and GH tumours, particularly when other modalities have failed to do so. Some report a chelating agent, DOTA (1,4,7,10-tetraazacyclodo decane-N,N=,N,N tetraacetic acid), has been added to the octreotide for increased attraction to tumour cells. Octreotide has an affinity for somatostatin receptors SSR-2 and -5 which are overexpressed on neuroendocrine tumour cell membranes, tagging or identifying tumour on scintigraphy or with combined CT or PET scanning (Rufini et al. 2006).

Procedure: No fasting is required, but patients must be withdrawn from somatostatin therapy prior to scan. An IV cannula is placed and the patient is injected with In-DTPA octreotide. Single-photon emission computed tomography (SPECT) scans are obtained 4, 24 and 48 h later (Rufini et al. 2006). The patient is advised to drink water to help flush the radiolabeled tracer out through urine and stool. This will be excreted in 1–2 days and is not harmful to others.

16.5 DOTA-Peptide PET-CT Scanning

When ectopic sources of ACTH or growth hormone (GH) have not been identified by usual imaging, the somatostatin analogues DOTA-peptides may be utilized and have been proposed as superior in efficacy to octreotide (Deppen et al. 2016). This is a radioactive tracer that, once administered, will adhere to or 'tag' somatostatin receptors (SSR) expressed on both ACTH and GH tumours. Several DOTA-peptides such as ^{68}DOTATOC and ^{68}DOTATATE that have an affinity for SSR-2 and -5 are used in conjunction with Positron Emission Tomography with Computerized Tomography (PET-CT) scanning, and have been efficacious in identifying ectopic tumour anywhere in the body (Gilardi et al. 2014; Venkitaraman et al. 2014).

Procedure: The patient must avoid any treatment with somatostatin drugs (SSAs) the month prior to testing. No fasting is required, and normal medications (exclusive of SSAs) can be taken the morning of testing. The drug is prepared once the patient has arrived to the testing centre because of its short half-life. An IV can-

nula is placed, and the drug administered. After a 60-min wait, the patient is asked to void prior to scanning. Once scanning begins, the process will take approximately 30–45 min, and requires the patient to be as still as possible. After scanning, the images will be reviewed for quality prior to the patient's discharge. Fluid consumption and frequent voiding to eliminate the tracer is important after scanning. The procedure is usually tolerated well without side effects (The Christie Patient Information Service 2016).

As for all nuclear testing, breastfeeding should be discontinued for 24–48 h after administration of the agent. It is recommended that women with young children avoid contact with them for at least 24 h after testing (Venkitaraman et al. 2014).

16.6 Conclusions

Radiographic, tomographic and nuclear studies may be indicated for the diagnosis of pituitary or ectopic hypersecretory disorders. These are often time consuming and some patients may require an anxiolytic medication in order to complete imaging.

MRI is usually preferred over CT for the identification of sella and suprasella tumours. Safety is paramount when preparing a patient for MRI. This includes screening for magnet incompatible items, renal disorders, and prior reactions to contrast media. Paramagnetic contrast agents are administered intravenously to enhance the recognition of abnormalities.

Education and preparation is needed for all imaging and is particularly pertinent for patients undergoing nuclear medicine scans. Throughout testing, clear information, answered questions and psychological support are essential to achieve effective diagnosis and treatment outcomes.

References

Basics, neuroradiology. University of Wisconsin Updated Jan 4, 2018, 9:10 AM.

Buchfelder M, Schlaffer S. Imaging if the pituitary. In: Fliers E, Korbonits M, Romijn JA, editors. Handbook of clinical neurology. Vol. 124. 3rd series, Clinical neuroendocrinology. Elsevier B.V.; 2014.

Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. Semin Perinatol. 2013;37(5):301–4.

Byun WM, et al. MR imaging findings of Rathke's cysts: significance if intracystic nodules. AJNR Am J Neuroradiol. 2000;21:485–8.

Copel J, El-Sayed Y, Heine RP, Wharton KR. Committee Opinion No. 723: guidelines for diagnostic imaging during pregnancy and lactation. Obstet Gynecol. 2017;130(4):e210–6. https://doi.org/10.1097/AOG.0000000000002355.

Deppen SA, Blume J, Bobbey AJ, Shah C, Graham MM, Lee P, Delbeke D, Walker RC. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. J Nucl Med. 2016;57(6):872–8. https://doi.org/10.2967/jnumed.115.165803. Epub 2016 Jan 14.

EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. 23/11/2017. EMA/625317/2017 http://ema.europa.eu. Accessed 6.13.18.

Friedman TC, Zuckerbraun E, Lee ML, Kabil MS, Shahinian H. Dynamic pituitary MRI has high sensitivity and specificity for the diagnosis of mild Cushing's syndrome and should be part of the initial workup. Horm Metab Res. 2007;39(6):451–6.

Gilardi L, Colandrea M, Fracassi SL, Sansovini M, Paganelli G. 68Ga-DOTA0-Tyr3octreotide (DOTATOC) positron emission tomography (PET)/CT in five cases of ectopic adrenocorticotropin-secreting tumours. Clin Endocrinol. 2014;81:152–3.

Gupta K, Sahni S, Saggar K, Vashisht G. Evaluation of clinical and magnetic resonance imaging profile of pituitary macroadenoma: a prospective study. J Nat Sci Biol Med. 2018;9(1):34–8. https://doi.org/10.4103/jnsbm.JNSBM_111_17.h.

Gutenberg A, Larsen J, Lupi I, Rohde V, Caturegli P. A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. Am J Neuroradiol. 2009;30(9):1766–72. https://doi.org/10.3174/ajnr.A1714.

Hagiwara A, Inoue Y, Wakasa K, Haba T, Tashiro T, Miyamoto T. Comparison of growth hormone-producing and non-growth hormone-producing pituitary adenomas: imaging characteristics and pathologic correlation. Radiology. 2003;228(2):533–8. Epub 2003 Jun 20.

Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab. 2005;90(8):4955–62.

Koch KM, Hargreaves BA, Butts K, Chen PW, Gold GE, King KF. Magnetic resonance imaging near metal implants. J Magn Reson Imaging. 2010;32(4):773–87.

Maya MM, Pressman BD. Pituitary imaging. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2011. p. 645–69.

Potorac I, Petrossians P, Daly AF, Schillo F, Ben Slama C, Nagi S, Sahnoun M, Brue T, Girard N, Chanson P, Nasser G, Caron P, Bonneville F, Raverot G, Lapras V, Cotton F, Delemer B, Higel B, Boulin A, Gaillard S, Luca F, Goichot B, Dietemann JL, Beckers A, Bonneville JF. Pituitary MRI characteristics in 297 acromegaly patients based on T2-weighted sequences. Endocr Relat Cancer. 2015;22(2):169–77. https://doi.org/10.1530/ERC-14-0305. Epub 2015 Jan 2.

Radue E-W, Weigel M, Wiest R, Urbach H. Introduction to magnetic resonance imaging for neurologists. Continuum: Lifelong Learning in Neurology. 2016;22(5, Neuroimaging):1379–98.

Ramalho J, Ramalho M, Jay M, Burke LM, Semelka RC. Gadolinium toxicity and treatment. Magn Reson Imaging. 2016;34(10):1394–8. https://doi.org/10.1016/j.mri.2016.09.005. ISSN: 0730-725X, 1873-5894.

Ranganathan S, Lee SH, Checkver A, et al. Magnetic resonance imaging finding of empty sella in obesity related idiopathic intracranial hypertension is associated with enlarged sella turcica. Neuroradiology. 2013;55(8):955–61. https://doi.org/10.1007/s00234-013-1207-0.

Raschle N, Zuk J, Ortiz-Mantilla S, et al. Pediatric neuroimaging in early childhood and infancy: challenges and practical guidelines. Ann N Y Acad Sci. 2012;1252:43–50. https://doi.org/10.1111/j.1749-6632.2012.06457.x.

Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med. 2006;36(3):228–47.

Sahdev A, Reznek RH, Evanson J, Grossman AB. Imaging in Cushing's syndrome. Arq Bras Endocrinol Metabol. 2007;51(8):1319–28.

Seeburg DP, Dremmen MHG, Huisman TAGM. Imaging of the sella and parasellar region in the pediatric population. Neuroimaging Clin N Am. 2017;27:99–121. https://doi.org/10.1016/j.nic.2016.08.004.

The Christie Patient Information Service June 2016 CHR/NM/1157/24.05.16 Version 1 Review June 2019 www.christie.nhs.uk.

Venkitaraman B, Karunanithi S, Kumar A, Bal C, Ammini AC, Kumar R. ^{68}Ga-DOTATOC PET-CT in the localization of source of ectopic ACTH in patients with ectopic ACTH-dependent Cushing's syndrome. Clin Imaging. 2014;38(2):208–11. https://doi.org/10.1016/j.clinimag.2013.10.007. Epub 2013 Nov 7.

Weidman EK, Dean KE, Rivera W, Loftus ML, Stokes TW, Min RJ. MRI safety: a report of current practice and advancements in patient preparation and screening. Clin Imaging. 2015;39(6):935–7. https://doi.org/10.1016/j.clinimag.2015.09.002. Epub 2015 Sep 4.

Yousem DM, Grossman RI. Chapter 11: The sella and central. Skull base neuroradiology, The requisites. Mosby; 2010. p. 356–83. ISBN: 0323045219.

Key Reading

1. Radue E-W, Weigel M, Wiest R, Urbach H. Introduction to magnetic resonance imaging for neurologists. Continuum: Lifelong Learning in Neurology. 2016;22(5, Neuroimaging):1379–98.
2. Seeburg DP, Dremmen MHG, Huisman TAGM. Imaging of the sella and parasellar region in the pediatric population. Neuroimaging Clin N Am. 2017;27:99–121. https://doi.org/10.1016/j.nic.2016.08.004.
3. Weidman EK, Dean KE, Rivera W, Loftus ML, Stokes TW, Min RJ. MRI safety: a report of current practice and advancements in patient preparation and screening. Clin Imaging. 2015;39(6):935–7. https://doi.org/10.1016/j.clinimag.2015.09.002. Epub 2015 Sep 4.

Non-functioning Pituitary Adenomas

17

Judith P. van Eck
and Sebastian J. C. M. M. Neggers

Contents

17.1 **Introduction** ... 323

17.2 **Aetiology and Prevalence** ... 323
17.2.1 Aetiology ... 323
17.2.2 Prevalence ... 323

17.3 **Genetic Causes of Non-functioning Pituitary Adenomas** ... 324
17.3.1 Familial Isolated Pituitary Adenomas (FIPA) ... 324
17.3.2 Multiple Endocrine Neoplasia Type 1 Syndrome (MEN-1) ... 324

17.4 **Clinical Manifestations of Non-functioning Pituitary Adenomas** ... 324

17.5 **Micro- Versus Macroadenomas** ... 326
17.5.1 Pituitary Incidentalomas ... 326

17.6 **Assessment and Therapeutic Options** ... 327
17.6.1 Radiology Assessment ... 327
17.6.2 Hormonal Assessment ... 327

17.7 **Visual Field Examination** ... 329

17.8 **Therapeutic Options** ... 329
17.8.1 Pituitary Surgery ... 329
17.8.2 Radiotherapy ... 330
17.8.3 Expectative Approach ... 330
17.8.4 Medical Treatment ... 330
17.8.5 Headaches Assessment and Management ... 330

17.9 **Long-Term Management** ... 330

17.10 **Nursing Interventions** ... 331

References ... 332

J. P. van Eck (✉) · S. J. C. M. M. Neggers
Department of Medicine, Section Endocrinology,
Erasmus Medical Centre,
Rotterdam, The Netherlands
e-mail: j.vaneck@erasmusmc.nl;
s.neggers@erasmusmc.nl

Abstract

Non-functioning pituitary adenomas (NFPAs) occur in a substantial proportion of the population. Non-functioning pituitary adenomas occur sporadically and seldom

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_17

arise as components of familial tumour syndromes. Treatment of non-functioning pituitary adenomas depends on the clinical signs and symptoms, comorbidities and patient preferences. It is a process of shared decision making between the patient and a multidisciplinary team. Surgery is indicated when the pituitary adenoma abuts or compresses the optic chiasm and causes visual field loss or vision loss. The goal of pituitary surgery for NFPA is to prevent patients from incurring bitemporal hemianopsia or restore visual field deficits and/or double vision. In most cases, patients diagnosed with a NFPA need long-term follow-up in order to monitor for tumour growth, alterations in visual field examination, biochemical assessment of the anterior pituitary functions and hormone replacement therapy if needed. Endocrine nurses play a key role in educating patients about the aetiology of NFPA, surgical treatments and hormone replacement therapy.

Keywords

Non-functioning pituitary adenoma
Microadenoma · Macroadenoma
Incidentaloma · FSH · LH

Abbreviations

ACTH	Adreno corticotroph hormone
AIP	Aryl hydrocarbon receptor-interacting protein
BTH	Bitemporal hemianopsia
CT	Computed tomography
E2	Estradiol
FIPA	Familial isolated pituitary adenomas
FSH	Follicle stimulating hormone
FT4	Free thyroxine-4 hormone
HFA	Humphrey field analyser
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
MEN-1	Multiple endocrine neoplasia type 1 syndrome
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
PRL	Prolactin
T	Testosterone
TSH	Thyroid stimulating hormone

Key Terms

- **Non-functioning pituitary adenoma:** Non-functioning pituitary adenomas are slowly growing adenomas that originate in the pituitary gland. Non-functioning pituitary adenomas do not produce hormones that lead to classical endocrine syndromes.
- **Compression of the optic chiasm:** The optic chiasm is the area of the brain where the optic nerves partially cross over. Pituitary adenomas are the most common cause of compression of the optic chiasm. This may lead to bitemporal hemianopsia.
- **Bitemporal hemianopsia:** Bitemporal hemianopsia is a type of blindness or visual field deficit in which all the vision in the peripheral temporal field segments of both eyes is lost, leaving only the central, nasal fields to be perceived.
- **Hypopituitarism:** The loss of one or more anterior pituitary hormones leading to deficient hormone production in the corresponding target gland.
- **Panhypopituitarism:** The loss of all pituitary hormonal production.
- **Transsphenoidal pituitary surgery:** Transsphenoidal pituitary surgery can be done by an endoscope or a microscope. Surgical instruments are inserted into part of the brain by going through the nose and the sphenoid bone into the sphenoidal sinus cavity. Transsphenoidal surgery is used to remove tumours of the pituitary gland.

Key Points

- The prevalence of non-functioning pituitary adenomas based on population studies is 14–46 per 100,000. Of all pituitary adenomas 25% is clinically non-functioning. The clinical importance of a NFPA depends on the size and compression on surrounding structures.
- NFPA are classified by size, based on radiological imaging. A microadenoma is smaller than 1 cm, macroadenomas are larger than 1 cm. Incidentalomas are found by coincidence on imaging and can be a micro- and macroadenoma.
- When a NFPA is found, biochemical hormonal assessment is needed to exclude hypopituitarism. Visual field examination is needed when the NFPA abuts or compresses the optic chiasm.
- Pituitary surgery is indicated when compression of the optic chiasm leads to visual fields deficits and/or loss of visual acuity. Radiotherapy can be used after pituitary surgery for (re-growth of) the remnant.
- Endocrine nurses play a key role in educating patients about the treatment of pituitary adenomas, alarming symptoms, hypopituitarism hormone replacement therapy and long-term follow-up.

17.1 Introduction

Non-functioning pituitary adenomas and prolactinomas represent the largest group of all pituitary adenomas. Non-functioning pituitary adenomas are mostly slow growing benign tumours that are often detected incidentally. Patients may remain asymptomatic and a tumour may be found during imaging procedures for unrelated causes such as after a closed head injury or accident. In symptomatic patients, complaints secondary to mass effect on surrounding structures such as visual changes or headaches may prompt imaging and reveal a pituitary lesion. Incidentalomas can be a micro- or a macroadenoma. Symptomatic patients most often are found to have a macroadenoma. These complaints include: visual field deficits, loss of visual acuity, headaches and hypopituitarism and critically, apoplexy.

17.2 Aetiology and Prevalence

17.2.1 Aetiology

The aetiology of NFPAs to date remains uncertain. Pituitary adenomas represent a heterogeneous group of tumours. Pituitary adenomas are mostly benign monoclonal neoplasms that arise from any of the five hormone secreting cell types of the anterior lobe of the pituitary gland (Alexander et al. 1990). Most non-functioning pituitary tumours are sporadic mutations (95%), with only 5% arising as components of familial tumour syndromes such as multiple endocrine neoplasia type 1 (MEN-1) (Marques and Korbonits 2017). A number of different molecular mechanisms that lead to pituitary adenomas have been identified, although in the majority of the sporadic cases, the exact molecular pathogenesis remains unknown (Caimari and Korbonits 2016). Factors hypothesized to contribute to develop non-functioning pituitary adenomas include altered hypothalamic hormones, growth hormones, growth factors, proliferation factors, proteins and (proto) onco-genes (Herder et al. 2011). Also, research has demonstrated that growth hormone producing pituitary adenomas are more prevalent in highly polluted areas. The high prevalence was not explainable on the basis of a familial susceptibility or on a known genetic predisposition. More research is needed to study the prevalence of non-functioning pituitary adenomas and the role of environmental and industrial pollution in the formation of these tumours (Cannavò et al. 2010).

17.2.2 Prevalence

The majority of data on the prevalence of pituitary adenomas are extracted from morphological studies or from old clinical surveys, which are

based either on tertiary referral hospital census or on nation-wide cancer registries and likely underrepresent prevalence (Fernandez et al. 2010). Anatomical studies with results extracted either from serial autopsies or from magnetic resonance imaging have suggested the presence of a pituitary tumour in the general population is approximately 16.7% of cases (Ezzat et al. 2004). It is only within the last decade that more intensive population-based studies have been performed. Population-based studies give more reliable information about the clinical relevant non-functioning pituitary adenomas. The estimated prevalence of non-functioning pituitary adenomas based on population studies currently is 14–46 per 100,000 (Fernandez et al. 2010; Daly et al. 2006; Agustsson et al. 2015; Gruppetta et al. 2013). Non-functioning pituitary adenomas account for 25–30% of all pituitary adenomas (Alexander et al. 1990).

17.3 Genetic Causes of Non-functioning Pituitary Adenomas

Five percent of all pituitary adenomas (PAs) occur in a family setting, because of a genetic defect that predisposes family members to pituitary adenoma development, either in isolation or as part of a syndrome. Despite their relative rarity, hereditary PAs are important entities because they often present in younger patients, have a more aggressive course, and are more refractory to therapy (Gadelha et al. 2013). Non-functioning pituitary adenomas occur in families with FIPA (Familial Isolated Pituitary adenomas) and MEN-1 (Multiple Endocrine Neoplasia type 1).

17.3.1 Familial Isolated Pituitary Adenomas (FIPA)

FIPA is characterized by the occurrence of two or more cases of pituitary adenomas in a family in the absence of other associated tumours (Beckers et al. 2013). In FIPA families, individuals may have the same PA subtype among affected subjects (homogeneous FIPA), or a mixture of different types of PAs may occur in the same kindred (heterogeneous FIPA) (Daly and Beckers 2015). In 25% of individuals in FIPA families, a germline mutation of the aryl hydrocarbon receptor-interacting protein (AIP) gene can be identified. AIP mutation was also found in >10% of patients with a macroadenoma prior to age 30 and in 20% of children with macroadenomas (Vasilev et al. 2012).

17.3.2 Multiple Endocrine Neoplasia Type 1 Syndrome (MEN-1)

MEN-1 is a rare hereditary cancer syndrome characterized by the occurrence of endocrine and non-endocrine tumours. The three main components of MEN-1 are primary hyperparathyroidism, duodenopancreatic neuroendocrine tumours and pituitary adenomas (Chandrasekharappa et al. 1997). MEN-1 pituitary disease is dominated by prolactinomas, but systematic screening of MEN-1 patients shows a large number of non-symptomatic small non-functioning pituitary adenomas (De Laat et al. 2015). The diagnosis of MEN-1 is established in one of these scenarios: a patient with 2 or more MEN-1-associated tumours; a patient with one MEN-1-associated tumour and a first-degree relative with MEN-1; a mutant gene carrier, that is, an individual with a MEN1 mutation but no clinical, biochemical or structural evidence of MEN-1 (Thakker et al. 2012). Genetic counselling and testing is recommended for family members diagnosed with MEN-1.

17.4 Clinical Manifestations of Non-functioning Pituitary Adenomas

Non-functioning pituitary adenomas account for 25–30% of all pituitary adenomas (Alexander et al. 1990). Non-functioning pituitary adenomas (NFPAs) produce small quantities of hormones (e.g. gonadotrophins

(LH, FSH), TSH or fragments of hormones (e.g. alpha subunits). The production of small quantities of these hormones does not lead to classic clinical syndromes like acromegaly and Cushing's disease (see Chaps. 8 and 9). Also, alpha subunits are not biologically active when beta-subunits are not produced (Edmonds et al. 1975). These adenomas are therefore considered as 'non-functioning'. Individuals harbouring a NFPA usually present with one or a combination of symptoms secondary to mass effect on surrounding tissues and include: visual field defects, double vision, loss of visual acuity, headache and hypopituitarism (Ferrante et al. 2006; Greenman and Stern 2015).

Visual field deficits are caused by suprasellar extension of the adenoma leading displacement of the optic pathways (Fig. 17.1). It results often in a unique bitemporal hemianopsia which is typical for large pituitary adenomas, or other visual field defects (Lee et al. 2015). Bitemporal hemianopsia is a visual field deficit in which all the vision in the peripheral temporal fields of both eyes is lost, leaving only the nasal or central visual fields to be perceived (Lee et al. 2015). Incomplete bitemporal visual field defects are much more common than true hemianopsia (Lee et al. 2015). The visual acuity may also be decreased (Ogra et al. 2014). 40–70% of the patients with NFPA present with visual field defects (Ferrante et al. 2006; Lee et al. 2015; Ogra et al. 2014). When bitemporal hemianopsia and/or decreased visual acuity has/have been demonstrated, there is a need for neurosurgical intervention in order to restore visual functions. When compression of the optic chiasm is left untreated complete blindness can ensue (Müslüman et al. 2011).

Headache is a common presenting symptom and occurs in approximately 40–60% of patients harbouring a non-functioning pituitary adenoma (Ferrante et al. 2006; Ebersold et al. 1986; Comtois et al. 1991). The aetiology is not very clear, but studies have demonstrated an association between the presence of headache and tumour size, optic chiasm compression, sellar destruction and cavernous sinus invasion (Gondim et al. 2009; Cottier et al. 2000). Also,

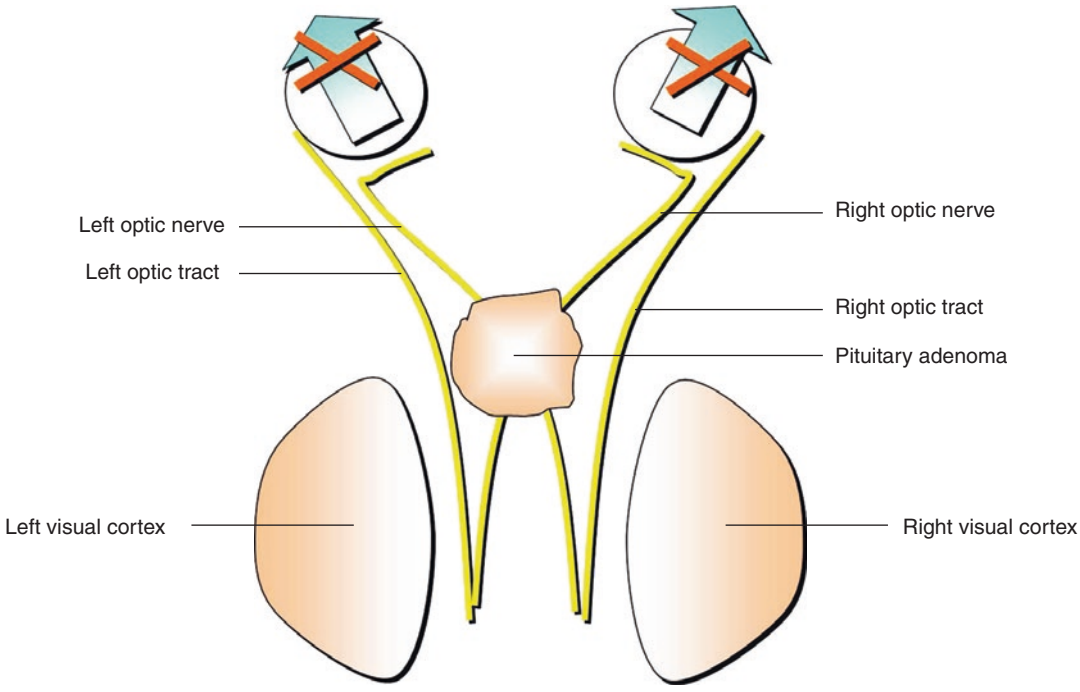


Fig. 17.1 Compression of the optic chiasm by the pituitary adenoma leading to bitemporal hemianopsia

a family history for headaches is a risk factor for patients harbouring a pituitary adenoma (Yu et al. 2017). There are studies that show that neurosurgical resection of the pituitary adenoma may relieve the patients of some chronic headaches (Ebersold et al. 1986; Comtois et al. 1991; Wolf et al. 2016). Another recent study demonstrated no significant improvement in headaches after pituitary surgery (Siegel et al. 2017). For this reason headache alone may not be a valid indication for transsphenoidal pituitary surgery.

Hypopituitarism. Hypopituitarism is the lack of production of one or more anterior pituitary hormones. It may result in growth hormone deficiency, hypogonadotropic hypogonadism, secondary hypothyroidism and secondary adrenal insufficiency. Hypopituitarism occurs in variable degrees and when assessed, found in the majority of patients with non-functional pituitary adenomas (Ferrante et al. 2006; Jaffe 2006; Nomikos et al. 2004). Hypopituitarism is caused by the mass effect of the pituitary adenoma on normal pituitary tissue or as a result of compression of the hypophyseal portal circulation by the tumour mass. Recovery from hypopituitarism after decompression surgery has been described (Berg et al. 2010; Fatemi et al. 2008; Jayasena et al. 2009; Yedinak et al. 2015), but is unlikely if hypothalamic or pituitary tissue has been destroyed (e.g. by radiation therapy, haemorrhage or surgery) (Vance 1994).

Pituitary apoplexy is a rare endocrine emergency caused by an acute bleeding in a pituitary macroadenoma, resulting in a rapid increase in tumour size, that may lead to acute severe headache, visual field deficits, loss of vision and hypopituitarism (Rolih and Ober 1993; Brougham et al. 1950). Diagnosis is confirmed by Magnetic Resonance Imaging (MRI) and visual field examination. MRI is the radiologic investigation of choice and much more sensitive than a CT scan (Rajasekaran et al. 2011). Emergency pituitary surgery is indicated in case of severe visual field deficits, loss of visual acuity or severe headaches. Stress dose glucocorticoid replacement may be lifesaving in apoplexy.

17.5 Micro- Versus Macroadenomas

Pituitary adenomas are being classified by size, confirmed by radiology assessment. Microadenomas have a tumour size smaller than 10 mm on radiology imaging. Tumours that exceed the size of 10 mm are classified as macroadenomas. In macroadenomas, the sella turcica is enlarged. Macroadenomas are often symptomatic due to the mass effect of the tumour.

Microadenomas are located within the normal borders of the sella turcica. Symptomatology in non-functional microadenomas is often absent, due to normal secretion patterns of pituitary hormones and the fact that microadenomas also rarely give compression to surrounding structures. Small intrasellar non-functioning pituitary lesions occur in 10–20% of the population or more in some reports. They may require monitoring for growth but if non-functioning are not usually of clinical importance (Agustsson et al. 2015). They may need to be further evaluated in the presence of symptoms of hypopituitarism.

17.5.1 Pituitary Incidentalomas

Pituitary incidentalomas are lesions that are detected on examination of a patient for other reasons. Patients are most often asymptomatic with respect to the tumour. Incidentalomas may be found during imaging procedures for symptoms such as headaches, after head trauma or symptoms involving the neck or central nerve system (Paschou et al. 2016). Pituitary incidentalomas can be microadenomas or macroadenomas. They can be functional and non-functional. When a pituitary incidentaloma is detected on imaging, hypopituitarism and hypersecretion need to be excluded (Molitch and Russell 1990). Non-functioning macro-incidentalomas should either be surgically removed or, if completely asymptomatic, followed closely with repeat scans (Molitch and Russell 1990). Recommendations vary regarding the interval of scanning. The interval decision is often based on symptoms, tumour

growth, proximity to the optic chiasm and can be recommended from every 6 months up to every 5 years.

17.6 Assessment and Therapeutic Options

17.6.1 Radiology Assessment

17.6.1.1 Magnetic Resonance Imaging (MRI)

An MRI scan is considered the imaging modality of choice for the diagnosis of pituitary disorders because of its multiplanar capability and its good soft tissue contrast (Ezzat et al. 2004). The use of MRI has preferred over the use of CT because MRI allows better recognition of normal structures and has a higher resolution in defining tumours. Imaging of the pituitary has been performed in coronal and sagittal planes at 1.5–2 mm interval. Using this procedure, microadenomas of 3–5 mm can be detected. Gadolinium is a non-iodinated and most often the contrast agent of choice during this procedure and gives the opportunity to detect the smallest pituitary lesions distinguishing between pituitary tissue and the pituitary lesion (Gao et al. 2001). It also clarifies the position of the adenoma in relation to surrounding structures, e.g. the optic chiasm, and arteria carotis interna (the internal carotid arteries). It is important to note that patients with high creatinine or renal disease are not candidates for gadolinium contrast. Patients should be screened closely for metal implants or occupational risk of retained metal fragments and may need x-rays prior to MR scanning.

17.6.1.2 Computed Tomography (CT)

In known pituitary lesions, computed tomography is used to evaluate bone changes of the sella and calcifications in suspected craniopharyngiomas. CT is a second choice procedure for imaging pituitary lesions in patients when there is a contra-indication for MRI because of metal items in situ, e.g. a pacemaker or arterial/peripheral stents and claustrophobia (Pressman 2017).

17.6.2 Hormonal Assessment

In patients harbouring non-functioning pituitary adenomas, biochemical hormonal assessment is essential in diagnosing and treatment of hypopituitarism. Hypopituitarism in patients with pituitary adenomas is caused by interruption of the hypothalamic-pituitary-portal circulation by the tumour mass or by a direct destruction of hormone-producing tissue of the anterior pituitary. Both contribute to possible necrosis of normal pituitary gland which results in irreversible hypopituitarism and possibly panhypopituitarism (loss of all anterior pituitary functions) (Arafah 1986).

In cases with pituitary insufficiency, deficiency of the target organ hormones is found, without the expected compensatory rise in pituitary hormone levels. Therefore, measuring pituitary hormones alone is of limited or no value in diagnosing hypopituitarism.

In addition to measuring pituitary hormones, blood levels of target gland hormones are measured by immunoassays under standardized circumstances or conditions in order to interpret the results correctly (Table 17.1).

The anterior part of the pituitary produces stimulating hormones for the production of

1. *The adrenal hormone cortisol*
   The hypothalamus-pituitary-adrenal axis (HPA) has a diurnal day rhythm. The adrenal hormone cortisol reaches a peak level between 8.00 and 9.00 A.M. To evaluate the HPA-axis integrity morning cortisol is measured (Fig. 17.2). Further dynamic testing may also be needed (See Chap. 5).

Table 17.1 Anterior pituitary functions and end-organ hormones

Pituitary hormone	Pituitary end organ and hormones
Thyroid Stimulating Hormone—TSH	Thyroid—FT4
Adreno corticotroph releasing hormone—ACTH	Adrenals—cortisol
Gonadotrophic hormones: LH/FSH	Ovaries—estrogens (F)/ testis—testosterone (M)
Growth hormone—GH	Liver—IGF-1
Prolactin	

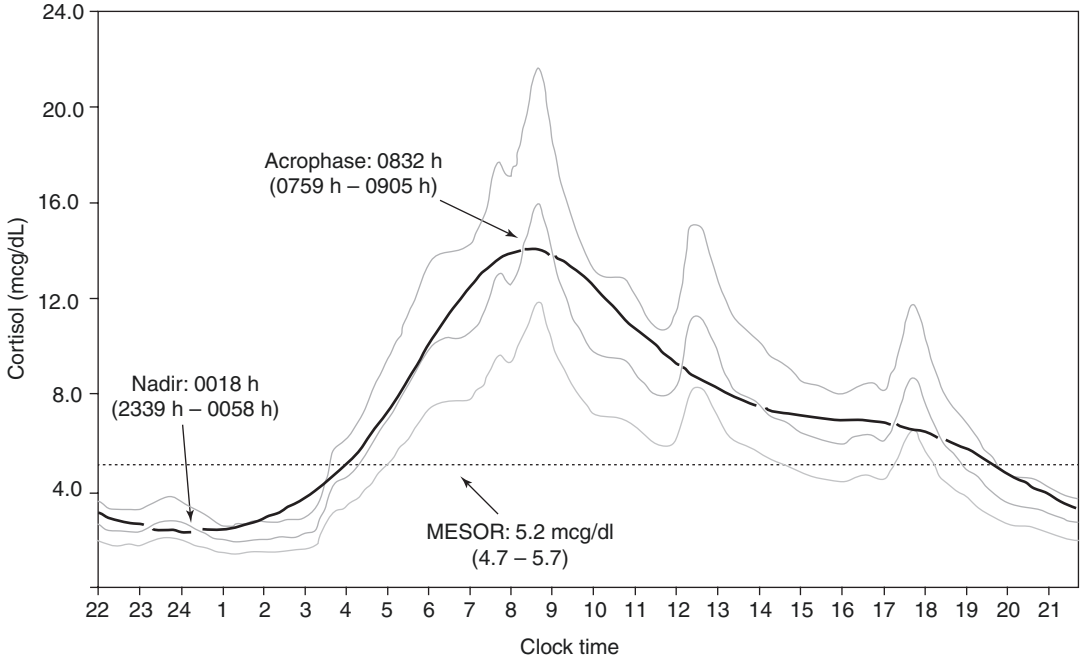


Fig. 17.2 Circadian rhythm of cortisol. Adapted from: Debono, M., et al. (2009). 'Modified-release hydrocortisone to provide circadian cortisol profiles'. The Journal of Clinical Endocrinology & Metabolism **94**(5): 1548–1554

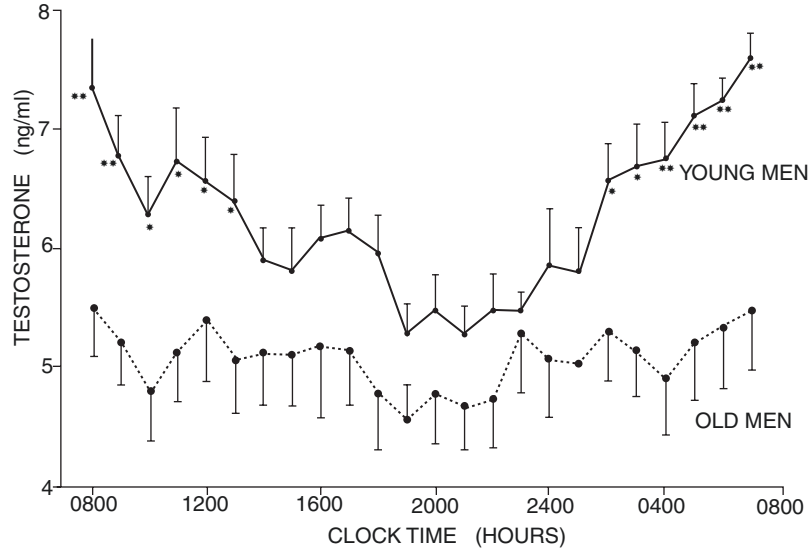


Fig. 17.3 Circadian rhythm of testosterone in men. Adapted from: Bremner, W. J., et al. (1983). 'Loss of circadian rhythmicity in blood testosterone levels with ageing in normal men'. The Journal of Clinical Endocrinology & Metabolism **56**(6): 1278–1281

2. *Thyroid hormone*
   To evaluate the hypothalamus-pituitary-thyroid axis, FT4 is measured. TSH levels in pituitary patients are normal to low-normal and with pituitary damage and surgery TSH is no longer a reliable contribution in the evaluation of the hypothalamus-pituitary-thyroid axis.

3. *Gonadal hormone*
   Gonadal hormones are stimulated by LH and FSH and produced in the ovaria and testes (Fig. 17.3). LH, FSH and testosterone are measured in men. Testosterone reaches a peak level between 08:00 and 10:00 A.M. and therefore it is best measured in the morning.

In women, LH, FSH and oestradiol are measured for evaluation of the hypothalamus-pituitary-gonadal axis and results are time of the menstrual cycle and menopausal status dependent.

4. *Growth hormone (GH)*
   To evaluate the hypothalamus-pituitary-growth hormone axis, insulin-like growth factor-1 (IGF-1) is measured. It is produced by the liver after stimulation from growth hormone produced in the pituitary. Growth hormone is secreted in a pulsatile fashion by the anterior pituitary and therefore a random sample is of little value in the evaluation of growth hormone deficiency or excess. The GH axis function requires further evaluation by dynamic tests (See Chap. 5).
5. *Prolactin*
   Prolactin is inhibited by the production of dopamine in the hypothalamus, but can be slightly elevated in patients with a large non-functioning pituitary adenoma due compression of the pituitary stalk that can disrupt the dopamine inhibition of prolactin production in the anterior pituitary (Chahal and Schlechte 2008).

For more information about pituitary function and dynamic pituitary testing, see Chaps. 1 and 5.

17.7 Visual Field Examination

Visual field analyses reflect the degree of the compression to the optic nerve that results the structural damage of the nerve. Visual fields can be evaluated by Goldmann and Humphrey perimetry. The Goldmann perimeter is a hollow white spherical bowl positioned at set distance in front of the patient (Fig. 17.4). An examiner presents a test light of variable size and intensity in a variety of visual fields. The Humphrey perimetry is an automated test. The patient is required to fixate at a central point with each eye while a light of variable intensity is flashed in the peripheral field of vision. The patient is required to acknowledge the flashing light by pressing a button.

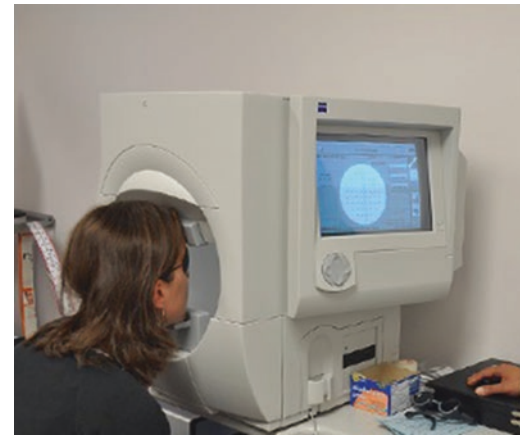


Fig. 17.4 Humphrey's visual field examination

Informal visual field exams by confrontation can also be accomplished in clinic with the practitioner seated 3–4 ft from the patient. With both practitioner and patient facing each other, each cover one eye as the practitioner holds up fingers equidistant between them. Each visual quadrant is tested when the patient correctly perceives the number of digits displayed in each visual field quadrant. Formal testing is indicated with any deficiencies when compared with the examiner's field of vision.

Formal evaluation of visual fields pre- and postoperatively or during long-term follow-up provides a standard quantitative method in assessing the progression of visual field loss (Anik et al. 2011). Other causes of visual field deficits should be ruled out by the ophthalmologist, such as glaucoma and cataract.

17.8 Therapeutic Options

Treatment of non-functioning pituitary adenomas depends on the clinical signs and symptoms, comorbidities and personal circumstances. It is a process of shared decision making of the multidisciplinary team, together with the patient.

17.8.1 Pituitary Surgery

In patients harbouring a non-functional pituitary adenoma, pituitary surgery is indicated when the

pituitary adenoma abuts or compresses the optic chiasm. The goal of pituitary surgery is to prevent patients from incurring bitemporal hemianopsia or to restore visual field deficits and visual field acuity loss. Pituitary surgery can be performed by transsphenoidal approach with a microscope or endoscope. In giant adenomas, a transcranial surgery is usually indicated (See Pituitary Surgery Chap. 12).

17.8.2 Radiotherapy

In NFPA radiotherapy is commonly used for postoperative adenoma remnants with invasive character that are not accessible surgically. The timing of radiation for NFPA is a current subject of controversy. Some radiotherapists recommend radiotherapy after initial surgery. Others use radiotherapy only if further growth of the residual adenoma is observed. Read more about radiotherapy in Chap. 12.

17.8.3 Expectative Approach

In patients harbouring a non-symptomatic non-functioning pituitary adenoma with no compression to the optic chiasm, one can 'wait and scan' or 'wait and watch'. This approach is to closely monitor the evolution of the adenoma. When, or if, growth of the adenoma occurs and/or visual field deficits are demonstrated, the indication for pituitary surgery needs to be reconsidered.

17.8.4 Medical Treatment

In NFPA, the goal of treatment is tumour reduction or stabilization of tumour size in order to reduce signs and symptoms caused by compression of the tumour on surrounding structures (e.g. optic chiasm). Currently, no treatment medical treatment modality has been found that has demonstrated reliable reduction in tumour size of NFPA (Greenman 2007).

There were attempts to use dopamine agonists to address tumour growth after surgical resection of a NFPA macroadenomas. In two small nonrandomized studies it was found that with D2 tumour expression some benefit may be achieved with respect to stabilization of any residual tumour in 61–70% (Greenman et al. 2005; Pivonello et al. 2004). There may also be some potential benefit in rare cases in whom radiotherapy and a second surgical intervention are less attractive (Neggers and Lelij van der 2014). However, overall there seems to be a limited role for dopamine agonists in NFPA.

17.8.5 Headaches Assessment and Management

Assessment of pain should be integrated in the diagnostic workup and follow-up of patients with a non-functioning pituitary adenoma. Headaches assessment can be performed by using structured questionnaires, or in a less structured way, as long as pain is not neglected. In a proportion of patients, a referral to a neurologist may be useful. Different treatment strategies are often necessary (optimization of endocrinological treatment, pharmaceutical pain management, physiotherapy, behavioural psychotherapy when appropriate, etc.) (Dimopoulou et al. 2014).

17.9 Long-Term Management

Patients with a non-functioning pituitary adenoma, especially when patients have undergone pituitary surgery, in most cases need lifelong follow-up of the adenoma. Radiologic assessment by MRI is needed to follow the size of the pituitary adenoma or any residual tumour. When the optic chiasm is involved, repeated perimetry to follow the visual fields and visual acuity is also needed. Usually this can be discontinued or performed less frequently during long-term follow-up after pituitary surgery. Regular biochemical assessment is essential to follow up the anterior pituitary functions. Long-term hypopituitarism after surgery is possible and may be more frequent if the patient received additional radiotherapy. However, hormonal assessment is essential to optimize hor-

mone replacement therapy. Treatment of hypopituitarism with hormone replacement therapy is needed to improve symptomatology associated with hypopituitarism, to avoid potentially life-threatening situations in the case of adrenal insufficiency and to protect patients from the long-term sequela of untreated hypopituitarism such as osteoporosis and cardio-vascular disease.

17.10 Nursing Interventions

At the point of diagnosis, patients often fear this tumour is cancerous and will spread to other parts of the body. Patient education may start with reassurance and a description of the characteristics of adenomas versus cancerous tumours (See Imaging Chap. 5). The prevalence of pituitary carcinomas is less than 0.1% and if surgery is needed, the diagnosis will be confirmed by pathology (Heaney 2011). Explain that if metastasis occurs it is usually related to cancer from other locations such as lung or breast to the pituitary and not from the pituitary to other organs. Patients meeting criteria for MEN-1, however, will need further evaluation and psychological support as described above.

Patients often require multiple tests (as described above) and if better informed can more actively participate in and adhere to a plan of assessment and care. Patient preparation enhances trust, decreases anxiety and achieves a more seamless transition between disciplines such as neuro-ophthalmologists, neurosurgeons, neuroradiologists, ear-nose and throat (ENT) specialists, dynamic or invasive testing units or genetic testing and counsellors.

Involving the patients' family or support person(s) in disease-related education efforts using multiple educational modalities such as print, audio-visual methods, demonstration and verbal instruction is important for understanding and retention of information. It is important to take into account learning styles, literacy and culture (Marcus 2014). Referral to and/or the use of websites with endorsed patient educational material such as provided by the European Society of Endocrinology, the Endocrine Society (USA) Hormone Health Network and patient support organizations such as the World Alliance of Pituitary Organizations (WAPO) can provide both education and direct patient access to appropriate support.

How the information regarding the patient's tumour is delivered sets the stage for patient trust and subsequent learning, particularly at an initial visit after tumour discovery. Using approaches such as a modification of the SPIKE protocol for giving 'bad' news may be useful (Baile et al. 2000). This involves setting up the encounter in a private consultation, making a connection with the patient, preparing for the discussion and avoiding highly emotive wording such as 'brain tumour' or technical jargon. Check the understanding of the patient and family members to critical information given and invite them to ask questions regarding the information they require. Provide information as requested by both the patient and family and use references, written materials, etc. that can read in a more relaxed manner at home. Lastly address the patient and families emotions and immediate concerns such as preparation for surgery, work-related issues, expectations postoperatively such as steroids, monitoring of blood levels of some hormones for events while inpatient or after discharge such as diabetes insipidus, syndrome of inappropriate antidiuretic hormone and adrenal insufficiency (See Chap. 12).

Patient need to be aware that they will have regular, often lifelong, follow-up, although the follow-up interval may vary according to the patient's clinical needs, treatment location and patient access to care. It is important for the patient to be aware of unexpected signs and symptoms occurring in the meantime. Symptoms such as severe, sudden onset headache (often described as the 'worst headache of my life'), progressive headache, particularly associated with nausea and vomiting, and any new visual changes should be evaluated by the pituitary team immediately (See Endocrine Emergencies). Given the long-term relationship these patients form with their pituitary team, endocrine nurses play a key role in educating patients about signs and symptoms of changes in pituitary function

and normal and abnormal symptoms across the life cycle. Nurses support the patient maximizing their functional capacity and quality of life in the context of pituitary diseases.

References

Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, et al. The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. Eur J Endocrinol. 2015;173(5):655–64.

Alexander JM, Biller BM, Bikkal H, Zervas NT, Arnold A, Klibanski A. Clinically nonfunctioning pituitary tumors are monoclonal in origin. J Clin Investig. 1990;86(1):336.

Anik I, Anik Y, Koc K, Ceylan S, Genc H, Altintas O, et al. Evaluation of early visual recovery in pituitary macroadenomas after endoscopic endonasal transphenoidal surgery: quantitative assessment with diffusion tensor imaging (DTI). Acta Neurochir. 2011;153(4):831–42.

Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab. 1986;62(6):1173–9.

Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES—a six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302–11.

Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocr Rev. 2013;34(2):239–77.

Berg C, Meinel T, Lahner H, Mann K, Petersenn S. Recovery of pituitary function in the late-postoperative phase after pituitary surgery: results of dynamic testing in patients with pituitary disease by insulin tolerance test 3 and 12 months after surgery. Eur J Endocrinol. 2010;162(5):853–9.

Brougham M, Heusner AP, Adams RD. Acute degenerative changes in adenomas of the pituitary body—with special reference to pituitary apoplexy. J Neurosurg. 1950;7(5):421–39.

Caimari F, Korbonits M. Novel genetic causes of pituitary adenomas. Clin Cancer Res. 2016;22(20):5030–42.

Cannavò S, Ferraù F, Ragonese M, Curtò L, Torre ML, Magistri M, et al. Increased prevalence of acromegaly in a highly polluted area. Eur J Endocrinol. 2010;163(4):509–13.

Chahal J, Schlechte J. Hyperprolactinemia. Pituitary. 2008;11(2):141.

Chandrasekharappa SC, Guru SC, Manickam P, Olufemi S-E, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science. 1997;276(5311):404–7.

Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J. The clinical and endocrine outcome to trans-sphenoidal microsurgery of nonsecreting pituitary adenomas. Cancer. 1991;68(4):860–6.

Cottier JP, Destrieux C, Brunereau L, Bertrand P, Moreau L, Jan M, et al. Cavernous sinus invasion by pituitary adenoma: MR imaging. Radiology. 2000;215(2):463–9.

Daly AF, Beckers A. Familial isolated pituitary adenomas (FIPA) and mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocrinol Metab Clin N Am. 2015;44(1):19–25.

Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metabol. 2006;91(12):4769–75.

De Laat JM, Dekkers OM, Pieterman CRC, Kluijfhout WP, Hermus AR, Pereira AM, et al. Long-term natural course of pituitary tumors in patients with MEN1: results from the DutchMEN1 study group (DMSG). J Clin Endocrinol Metabol. 2015;100(9):3288–96.

Dimopoulou C, Athanasoulia AP, Hanisch E, Held S, Sprenger T, Toelle TR, et al. Clinical characteristics of pain in patients with pituitary adenomas. Eur J Endocrinol. 2014;171(5):581–91.

Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV. Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. J Neurosurg. 1986;64(5):713–9.

Edmonds M, Molitch M, Pierce JG, Odell WD. Secretion of alpha subunits of luteinizing hormone (LH) by the anterior pituitary. J Clin Endocrinol Metabol. 1975;41(3):551–5.

Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas. Cancer. 2004;101(3):613–9.

Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, et al. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. Neurosurgery. 2008;63(4):709–18.

Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol. 2010;72(3):377–82.

Ferrante E, Ferraroni M, Castrignano T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol. 2006;155(6):823–9.

Gadelha MR, Trivellin G, Ramírez LCH, Korbonits M. Genetics of pituitary adenomas. Endocrine tumor syndromes and their genetics. Front Horm Res. 2013;41:111–40. Karger Publishers.

Gao R, Isoda H, Tanaka T, Inagawa S, Takeda H, Takehara Y, et al. Dynamic gadolinium-enhanced MR imaging of pituitary adenomas: usefulness of sequential sagittal and coronal plane images. Eur J Radiol. 2001;39(3):139–46.

Gondim JA, de Almeida JP, de Albuquerque LA, Schops M, Gomes E, Ferraz T. Headache associated with pituitary tumors. J Headache Pain. 2009;10(1):15–20.

Greenman Y. Dopaminergic treatment of nonfunctioning pituitary adenomas. Nat Rev Endocrinol. 2007;3(8):554.

Greenman Y, Stern N. Optimal management of nonfunctioning pituitary adenomas. Endocrine. 2015;50(1):51–5.

Greenman Y, Tordjman K, Osher E, Veshchev I, Shenkerman G, Reider-Groswasser II, et al. Postoperative treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists decreases tumour remnant growth. Clin Endocrinol. 2005;63(1):39–44.

Gruppetta M, Mercieca C, Vassallo J. Prevalence and incidence of pituitary adenomas: a population based study in Malta. Pituitary. 2013;16(4):545–53.

Heaney AP. Clinical review: pituitary carcinoma: difficult diagnosis and treatment. J Clin Endocrinol Metab. 2011;96(12):3649–60.

Herder dWW, Feelders RA, Van der Lelij AJ. Clinically non-functioning tumors and gonadotropinomas. In: Wass JAH, editor. Oxford textbook of endocrinology and diabetes. Oxford; 2011. p. 209–18.

Jaffe CA. Clinically non-functioning pituitary adenoma. Pituitary. 2006;9(4):317–21.

Jayasena CN, Gadhvi KA, Gohel B, Martin NM, Mendoza N, Meeran K, et al. A single early morning serum cortisol in the early post operative period following transphenoidal surgery for pituitary tumours accurately predicts hypothalamo-pituitary-adrenal function. Endocr Abstr. 2009;19((Jayasena C.N.; Gadhvi K.A.; Gohel B.; Martin N.M.; Meeran K.; Dhillo W.S.) Department of Investigative Medicine, Imperial College London, Hammersmith Hospital, London, United Kingdom):P272.

Lee IH, Miller NR, Zan E, Tavares F, Blitz AM, Sung H, et al. Visual defects in patients with pituitary adenomas: the myth of bitemporal hemianopsia. AJR Am J Roentgenol. 2015;205(5):W512–8.

Marcus C. Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. Health Psychol Behav Med. 2014;2(1):482–95.

Marques P, Korbonits M. Genetic aspects of pituitary adenomas. Endocrinol Metab Clin. 2017;46(2):335–74.

Molitch ME, Russell EJ. The pituitary "incidentaloma". Ann Intern Med. 1990;112(12):925–31.

Müslüman AM, Cansever T, Yılmaz A, Kanat A, Oba E, Çavuşoğlu H, et al. Surgical results of large and giant pituitary adenomas with special consideration of ophthalmologic outcomes. World Neurosurg. 2011;76(1):141–8.

Neggers S, Lelij van der A-J. Medical approach to pituitary tumors. In: Clinical neuroendocrinology. Elsevier; 2014.

Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas—a study on 721 patients. Acta Neurochir. 2004;146(1):27–35.

Ogra S, Nichols AD, Stylli S, Kaye AH, Savino PJ, Danesh-Meyer HV. Visual acuity and pattern of visual field loss at presentation in pituitary adenoma. J Clin Neurosci. 2014;21(5):735–40.

Paschou SA, Vryonidou A, Goulis DG. Pituitary incidentalomas: a guide to assessment, treatment and follow-up. Maturitas. 2016;92:143–9.

Pivonello R, Matrone C, Filippella M, Cavallo LM, Di Somma C, Cappabianca P, et al. Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. J Clin Endocrinol Metab. 2004;89(4):1674–83.

Pressman BD. Pituitary imaging. Endocrinol Metab Clin N Am. 2017;46(3):713–40.

Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, et al. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol. 2011;74(1):9–20.

Rolih CA, Ober KP. Pituitary apoplexy. Endocrinol Metab Clin N Am. 1993;22(2):291–302.

Siegel S, Carneiro RW, Buchfelder M, Kleist B, Grzywotz A, Buslei R, et al. Presence of headache and headache types in patients with tumors of the sellar region—can surgery solve the problem? Results of a prospective single center study. Endocrine. 2017;56(2):325–35.

Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metabol. 2012;97(9):2990–3011.

Vance ML. Hypopituitarism. N Engl J Med. 1994;330(23):1651–62.

Vasilev V, Daly A, Naves L, Zacharieva S, Beckers A. Clinical and genetic aspects of familial isolated pituitary adenomas. Clinics. 2012;67:37–41.

Wolf A, Goncalves S, Salehi F, Bird J, Cooper P, Van Uum S, et al. Quantitative evaluation of headache severity before and after endoscopic transsphenoidal surgery for pituitary adenoma. J Neurosurg. 2016;124(6):1627–33.

Yedinak C, Hameed N, Gassner M, Brzana J, McCartney S, Fleseriu M. Recovery rate of adrenal function after surgery in patients with acromegaly is higher than in those with non-functioning pituitary tumors: a large single center study. Pituitary. 2015;18(5):701–9.

Yu B, Ji N, Ma Y, Yang B, Kang P, Luo F. Clinical characteristics and risk factors for headache associated with non-functioning pituitary adenomas. Cephalalgia. 2017;37(4):348–55.

Key Reading

1. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, et al. The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. Eur J Endocrinol. 2015;173(5):655–64.
2. Marques P, Korbonits M. Genetic aspects of pituitary adenomas. Endocrinol Metab Clin North Am. 2017;46(2):335–74.
3. Dimopoulou C, Athanasoulia AP, Hanisch E, Held S, Sprenger T, Toelle TR, et al. Clinical characteristics of pain in patients with pituitary adenomas. Eur J Endocrinol. 2014;171(5):581–91.
4. De Laat JM, Dekkers OM, Pieterman CRC, Kluijfhout WP, Hermus AR, Pereira AM, et al. Long-term natural course of pituitary tumors in patients with MEN1: results from the DutchMEN1 study group (DMSG). J Clin Endocrinol Metabol. 2015;100(9):3288–96.

Thyroid Stimulating Hormone Secreting Adenoma (TSHoma)

18

Christine Yedinak

Contents

18.1 **Introduction** 336
18.2 **Definition** 337
18.3 **Epidemiology** 337
18.4 **Hypothalamic–Pituitary–Thyroid (HPT) Axis** 337
18.5 **Pathology** 338
18.6 **Assessment** 339
18.7 **Treatment** 340
18.8 **Nursing Care** 341
18.9 **Conclusions** 342
References 342

Abstract

Pituitary thyroid stimulating hormone (TSH) hypersecreting adenomas are rarer than any other hypersecretory pituitary adenoma. The etiology of these tumors is not known. TSHomas cause central hyperthyroidism, with elevation of the thyroid hormones without suppression of TSH. Although reported to occur at most ages, there is a higher prevalence with increasing age.

Most patients present with macroadenomas (>1 cm), headaches, and visual changes associated with tumor enlargement and optic nerve pathway compression. Others present with symptoms of thyrotoxicosis. Early diagnosis and treatment is recognized as the best means of avoiding complications such as vision loss, cardiac arrhythmias, or bone loss. New imaging modalities have improved diagnosis and made early treatment possible.

Treatment has two goals: normalization of TSH hypersecretion and tumor control. Primary therapy is aimed at tumor removal in order to normalize TSH, but medical therapy may be indicated if hypersecretory tumor remnants remain or

C. Yedinak (✉)
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: Yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_18

there is tumor regrowth. There is little data regarding long-term outcomes, late effects, or quality of life. This is likely related to the rarity of the disease.

Keywords
Thyroid stimulating hormone · TSHoma · Pituitary adenoma · Central hyperthyroidism · Thyrotoxicosis

Abbreviations

ACTH	Adrenocorticotrophic hormone
AIP	Aryl hydrocarbon receptor-Interacting Protein gene
CT	Computerized tomography
FSH	Follicle stimulating hormone
FT4	Free thyroxine
GSU	Glycoprotein hormone subunits
HPA	Hypothalamic–pituitary–adrenal (axis)
HPT	Hypothalamic–pituitary–thyroid axis
LAR	Long acting release
LH	Luteinizing hormone
MEN-1	Multiple endocrine neoplasia type 1
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SSA	Somatostatin analogues (ligands)
SSTR	Somatostatin receptor
TRH	Thyroid releasing hormone
TSH	Thyroid stimulating hormone
TSHoma	Thyroid stimulating hormone producing pituitary adenoma

Key Terms

- **Central hyperthyroidism:** over production of thyroid stimulating hormone from the pituitary leading to enlargement of the thyroid and thyrotoxicosis.
- **Thyroid ablation:** the destruction of the thyroid gland using radioactive iodine.
- **TSH β subunit**: the portion of TSH that determines the THS receptor activity in thyroid follicular cells.
- **Thyroid feedback loop:** the production and release of thyroid hormones T3 and T4 act on the hypothalamus and the pituitary to regulate their own production.

Key Points

- TSHomas are rare pituitary adenomas, frequently misdiagnosed as hyperthyroidism.
- Thyroid levels are regulated by the Hypothalamic–Pituitary–Thyroid (HPT) axis feedback loop.
- A detectable TSH level when FT4 levels are high is suggestive of a pituitary source of hyperthyroidism or TSHoma.
- Exogenous administration of T3 suppresses TSH β transcription and production.
- There has been a significant increase in the diagnosis of TSHomas, likely related to better imaging and diagnostic testing.
- Treatment options are similar to other pituitary adenomas with surgery as first-line and medical therapy as second-line therapies. Radiation therapy remains an option in unresponsive tumors.
- Research data is limited, particularly with respect to long-term impact on the patient and their quality of life.

18.1 Introduction

The diagnosis of TSHoma has increased fivefold in some countries, attributed to better and more frequent imaging (Tjörnstrand and Nyström 2017) and likely more awareness of the disorder. The mean age at presentation is in the fourth decade in both genders with age impacting the size of the tumor. Younger patients tend to present with smaller tumors that are more amenable to surgical removal and enjoy a higher frequency of remission (Tjörnstrand and Nyström 2017).

Early treatment requires the recognition that symptoms and biochemistry are associated with central and not primary hyperthyroidism. Historically misdiagnosed, this disorder has been associated with inappropriate thyroid ablation and thyroidectomies (Tjörnstrand and Nyström 2017; Greenman 2017). Improved biochemical test accuracy, ultrasound, and newer imaging techniques such as PET/CT scans with 68Ga-DOTATOC

promise even more accurate tumor location and more specific treatment. Improved histopathology allows the determination of tumor cell receptors that may help predict response to medical therapies and potential indicators of tumors more likely to recur (Greenman 2017).

Delay in diagnosis continues to be 6–12 years, depending on prior treatment and data regarding long-term outcomes is scarce (Greenman 2017). However, increased incidence has generated more interest in research for future impact.

18.2 Definition

Central hyperthyroidism is the result of autonomous secretion of Thyroid Stimulating Hormone (TSH) and may present with symptoms of thyrotoxicosis. First recognized in the 1960s, central hyperthyroidism is caused by a pituitary TSH secreting adenoma that causes excess production of active thyroxine from the thyroid gland, which subsequently fails to suppress the production of TSH (Tjörnstrand and Nyström 2017). TSH cells only represent about 5% of all pituitary cells which may help to explain the lower prevalence of TSHomas.

18.3 Epidemiology

Among pituitary adenomas, TSHomas are the most rare and represent about 0.4–3% of all pituitary adenomas based on postsurgical and postmortem reports (Tjörnstrand and Nyström 2017; Beck-Peccoz et al. 2015). However, there has been a significant increase in the incidence, which is likely related to a combination of better and more frequent use of imaging and greater recognition of the disease (Tjörnstrand and Nyström 2017). Prevalence of TSHomas is similar in both genders, with a mean age at presentation of 45 years. However, the reported ages at diagnosis range from 8 to 84 years (Beck-Peccoz et al. 2013). Familial cases have been reported in MEN-1 in association with AIP mutations (Beck-Peccoz et al. 2013).

18.4 Hypothalamic–Pituitary–Thyroid (HPT) Axis

TSH is produced by thyrotropes in the pituitary gland and comprises both α (alpha) and β (beta) subunits (Sarapura and Samuels 2017). These are genetically coded by two different genes on two different chromosomes. The genes are transcribed in the thyrotropes and combined to produce TSH. The β-subunit determines the downstream activity of TSH. The TSH α-subunit is a gene promotor important in the regulation of thyroid releasing hormone (TRH). TSH production is regulated by thyroid releasing hormone (TRH) from the hypothalamus which in turn is inhibited after thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) are produced from the thyroid (Sarapura and Samuels 2017) (Fig. 18.1).

TRH is transported from the hypothalamus to the pituitary via the hypophyseal portal system (the blood vessels connecting the hypothalamus and the pituitary) where it binds to the surface of thyrotrope cells (Sarapura and Samuels 2017). This starts a cascade of events within the cell to produce TSH. TSH enters the portal circulation and attaches to the cell surface of the thyroid follicular cells to stimulate iodinated thyroglobulin to release T4 and T3. Although T4 has some independent activity peripherally, it is essentially a prohormone for the more metabolically active T3 in peripheral cells. Some T4 is de-iodinated and converted to T3 in the thyroid itself, but the majority is converted in the liver (Nomura et al. 1975). T3 promotes metabolic activity and numerous life sustaining activities in almost all body cells including myocardial contractility, rate and relaxation, fetal neurologic development, and more (Cooper and Ladenson 2011). T3 production is the main regulator of TSH β transcription (Sarapura and Samuels 2017). Therefore, this activity is inhibited by administration of exogenous forms of T3 (triiodothyronine). The serum measurement of free T4 and T3 (T4 and T3 that are not bound to protein) is a more accurate measurement of the levels of both that are available to exert cellular effects (Sarapura and Samuels 2017) (for more details, see Sect. 4 Chap. 26).

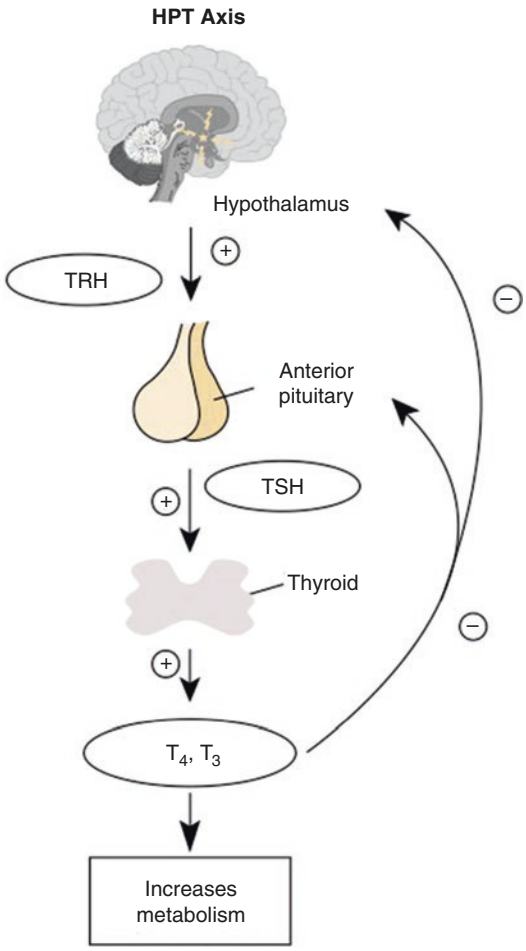


Fig. 18.1 Thyroid feedback loop. The hormones that make up the HPT axis control the metabolic processes of all cells in the body. The secretion of TRH from the hypothalamus activates the pituitary to release of TSH, which in turn promotes the production and release of T4 and T3 by the thyroid gland. Negative feedback effects of T4 and T3 on both the hypothalamus and the pituitary regulate the HPT axis function. Permission: https://embryology.med.unsw.edu.au/embryology/index.php?curid=10638; http://tedct.org.uk

18.5 Pathology

Although the cause of these tumors is unknown, multiple factors such as genetic mutations, overactivation of cell proliferation, and lack of TSH suppression are suspected (Sarapura and Samuels 2017). Defective negative feedback with decreased levels of T3, defective enzymatic deiodination, or increased conversion of T4 to inactive reverse T3 (rT3) may also be pathologic mechanisms. Reverse T3 levels have been found to be significantly elevated in the sera of patients with TSHomas (Greenman 2017). There may also be a relationship between defective TRH suppression and significant elevations in serum levels of free α-subunits (Sarapura and Samuels 2017).

Dopamine and somatostatin both inhibit TSH. TSH tumor cells are also known to express somatostatin receptor subtypes 1, 2, 3, and 5 which present a target for medical therapy (Greenman 2017). Detailed postoperative histopathology reports including this information can help direct medical therapies if needed.

During pituitary cell embryonic development, TSH, Growth Hormone (GH), and prolactin (PRL) are generated from the Prop-1/Pit 1 lineage. Most TSHomas secrete only excess TSH, but up to 1/3rd may co-secrete growth hormone (GH), prolactin (PRL) or have plurihormonal secretion (Greenman 2017; McDermott and Ridgway 1998). Despite co-secretion, few patients appear to present with symptoms associated with co-secreted hormones. Co-secretion may be found clinically and confirmed on microscopic histopathology of tumor samples taken intraoperatively (Tjörnstrand and Nyström 2017).

The majority of TSHomas are macroadenomas (80–90%) that are often found to be invasive. Increased mitotic activity has also been reported based on positive staining on pathology of >3% of cells for p53 and Ki67, although reports vary in this regard (Tjörnstrand and Nyström 2017; Greenman 2017). Prior to the development of sensitive TSH immunoassays, many patients were misdiagnosed and underwent thyroid ablation, which may have contributed to late diagnosis and increased incidence of large and more invasive tumors (Greenman 2017; McDermott and Ridgway 1998).

The patient may present with mild, inappropriately mild (given biochemistry), or severe symptoms of thyrotoxicosis, such as weight loss, nervousness, irritability, easy fatigability,

muscle spasms, intolerance to hot weather, excessive sweating, shakiness and fine motor tremors, palpitations, increased bowel movements, and muscle weakness with loss of muscle mass and bone density. Reports of headaches, changes in vision, and visual field deficits secondary to mass effect as the tumor expands are not uncommon (Greenman 2017) (Fig. 18.2). Symptoms of hyperthyroidism may also be masked by those of co-secreted hormones such as growth hormone or prolactin and include: amenorrhea, galactorrhea, hypogonadism, decreased libido, infertility, breast discomfort or discharge or growth of hand or shoe size, sweating, widening gaps between teeth (Tjörnstrand and Nyström 2017). On physical examination, ophthalmopathy and pretibial myxedema are usually absent or if present orbitopathy may be unilateral (Fig. 18.3). A large goiter is usually present (even after partial thyroidectomy) and skin may be hot, moist, and velvety. Tachycardia and/or atrial fibrillation may be present or symptoms of cardiac failure (Beck-Peccoz et al. 2013, 2015 Brucker-Davis et al. 1999).

18.6 Assessment

Assessment includes biochemical assessment, thyroid ultrasound, and MRI. Both a random serum free T4 (FT4) and TSH should be measured. Serum TSH may be normal or elevated, but free T4 and T3 are significantly elevated and are considered the most sensitive indicator of the presence of a TSHoma (Greenman 2017; Beck-Peccoz et al. 2015). Measurement of glycoprotein hormone subunits (GSU) may reveal an imbalance of α-subunit and β-subunit (GSU) with an elevated α-GSU. This may only be useful in the presence of a macroadenoma (Greenman 2017). An elevated α-subunit/TSH ratio has also been reported as a sensitive indicator of TSHoma in a patient with an intact thyroid (Carmichael 2017). Elevated FT4 and FT3, in the presence of a detectable TSH, rules out Grave's disease and argues for TSHoma (Beck-Peccoz et al. 2015).

In the presence of elevated or detectable TSH with elevated FT4 and FT3 and/or compressive symptoms (headache and visual deficits), a head CT or MRI should be performed to confirm a pituitary tumor. Rare ectopic TSH secretion (usu-

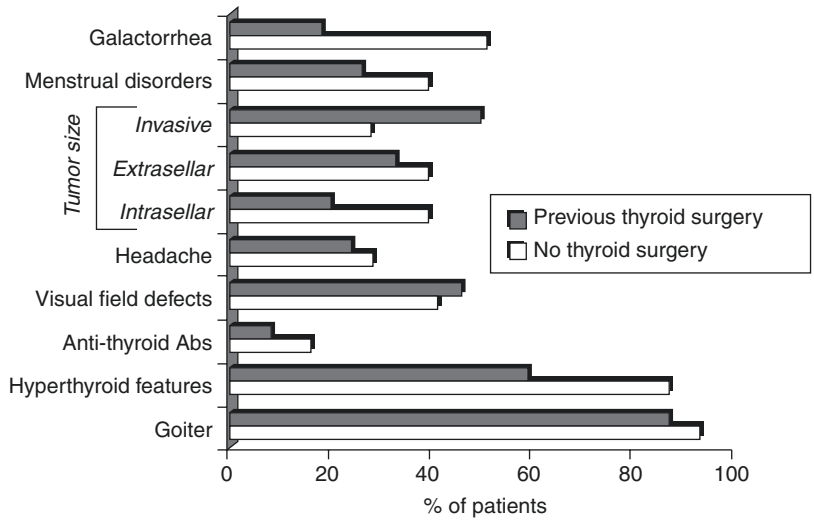


Fig. 18.2 Clinical manifestations in patients with TSH-secreting adenomas. The presence of goiter is indicative of TSHoma, even in patients after partial thyroidectomy. Hyperthyroid features may be overshadowed by those of associated hypersecretion/deficiency of other pituitary hormones. Invasive tumors are seen in about half of the patients with previous thyroidectomy and in 1/4 of untreated patients (permission Beck-Peccoz 2015)

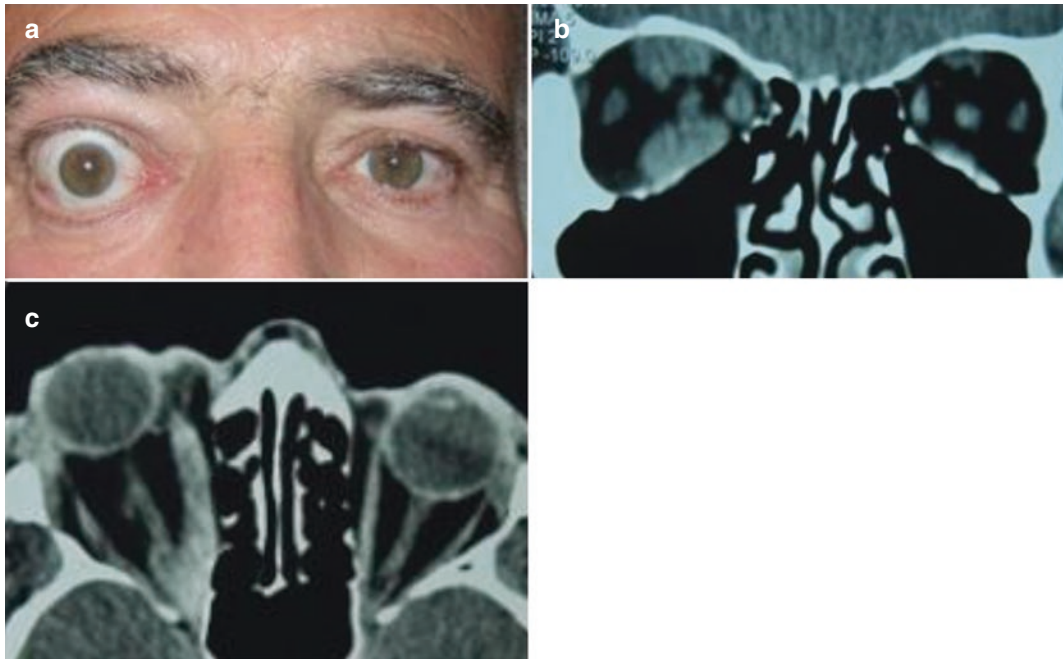


Fig. 18.3 (**a**) right unilateral orbitopathy. (**b**) bilateral orbitopathy (**c**) left orbitopathy. From: Kashkouli MB, et al. Indian J Ophthalmol. 2011 Sep-Oct; 59(5): 363–366. doi: https://doi.org/10.4103/0301-4738.83612. This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported

ally pharyngeal) has been described (Beck-Peccoz et al. 2013). If the lesion on CT/MRI is a microadenoma, resistance to thyroid hormone needs to be considered and an incidentaloma ruled out (Beck-Peccoz et al. 2015). Thyroid ultrasound and fine needle biopsy are recommended for nodular goiter, in consideration of a higher risk of thyroid cancer in TSHomas (4.8% of cases) (Beck-Peccoz et al. 2015). Guidelines suggest that other biomarkers such as cholesterol, LDL, triglycerides, ferritin, erythrocyte microcytosis, resting energy expenditure, and cardiac function parameters are of limited diagnostic value (Beck-Peccoz et al. 2013).

Dynamic testing may be indicated if no defined pituitary or ectopic mass is found or when there is concern for resistance to thyroid hormone. A TRH test and/or T3 suppression test are first-line tests and an octreotide infusion to suppress TSH may be useful. TRH dynamic testing measures the increase in TSH after administration of exogenous TRH, with doubling of baseline levels considered a positive test (Tjörnstrand and Nyström 2017). This test is done infrequently and TRH is no longer available in some countries including the USA (Salvatori et al. 2010). Scintigraphy radiolabeled octreotide scans and PET/CT scans with 68Ga-DOTATOC may be useful in locating a rare ectopic source of TSH (Tjörnstrand and Nyström 2017).

18.7 Treatment

First-line treatment is tumor removal in appropriate cases and suppressive therapy if the patient is not a candidate for surgical options. Surgical tumor resection can achieve a remission rate of 60% in patients with macroadenomas in the hands of an experienced surgeon (Beck-Peccoz et al. 2013, 2015). Although controversial, antithyroid

drugs such as methimazole or propylthiouracil and/or medical suppressive therapies with cabergoline or somatostatin therapy are recommended by some clinicians prior to surgical tumor removal to decrease TSH (Beck-Peccoz et al. 2015).

If TSH remains elevated after tumor removal, medical suppressive therapy is indicated. Although TSHomas express several somatostatin receptors (SSTR 1, 2, 3, and 5), SSTR2 is most frequently expressed in subtypes 2A and 2B (Tjörnstrand and Nyström 2017). First-generation somatostatin ligands/analogues (SSAs) such as octreotide LAR®, lanreotide SR®, or lanreotide Autogel® are recommended for suppressive therapy based on their affinity to act on SSTR2 and SSTR5 receptors (Tjörnstrand and Nyström 2017; Beck-Peccoz et al. 2013). All preparations may not be available in some countries. There is evidence that euthyroidism is restored in up to 90% of cases with goiter and tumor shrinkage achieved in 30 and 40% of cases respectively after medical therapy (Beck-Peccoz et al. 2013). Patients report side effects of treatment including diarrhea and should be monitored for symptoms of cholelithiasis.

Ongoing follow-up is recommended, but data regarding appropriate intervals is scarce (Beck-Peccoz et al. 2013). Likewise there are few reports of recurrence rates and even fewer regarding quality of life in patients after treatment of a TSHoma.

18.8 Nursing Care

Assessment of patient history with emphasis on their past medical history and family history of pituitary, thyroid, or parathyroid tumors is important. Evaluate the patient's and families understanding of the process of medical evaluation and the path to the anticipated diagnosis. This process may be complex if multiple imaging modalities, fine needle biopsy, cardiac and bone evaluations are required. Preparation for some procedures is essential and must be reviewed with the patient in advance. Determine if the patient/family has adequate resources at their disposal and if further support is required in any functional domain.

Patient education may be a staged process, as each test is resulted and the diagnosis is confirmed. Disease-related education along with information and coordination of care for any concomitant diseases revealed in the process of assessment may be indicated. Preparation for surgery and pretreatment with an antithyroid medication involves coordination between the patient and the operative team.

Further assessment postoperatively may reveal persistent TSH secretion, indicating the need for medical therapy. A detailed explanation of the purpose for treatment and treatment options that demonstrate clear value to the patient both with respect to short-term symptoms and long-term outcomes will enhance adherence. SSA therapies are currently injectable, some of which have been shown to be safe and effectively administered at home by the patient or family (Salvatori et al. 2010). Assessment of the patient/family's capacity and willingness to deliver this treatment as prescribed in the home is required in some countries. Drug administration may also involve coordinating home nursing support and/or in office teaching. The treatment plan should evolve as an interaction between patient, family, and all health care providers.

Long-term follow-up will be required. At each visit, assessment of the patient's understanding of the disease and treatment in the context of their changing symptoms and understanding is advised to facilitate self-care. Regular biochemical testing, including liver function testing, TSH and FT4 are recommended. This may need to be done as frequently at least 2–3 times in the first year postoperatively or until the patient is stable (Beck-Peccoz et al. 2013). Ophthalmologic and visual field examinations are recommended as a baseline pre- and postoperatively for patients with a history of large macroadenomas. These may be best obtained in between MRIs that are recommended every 1–2 years at least for the first 5 years postoperatively (Beck-Peccoz et al. 2013). Coordination of follow-up at a location that is convenient for the patient is more likely to result in long-term adherence (Yedinak et al. 2018; Craig et al. 2014).

18.9 Conclusions

Historically, many patients with elevated TSH and symptoms of hyperthyroidism were inappropriately treated with thyroid ablation or thyroidectomy. This may have inadvertently promoted TSHoma growth. With improved ultrasonic techniques and TSH sensitivities and the availability of sophisticated CT/MRI techniques, the incidence and prevalence of the disease has significantly increased but diagnostic accuracy has substantially improved. This has also spurred a substantial increase in research. Despite diagnostic advances, treatment delays are estimated to be over 6 years from the onset of symptoms and over 12 years for patients post thyroid ablation or thyroidectomy. TSHomas are still most often found as macroadenomas and present with symptoms of mass effect and/or thyrotoxicosis.

Treatments include surgical and medical approaches, with surgical removal of the TSHoma as the first choice in therapy. Somatostatin ligands remain the next most effective treatment in cases of residual or recurrent disease. There is limited data about the long-term outcomes and quality of life for these patients, but best outcomes are achieved with early diagnosis and treatment of microadenomas. The minimum follow-up recommendations are for monitoring of MRI and serum biochemistries yearly for the first 5 years postoperatively. However, lifelong intermittent follow-up may be indicated.

References

Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2:76–82. https://doi.org/10.1159/000351007.

Beck-Peccoz P, Lania A, Persani L. Chapter 24: TSH-producing adenomas. In: Jameson JL, DeGroot LJ, editors. Endocrinology. 7th ed. Philadelphia: W.B. Saunders Pub.; 2015. p. 266–74.

Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub BD. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab. 1999;84:476–86.

Carmichael JD. Anterior pituitary failure. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. p329–63.

Cooper DS, Ladenson PW. The thyroid gland. In: Gardner DG, Shoback DM, editors. Greenspan's basic and clinical endocrinology. 9th ed. The McGraw-Hill Companies, Inc.; 2011. p. 170–89.

Craig BM, Reeve BB, Brown PM, et al. US valuation of health outcomes measured using the PROMIS-29. Value Health. 2014;17(8):846–53. https://doi.org/10.4172/clinical-practice.1000386. Review.

Greenman Y. Thyrotropin-secreting pituitary tumors. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 573–88.

McDermott MT, Ridgway C. Central hyperthyroidism. Endocrinol Metab Clin N Am. 1998;27(10):187–203.

Nomura S, Pittman CS, Chambers JB, Buck MW, Shimizu T. Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. J Clin Invest. 1975;56(3):643–52.

Salvatori R, Nachtigall LB, Cook DM, Bonert V, Molitch ME, Blethen S, Chang S, SALSA Study Group. Effectiveness of self- or partner-administration of an extended-release aqueous-gel formulation of lanreotide in lanreotide-naïve patients with acromegaly. Pituitary. 2010;13(2):115–22.

Sarapura VD, Samuels MH. Thyroid-stimulating hormone. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 163–201.

Tjörnstrand A, Nyström HF. Diagnosis of Endocrine Disease: diagnostic approach to TSH-producing pituitary adenoma. Eur J Endocrinol. 2017;177(4):R183–97.

Yedinak C, Pulaski-Liebert K, Adelman DT, Williams J. Acromegaly: current therapies benefits and burdens. Clin Pract. 2018;15(2):499–511.

Key Reading

1. Greenman Y. Thyrotropin-secreting pituitary tumors. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 573–88.
2. Beck-Peccoz P, Lania A, Persani L. Chapter 24: TSH-producing adenomas. In: Jameson JL, DeGroot LJ, editors. Endocrinology. 7th ed. Philadelphia: W.B. Saunders Pub.; 2015. p. 266–74.

19 Prolactin Producing Adenomas: Prolactinomas and Hyperprolactinemia

Christine Yedinak

Contents

19.1 **Introduction** 345

19.2 **Prolactin Physiology** 346
19.2.1 Embryonic Cell Differentiation and Lactotrophs Proliferation 346
19.2.2 Prolactin Production 347
19.2.3 Prolactin Variants 348
19.2.4 Prolactin Receptor Activity 348

19.3 **Causes of Elevated Prolactin** 350
19.3.1 Physiologic 350
19.3.2 Pharmacologic 351
19.3.3 Pathologic 351

19.4 **Tumor Recurrence** 358

19.5 **Quality of Life (QoL)** 358

19.6 **Nursing Care Summary** 359
19.6.1 Assessment 359
19.6.2 Diagnosis 359
19.6.3 Implementation 360
19.6.4 Evaluation 360

References 361

Abstract

Prolactinomas (PPAs) are the most common type of secretory pituitary adenomas. The majority of prolactinomas are found in women on evaluation of amenorrhea, infertility, and new onset or persistent lactation after discontinuation of breastfeeding. Although galactorrhea may also be a sentinel symptom in males, this is not as common, and is often preceded by sexual dysfunction. Diagnosis may not occur, particularly in males or postmenopausal women, until midlife when tumor growth impacts the optic chiasm and/or visual deficits are found, prompting ophthalmology review and subsequent imaging. Likewise, pituitary adenomas may be an incidental finding on a head CT or MRI obtained during a workup for headaches, after a head trauma, or other symptoms.

C. Yedinak (✉)
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_19

In addition to a brain MRI to determine tumor size, location, and characteristics, all pituitary hormonal expressions are usually evaluated. Both macroadenomas (MA) and microadenomas (mA) may cause anterior pituitary hormone deficits, and further dynamic testing may be needed. Posterior pituitary hormone deficits are quite rare and would only occur with very large tumors. Prolactin (PRL) assays may vary, so obtaining a diluted PRL level is necessary when levels are high in patients with large tumors (usually >3 cm diameter) to avoid misinterpretation of results secondary to the assay "hook effect." Evaluation of macroprolactin (biologically inactive PRL) may also be needed in patients without symptoms in order to avoid unnecessary treatment.

Treatment may depend on presenting symptoms and deficiencies. However, prolactinomas are most frequently responsive to dopamine agonist (DA) medications that both normalize prolactin levels and can shrink tumors. Normalization of PRL most often restores fertility, resolves galactorrhea, and significantly improves headaches. Likewise, visual deficits will often resolve or significantly improve with tumor shrinkage. Intolerance or resistance to dopamine agonists, tumor growth while on dopamine agonists, co-secretion with another hormone or a need for a biopsy for histopathology are criteria for transsphenoidal tumor resection. Best postoperative results are achieved by an experienced neurosurgeon. However, treatment with medical therapies (DA), other hormone replacements, or radiation therapy may still be needed postoperatively to control prolactin levels or residual tumor growth.

Keywords
Prolactin · Prolactinoma · Hyperprolactinemia
Hypogonadism · Infertility · Galactorrhea

Abbreviations

AP	Anterior pituitary
DA	Dopamine agonist
FSH	Follicle stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
ICD	Impulse control disorder
LH	Luteinizing hormone
MA	Macroadenomas/adenomas >1 cm
mA	Microadenomas/adenomas <1 cm
MRI	Magnetic resonance imaging
PA	Pituitary adenoma
PPA	Prolactin producing adenoma/ prolactinoma
PRF	Prolactin releasing factors
PRL	Prolactin
QoL	Quality of life

Key Terms

- **Prolactin receptor:** is a cell surface molecule to which prolactin binds, causing attachment to a second receptor that changes the configuration of the cell membrane and allows the movement of prolactin into the cell.
- **Prolactin transcription:** is the first step in encoding the RNA within the cell with the functional instructions from the prolactin DNA molecule.
- **Dopamine inhibition:** occurs when dopamine, manufactured in the hypothalamus, travels down neuronal projections into the pituitary gland. It is released and attaches to dopamine-2 (D2) receptors on lactotrophs in the pituitary inhibiting the production of dopamine.
- **Dopamine agonists:** act on the D2 receptors on lactotrophs to inhibit the production of prolactin from the pituitary.
- **Hyperprolactinemia:** occurs when the blood levels of prolactin are above the normal range. The normal range is gender specific.
- **Hypogonadism:** occurs when GnRH and subsequent LH/FSH release from the pituitary is suppressed resulting in ovarian or testicular dysfunction.

Key Points

- Prolactin is a hormone with a primary role in lactation but a broad range of biologic activity.
- Hyperprolactinemia has a range of physiologic, pharmacologic and pathologic etiologies.
- Prolactinomas occur in children and adults of all ages.
- Dopamine agonists are effective and are recommended as first line medical treatment for prolactinomas.
- Macroprolactinomas are more common in adolescent boys, women after menopause and older men and have a high lifetime rate of recurrence.
- Surgery and radiation therapy are only required to treat prolactinomas when first line treatment fails.

19.1 Introduction

Understanding of the role of PRL in lactation began emerging in the late 1920s, and by 1950s it was demonstrated that PRL secretion was inhibited by dopamine from the hypothalamus. However, isolation of the hormone PRL in humans did not occur until around 1971 (Grattan 2015).

Normal lactotrophs or prolactin producing cells make up an estimated 15–50% of all the anterior pituitary cells in males and females (Gillam and Molitch 2011a). Inhibition of prolactin production largely stems from dopamine release by the hypothalamus that travels down the portal venous system and attaches to the D2 receptors in the pituitary (Melmed et al. 2011). There are PRL releasing factors as well.

The major function of PRL is to promote lactation in humans, but it is also involved in numerous other adaptive functions in various systems in animals (Grattan 2015). During pregnancy, hyperplasia of the lactotrophs occurs which substantially increases the PRL level, promoting proliferation of the mammary glands and lactation. This level is sustained through breastfeeding, and will slowly return to normal after delivery and cessation of breastfeeding (Klibanski 2010).

Hyperprolactinemia can occur related to disruption of the pituitary stalk (such as in the case of a large macroadenoma) due to decreased dopamine reaching the lactotrophs, from over production from a PRL adenoma cell overproduction (prolactinoma) in the pituitary, poor clearance of prolactin (particularly macroprolactin), and/or other drug effects (Romijn 2014). Some herbal preparations such as Milk Thistle (not Blessed Thistle) and Fennel have been shown to increase PRL in clinical studies. Signs and symptoms associated with elevated prolactin are similar, despite the etiology of the elevation. Hypogonadism and infertility commonly result from elevated PRL levels in both sexes.

Prolactinomas comprise approximately 50–66% of all pituitary adenomas, are frequently microadenomas and more common in woman between 20 and 50 years (Molitch 2017). Diagnostic criteria for a prolactinoma are elevated blood levels of prolactin and the presence of a pituitary tumor on MRI (Melmed et al. 2011). Although prolactinomas are also found in children, they are rare, being more common in females during adolescence (Salenave et al. 2015; Hoffmann et al. 2018).

High PRL levels can be accompanied by symptoms such as headaches, menstrual abnormalities and galactorrhea (lactation) or visual deficits (Gillam and Molitch 2011a; Romijn 2014; Molitch 2017). Restoration of fertility, relief of symptoms, and tumor shrinkage can usually be achieved with dopamine agonist therapies (DA) which is most often first line therapy. Transsphenoidal surgery may be necessary in cases resistant to DA, when CSF leak develops and/or in cases with a large aggressive tumor not responding to the DA. There remains ongoing debate regarding the need for lifelong treatment, the cost-effectiveness of DA therapies versus surgical resection, and the risks and benefits of both surgery and long-term treatment (Gillam and Molitch 2011a; Romijn 2014; Molitch 2017; Ikeda et al. 2013; Jethwa et al. 2016; Zygourakis et al. 2017).

19.2 Prolactin Physiology

Prolactin is produced in lactotroph cells of the pituitary gland. Primarily associated with lactation, recent studies are revealing that prolactin is also produced in numerous extra pituitary tissues, such as the endothelial cells, mammary cells, the decidua, immune cells, skin and hair follicles, adipose tissue, the cochlea, the brain, the thymus, and more (Marano and Ben-Jonathan 2014). In fact, PRL may be produced in most tissues and either independently or cooperatively have a wide range of regulatory and biologic functions, although these other functions in humans are of uncertain physiologic significance (Marano and Ben-Jonathan 2014). PRL exerts its effects in an autocrine, paracrine, and/or endocrine fashion by attaching to a diversity of prolactin receptors expressed in various tissues including in the pituitary gland itself (Ignacak et al. 2012).

19.2.1 Embryonic Cell Differentiation and Lactotrophs Proliferation

During embryonic development, there is continual interaction between the hypothalamus and the pituitary during which transcription factors are produced that determine the differentiation of cell lines in the pituitary (Gillam and Molitch 2011a). Prophet of Pit-1 (Prop1) gene/transcription factor controls the development of all non-corticotroph cells including PRL, whereas POU1F1 (Pit-1) transcription factor is necessary for the development and proliferation of thyrotrophs and somatomammotrophs. The differentiation of somatomammotrophs to somatotrophs and lactotrophs and proliferation of lactotrophs occurs under the influence of estrogen (Gillam and Molitch 2011a). Transcription factor Pit-1 and other factors also regulate the cellular level synthesis of PRL. Pit-1 interacts with other regulatory proteins, specific DNA elements, and target promotors of the gene altering the structure of the signal that either allows or inhibits transcription and thereby influencing PRL production (Gillam and Molitch 2011a) (Fig. 19.1). The structure of PRL is similar to that of GH with many lactotrophs arising for GH cells and approximately 25% of GH adenomas co-secreting prolactin (Bernard et al. 2015; Grossman and Besser 1985). Lactotrophs comprise 10–50% of all adenohypophyseal cells, are reported to be similar in number for both genders, and remain relatively stable with age in women but may decrease in men (Gillam and Molitch 2011a; Romijn 2014).

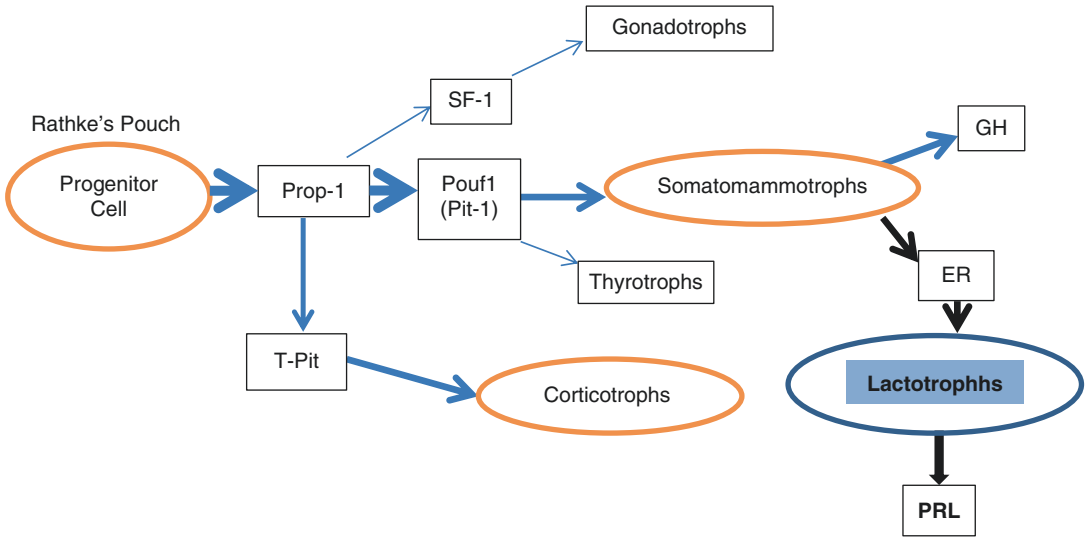


Fig. 19.1 Cell differentiation: Mammotrophs Prop-s and Pouf1 (Pit-1) are transcription factors that differentiate cell lineage. Estrogen stimulates the final differentiation of somatomammotrophs to lactotrophs (mammotrophs)

19.2.2 Prolactin Production

19.2.2.1 Dopamine Inhibition

The hypothalamus controls the secretion of PRL from the pituitary lactotrophs by using an inhibitory mechanism that is different than the control mechanisms of other anterior hormone production, which is predominantly stimulatory. Tonic basal PRL control is achieved through neuronal dopaminergic inhibition, which is considered the chief prolactin inhibiting factor, although other factors such as GABA may be contributory (Grattan 2015; Gillam and Molitch 2011a; Grossman and Besser 1985). Dopamine is manufactured in cell bodies in the arcuate nucleus of the hypothalamus, and delivered to the median eminence where it is released into the proximal portal vessel plexus and then transported down the portal vessels of the infundibulum (pituitary stalk) to the lactotrophs where it inhibits prolactin production (Fig. 19.2) (Grattan 2015). Prolactin itself may also provide some negative feedback to limit its

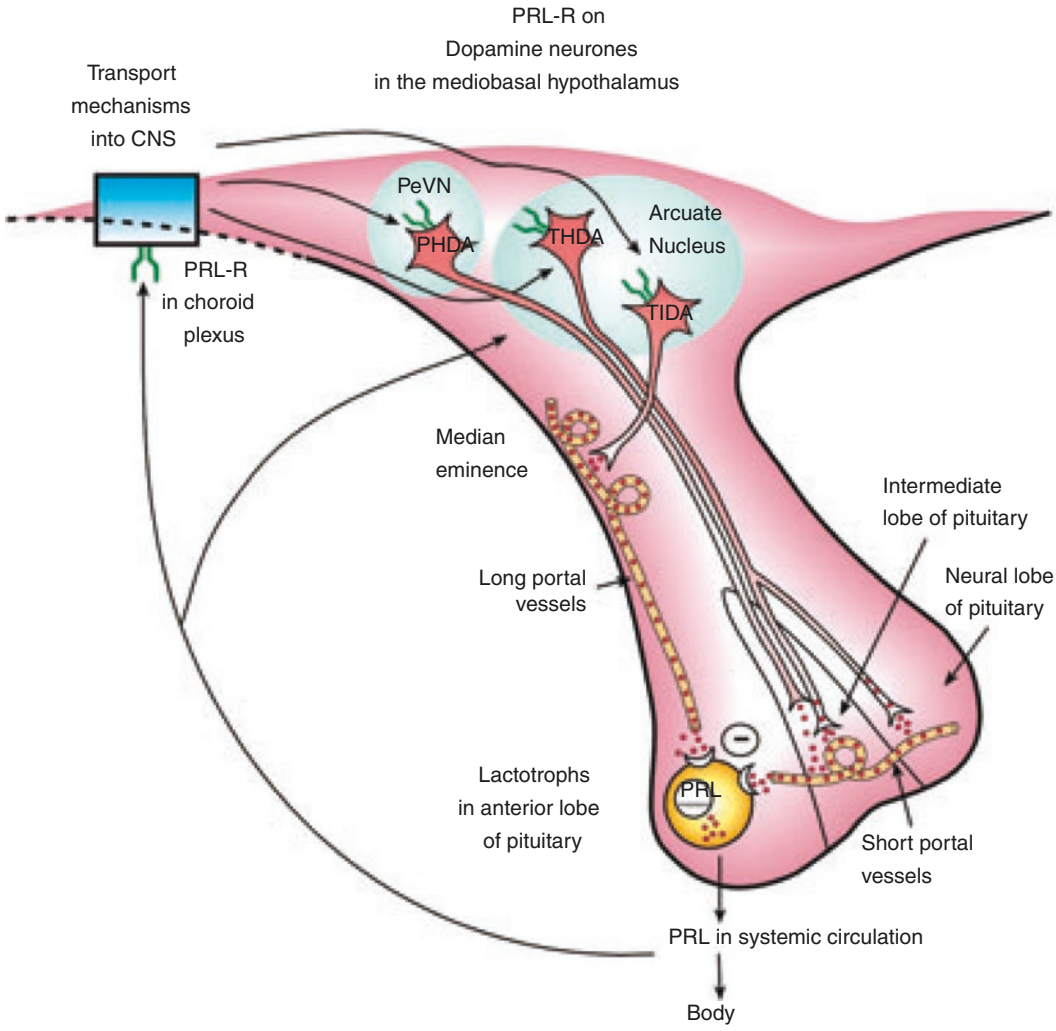


Fig. 19.2 In most conditions, the secretion of prolactin (PRL) from the anterior pituitary gland is predominantly under inhibitory control from the hypothalamus. Dopamine released from the Arcuate Nucleus in the median eminence of the hypothalamus travels down the pituitary stalk to attach to D2 receptors on lactotroph cells in the anterior pituitary inhibiting PRL production. From: Andrews ZB. Neuroendocrine Regulation of Prolactin Secretion During Late Pregnancy: Easing the Transition into Lactation. Journal of Neuroendocrinology, 2005, Vol. 17, 466–473. Figure 1. P 467. Copyright Permission: John Wiley and Sons

own production by attaching to prolactin receptors on dopamine neurons to control its own production in a tonic or basal fashion, although this has only been shown in animals (Grattan 2015).

19.2.2.2 Prolactin Releasing Factors (PRFs)

Prolactin Releasing Factors (PRFs) mediate rapid and slow prolactin release under demand conditions such as pregnancy, lactation, and/or physiologic stress (Low 2016). This mechanism maintains tight homeostatic control of blood levels of PRL1. Thyrotropin releasing Hormone (TRH) causes rapid release of PRL in human studies. The neuropeptide Vasoactive Intestinal Peptide (VIP) when released from the median eminence of the hypothalamus, has an additive effect to TRH to stimulate pituitary PRL secretion (Gillam and Molitch 2011a). Other PRFs include serotonin, opioids, and possibly other neuroactive peptides and neurotransmitters still under investigation in humans. PRL levels also rise as a result of the blockade or suppression of dopamine inhibition by neuroleptic and other drugs that block the dopamine receptor (Low 2016).

Pulsatile secretion of PRL occurs in a sleep dependent circadian pattern with highest levels being produced during non-REM sleep independent of breast stimulation (Gillam and Molitch 2011a; Dk et al. 1985). Lower pulse amplitude secretions occur during awake hours.

19.2.3 Prolactin Variants

Pituitary PRL is an anterior pituitary polypeptide hormone composed of 199 amino acids and produced by pituitary lactotroph cells (Gillam and Molitch 2011a). PRL is encoded by a single gene. However, a number of prolactin variants are known (Bernard et al. 2015). Many variants result from posttranslational changes associated with processes such as phosphorylation, glycosylation, sulfation, and deamidation causing structural changes to the PRL protein, impacting its end function or biological activity (Bernard et al. 2015). The majority of circulating pituitary prolactin is in the form of small or monomeric prolactin (molecular weight of 23 kDa) but both "big"(a covalently bound dimer of prolactin with a molecular weight 48–56 kDa), and "big big" (molecular weights >100 kDa) forms of prolactin have been found in plasma and in the pituitary gland (Romijn 2014; Bernard et al. 2015; Freeman et al. 2000). These heteromers and PRL complexed with immunoglobulins may cause an accumulation of large prolactin moieties termed "macroprolactin." These are less biologically active forms of prolactin.

Other PRL variants such as 14 kDa, 16 kDa, and 22 kDa are the result of cleavage of the "small" 23 kDa protein which is thought to happen outside the cell. These variants subsequently act at PRL receptor sites to independently or synergistically regulate target tissue activities such as in the retina, myocardium, chondrocytes, and mammary gland in animal studies (Bernard et al. 2015). Some studies have shown that 16 kDa PRL isoform has potent antiangiogenic and antitumoral effects and several researchers have connected 16 kDa PRL with peripartum cardiomyopathy and impaired cardiac capillary function (Bernard et al. 2015; Horseman and Gregerson 2014; Hilfiker-Kleiner et al. 2006, 2012; Dalzell et al. 2011).

19.2.4 Prolactin Receptor Activity

The PRL molecule attaches to receptor sites not only in the mammary glands but in diverse tissues. This attachment recruits and binds to a second receptor which changes the membrane conformation and PRL is transported into the cell. Although some forms of PRL use different cell signaling pathways, monomeric 23 kDa PRL transmits instructions to the cell nucleus for gene transcription, (cell proliferation or inhibition) via what is known as Janis Kinase 2-Signal Transduction and Activator of Transcription 5 (JAK2-STAT5) signaling pathway (Fig. 19.3) (Ignacak et al. 2012; Gorvin 2015). Instructions for both cell and receptor site proliferation are required for mammary gland development and lactation. This requires the cooperative activities of estrogen, progesterone, and other growth factors (Romijn 2014; Gorvin 2015). In the same way, PRL also affects fertility by inhibiting gonadotropin secretion and downstream testosterone production in men and egg development,

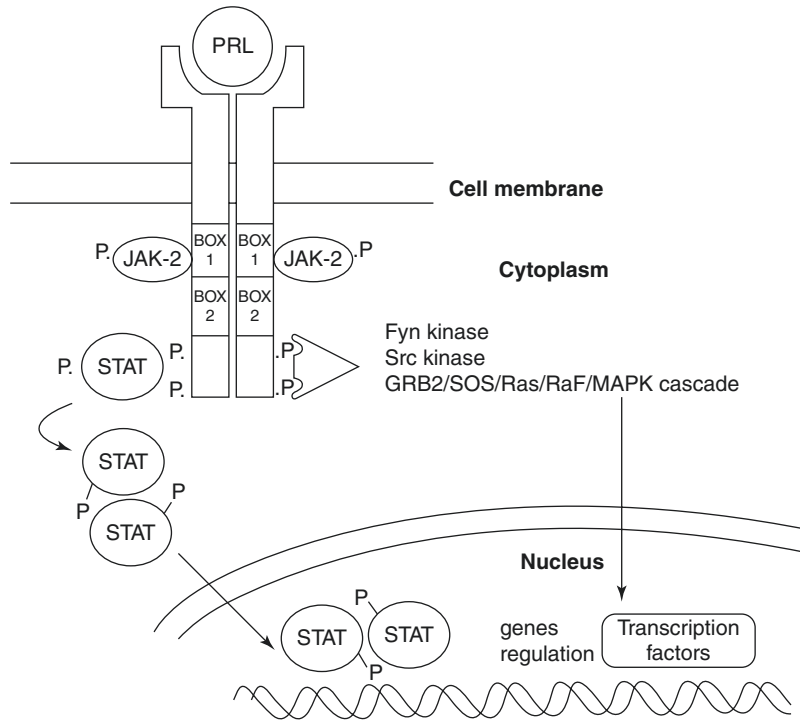


Fig. 19.3 Signal transduction pathways of the prolactin receptor activation. Prolactin effects target tissue changes by attaching to cell membrane receptors which activates a JAK-2/STAT cascade. This is transcribed in the cell nucleus to regulate gene expression. Ignacak A, Kasztelnik M, Sliwa T, Korbut RA, Rajda K, Guzik TJ. Prolactin - not only lactotrophin a "new" view of the "old" hormone. J Physiol Pharmacol. 2012 Oct;63(5):435–43. Fig. 2. p437. Reprinted with permission

ovulation, and blastocyst implantation in women (Gorvin 2015). PRL receptor site isoforms or mutations in different tissues could potentially affect the downstream signaling and ultimately alter the function(s) of PRL (Ignacak et al. 2012). Increased expression of PRL receptors and/or alterations in the JAK2-STAT5 signaling pathway have been implicated in tumorigenesis or tumor progression and have generated particular research interest with respect to the development of breast cancer (Bernard et al. 2015; Gorvin 2015). There is also much interest in the association of tumor invasiveness with the interaction between PRL and estrogen receptors.

19.2.4.1 Prolactin Receptors Expression

PRL receptors have been found to be expressed in most tissues. In mouse models they are highly expressed in the pancreatic B cell, impacting glucose-mediated insulin secretion, particularly during pregnancy. It is hypothesized that this mechanism may be associated with gestational diabetes in humans, but current evidence is not convincing (Gorvin 2015). Increased adipose tissues and changes in fat storage distribution, leptin and adiponectin levels have also been demonstrated in mice when PRL levels are increased during pregnancy (Gorvin 2015). Likewise, weight gain and insulin resistance have also been demonstrated in hyperprolactinemia in humans (Gillam and Molitch 2011a). PRL receptors expressed on leukocytes in the spleen and thymus suggest a role in the immune system function by enhancing T-cell activation and proliferation (Gorvin 2015). In humans, elevated prolactin levels have been found in patients with immune diseases such as lupus, rheumatoid arthritis, psoriasis, Sjogren's syndrome, uveitis, and multiple sclerosis, diseases that have been improved with therapy to lower PRL levels (Gillam and Molitch 2011a). Bone mass was also found to be decreased in hyperprolactinemic women that normalized with treatment to lower PRL levels but appears to be mediated primarily by the restoration of normal estrogen levels (Klibanski 2010). In mammals, prolactin has also been shown to reduce Na + and K+ renal excretion and adenosine triphosphatase activity, thereby affecting osmoregulation and, in particular, affecting human amniotic fluid transport (Ignacak et al. 2012).

19.3 Causes of Elevated Prolactin

Elevated prolactin (hyperprolactinemia) can be related to physiologic, pharmacologic, or pathologic causes including poor renal prolactin clearance. Hyperprolactinemia is idiopathic in up to 40% of cases (Romijn 2014; Ignacak et al. 2012; Majumdar and Mangal 2013). Normal physiologic causes are adaptive such as pregnancy and lactation (milk production). Other causes, particularly pathologic etiologies, effect biologic change and dysfunction (Grattan 2015) (Table 19.1).

19.3.1 Physiologic

Physiologic hyperprolactinemia is a response to pregnancy, nipple stimulation, exercise, and stress (Romijn 2014). The dominant physiologic role of prolactin in women is the development of the mammary glands in pregnancy and lactogenesis (milk production). Estrogen, progesterone, placental lactogen, insulin growth hormone, and cortisol also play a synergistic role (Gillam and Molitch 2011b). Recent studies have shown that the PRL level doubles from pre-pregnancy levels in the first trimester, during which time the size of the pituitary gland itself enlarges. PRL levels continue to climb to over 30 times above baseline with highest levels 24–48 h after delivery (vaginal or cesarean section) (Hu et al. 2017). Levels decrease again to normal in the first week postpartum in the absence of breastfeeding or are maintained throughout breastfeeding (Klibanski 2010; Cocks Eschler et al. 2018). An early study demonstrated that PRL levels in breastfeeding mothers during the first 6 weeks postpartum peak to 8.5 times baseline with suckling. After this time, and at least through to 28 week period of the study, prolactin levels normalized but increased to an average of 6 times baseline with suckling (Noel et al. 1974). Mothers who used a breast pump experienced similar elevated PRL levels after pumping.

Current evidence, from animal models, suggests that low maternal PRL levels at the end of pregnancy and high prolactin levels in the early postpartum period may negatively affect maternal nurturing behavior and may also be a factor in

Table 19.1 Etiology of hyperprolactinemia

Physiological	**Pituitary**	**Other**
Coitus	Acromegaly	Surgery
Exercise	Idiopathic	Trauma
Lactation	Lymphocytic hypophysitis or parasellar mass	Systemic disorders
Pregnancy	Macroadenoma (compressive)	Chest—neurogenic chest wall trauma, surgery, herpes
Sleep	Macroprolactinemia	Zoster
Stress	Plurihormonal adenoma	Chronic renal failure
Menses		
Pathological	Prolactinoma	Cirrhosis
Hypothalamic-pituitary stalk damage	Pituitary	Cranial radiation
Granulomas	Acromegaly	Epileptic seizures
Infiltrations	Idiopathic	Polycystic ovarian disease
Irradiation	Lymphocytic hypophysitis or parasellar mass	Surgery
Rathke's cyst	Macroadenoma (compressive)	Trauma
Trauma: pituitary stalk section, suprasellar surgery	Macroprolactinemia	Systemic disorders
Tumors: craniopharyngioma, germinoma, hypothalamic	Plurihormonal adenoma	Chest—neurogenic chest wall trauma, surgery, herpes
Metastases, meningioma	Suprasellar pituitary mass extension	Zoster
		Chronic renal failure

Ref: Melmed S, Kleinberg D 2008 Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR eds. Williams textbook of endocrinology 11th ed. Philadelphia: Saunders Elsevier; 185–261

poor transgenerational nurturing behaviors in offspring (Sairenjia et al. 2017; Mitani et al. 2018). Higher levels during pregnancy not only support lactation but play a significant role in inhibiting pregnancy during breastfeeding by suppressing gonadotropin release and thereby, ovulation (Majumdar and Mangal 2013).

Vigorous exercise induced elevations of PRL have been reported to briefly increase prolactin levels, especially under the influence of serotonin in depressed subjects (E et al. 2004; Noel et al. 1972). Other studies reported increased core body temperature and not exercise per se significantly increases PRL levels (Chang et al. 1986).

Major stress such as surgery and severe illness has been shown to transiently increase prolactin levels up to an average of 2–5 times baseline. Smaller increases were found after minor procedures, such as during colonoscopy and venipuncture (Melmed et al. 2011; Gillam and Molitch 2011b; Noel et al. 1972). With prolonged stress, levels decrease.

19.3.2 Pharmacologic

Pharmacologic causes are numerous and must be considered, particularly when the patient presents with no classical clinical symptoms associated with hyperprolactinemia and other causes (pregnancy, renal failure, hypothyroidism, and macroprolactin) have been excluded. Close scrutiny of the patient's history and concomitant medications is recommended (Table 19.2). To confirm a pharmacologic etiology, if possible, the offending medication should be withdrawn for 3–4 days and PRL rechecked (Molitch 2005). Withdrawal of antipsychotic and anti-depressive therapies requires consultation with the patient's psychiatric provider. Treatment options include discontinuing or switching from the offending agent to another therapeutic option.

Table 19.2 Drugs that interfere with dopaminergic function

Class	Drug
Major Tranquillizers	Thiazides Butyrophenones
Antipsychotics	Phenothiazines Haloperidol Amisulpride *Atypical* Risperidone Molindone
Antidepressants	*Serotonin Reuptake Inhibitors* (SSRIs) (minimal) *Tricyclics* Amitriptyline Desipramine Clomipramine *Monoamine oxidase inhibitors* Pargyline Clorgyline
Antihypertensives	Verapamil Methyldopa
Dopamine receptor blockers	Reserpine Alcohol Cocaine Heroin
Prokinetics (GI motility)	Metoclopramide (Reglan) Domperidone Diabeticorum
Serotonin 5-HT3 receptor antagonists	*Proton Pump Inhibitors (PPIs)* Omeprazole
Estrogens	Oral contraceptives
Opiates	Morphine

Ref: Molitch, Molitch (2005); and Chahal and Schlechte (2008)

19.3.3 Pathologic

Pituitary adenomas producing excess prolactin are the main cause of pathologic hyperprolactinemia. This may be the result of PRL receptor and/or transcription mutations and alterations in prolactin stimulating factors that inhibit dopamine tone (Glezer and Bronstein 2015). Systemic diseases such as liver failure, ACTH dependent Cushing's disease, and hypothyroidism can be contributory. Large sellar masses and inflammatory disorders that impinge on the pituitary stalk can interrupt dopaminergic inhibition of prolactin production causing serum PRL levels to rise (Klibanski 2010; Romijn 2014; Chahal and Schlechte 2008).

Poor renal clearance of prolactin causes elevated serum prolactin, particularly in chronic renal failure or related to the presence of large molecular weight prolactin. "Big" prolactin (a covalently bound dimer of prolactin with a molecular weight 48–56 kDa) and "big big"

(molecular weights >100 kDa) forms of prolactin have been found both in plasma and in the pituitary gland (Romijn 2014; Bernard et al. 2015; Freeman et al. 2000). These macroprolactins are aggregate forms of prolactin or complexes of PRL and IgG that are less biologically active and usually do not cause clinical symptoms. However, they can confound clinical diagnosis (Klibanski 2010; Bernard et al. 2015; Freeman et al. 2000; Gillam and Molitch 2011b). Women with macroprolactinemia may present with menstrual irregularities. Therefore, measurement of the bioactive monomeric prolactin is recommended using subfractionation (polyethylene glycol (PEG) precipitation) to avoid unnecessary treatment (Romijn 2014; Bernard et al. 2015; Gillam and Molitch 2011b; Olukoga and Kane 1999). Approximately 10–20% of patients presenting with hyperprolactinemia are found to have macroprolactinemia (Chahal and Schlechte 2008; Olukoga and Kane 1999; Smith et al. 2007).

19.3.3.1 Prolactinoma

Prolactinomas are benign pituitary tumors producing excess prolactin, resulting in hyperprolactinemia. They represent up to 66% of all pituitary adenomas (Grossman and Besser 1985; Cocks Eschler et al. 2018). Prevalence is estimated at 400–500 cases per million, with higher prevalence in females of childbearing age between 20 and 50 years than in men 10:1 (Ciccarelli et al. 2008; Chanson and Maiter 2017). Postmenopausal prevalence is similar for females and males but males tend to have larger and more aggressive tumors (Cocks Eschler et al. 2018).

Prolactinomas are classified by size with microadenomas (mA) being <10 mm and Macroadenomas (MA) >10 mm. In women with prolactinoma, 60% are found to have mA (Glezer and Bronstein 2015). MA have an estimated prevalence of 100 per million but a ratio of 1:8–9 females to males (Chanson and Maiter 2017). Prolactin levels correlate with tumor size with higher levels associated with larger tumors. Cancerous or malignant PPAs are extremely rare and estimated to represent one-third of the 0.1–0.2% occurrence of all malignant pituitary adenomas (Glezer and Bronstein 2015; Chanson and Maiter 2017).

The pathogenesis of prolactinomas is not fully understood, however, as in most pituitary adenomas, PPAs are monoclonal. It is hypothesized that PPAs develop as the result of a cascade of events that include genetic translational mutations, microRNA alterations, and/or epigenetic changes (Chanson and Maiter 2017). Aggressive PPAs may result from disinhibition of proliferation, lack of sensitivity to inhibitory signals, or lack of cell apoptosis (cell death) (Chanson and Maiter 2017).

Giant prolactinomas are defined as PPAs with the greatest diameter 40 mm or greater, with suprasellar extension and a baseline PRL level of more than 100 ng/L (Chanson and Maiter 2017). These tumors are more prevalent in adolescent boys and middle aged males.

19.3.3.1.1 Signs and Symptoms of Prolactinoma

Most commonly, patients present with symptoms of hypogonadism secondary to the suppression of pulsatile GnRH and subsequent low expression of pituitary gonadotrophs (LH/FSH), testosterone and decreased ovulation (Majumdar and Mangal 2013). Therefore, women present more frequently with oligomenorrhea, amenorrhea, and infertility. Males often present with erectile dysfunction. Both genders present with poor libido, although elevated prolactin may go undiagnosed in males much longer than females. After the age of 50, hypogonadism is often attributed to age and therefore this may further delay the correct diagnosis (Klibanski 2010; Chanson and Maiter 2017). Galactorrhea is more common in women, is not independently diagnostic of a prolactinoma and may not even be present, as estrogen and progesterone are required to prime lactation (Glezer and Bronstein 2015). Conversely, isolated galactorrhea may occur in the context of normal PRL if increased breast sensitivity to lactotrophic stimulation is present, increasing the clinical challenge in diagnosis (Chanson and Maiter 2017). As a result of prolonged hyperprolactinemia resulting in amenorrhea and chronic estrogen suppression, osteopenia and osteoporosis may develop

(Klibanski 2010). Decreased bone mass and anemia also occur in males secondary to low testosterone (Klibanski 2010). Headache is a common presenting symptom regardless of the size of tumor but is more common in men with larger tumors, as are visual changes and visual field deficits (Klibanski 2010).

Approximately 10–15% of patients with macroadenomas present with quadratic visual field deficits due to compression of the optic chiasm. Ophthalmoplegia (eye muscle paralysis) with the involvement of cranial nerves III, IV, and VI is present in approximately 10% of MA with cavernous sinus invasion (Chanson and Maiter 2017). Headaches, in clusters, are common in these patients, particularly when the tumor extends into the cavernous sinuses (Chanson and Maiter 2017).

19.3.3.1.2 Diagnosis

In the presence of symptoms, a serum prolactin level greater than 100 μg/L is suggestive of prolactinoma, and levels >250 μg/L and in particular >500 μg/L are indicative of a MA (Melmed et al. 2011; Gillam and Molitch 2011b). Levels <40 μg/L may be elevated by medications, chest stimulation, or stress. However, medication associated elevations can be as high as 200 μg/L. Impact of a tumor or disruption to the pituitary stalk can likewise present with high PRL, but usually <100 μg/L (Melmed et al. 2011). This is known as stalk effect.

Hyperprolactinemia in the context of associated symptoms warrants a gadolinium enhanced brain magnetic resonance imaging (MRI) to evaluate the presence, size, and location of a pituitary tumor, and to provide confirmation of a diagnosis of prolactinoma. If the tumor on MRI is shown to be compressing the optic chiasm, then formal visual field testing should be done. Surgical pathology is rarely needed (Cocks Eschler et al. 2018).

19.3.3.1.3 Measurement of Prolactin: Laboratory Assay

A venous blood sample is drawn to assess prolactin levels. Although dynamic tests have been employed in the past using provocative agents such as thyrotropin releasing hormone (TRH), chlorpromazine, levodopa domperidone and insulin induced hypoglycemia, these tests are now largely abandoned due to lack of specificity, expense, and effort (Chahal and Schlechte 2008). However, a repeat level is indicated to confirm PRL results in the event of a minimal increase (Gillam and Molitch 2011b).

Serum PRL has been shown to rise rapidly, although minimally in some subjects after breast stimulation or manipulation. Avoidance of these activities prior to drawing a PRL level is recommended. Vigorous exercise, high stress prior to a blood draw and/or the stress of venipuncture may also minimally increase levels (Melmed et al. 2011). Evaluation of renal and thyroid function and the possibility of pregnancy in sexually active females of child bearing age may need to be concurrently evaluated (Klibanski 2010).

Timing of blood draws may have an impact on PRL levels. Serum PRL level varies during the day, with highest pulsatile production occurring during sleep (Dk et al. 1985). Nadir levels occur around midday or 3–4 h after waking (Spiegel et al. 1994). To avoid medication effects, withdraw known confounding medications at least 3–4 days or more prior to the blood draw. Fasting is not required. However, there is some data that indicates higher PRL levels immediately after eating and with increased body temperature after vigorous exercise (Christensen et al. 1985). An early study found that normal levels for females were significantly higher than for males 1–25 ng/ml vs 1–20 ng/ml, respectively (Kleinberg et al. 1977).

Assay methodologies, reference ranges, and reporting units vary between laboratories and may impact comparison or trending of results (Farzami and Aliasgharpour 2017). A sandwich type 2 site immunoradiometric (IRMA) or chemiluminometric assay is preferred in clinical laboratories secondary to higher sensitivity. It is referenced to the fourth IS (2016 International Standard) 83/573 set by WHO (Medicines and Healthcare Regulatory Agency 2016). In this test, the PRL molecules become sandwiched between antibody layers, unbound PRL is washed off, and the level read. However, in some patients with very high PRL levels due to very large tumors

(>3 cm), the PRL (antigen) binding to the antibody is overwhelmed and only the remaining unbound prolactin is measured, resulting in a falsely low PRL measurement (Gillam and Molitch 2011b; Comtois et al. 1993). This is known as the "Hook Effect." A diluted prolactin assay is recommended to avoid false negative results associated with the effect reported using international standardization (IS) units-μg/L (Jeffcoate et al. 1986).

To test for macroprolactin, a polyethylene glycol precipitation method (PEG) or the gold standard method of gel filtration chromatography is used (Farzami and Aliasgharpour 2017).The latter is reportedly slow, costly, and labor intensive. Using PEG precipitation, monomeric 23 kDa PRL is separated from immunoglobulins that form "big" and "big big" forms of PRL to allow accurate evaluation of prolactin levels for clinical interpretation.

19.3.3.1.4 Treatment

Treatment is indicated for hyperprolactinemia in the presence of symptoms, and when MRI indicates a pituitary MA or an enlarging tumor (Klibanski 2010) (Table 19.3).

The Endocrine Society guidelines (2011) recommend that patients with Ma, no symptoms, and minimal PRL elevations be monitored with 1–2 yearly interval PRL levels and MRI, given current evidence of low risk of tumor growth (Melmed et al. 2011; Klibanski 2010). The optimal monitoring interval is unknown. However, treatment of amenorrhea with birth control (oral contraceptives) is recommended. Spontaneous resolution of hyperprolactinemia may occur in postmenopausal women and has been reported in up to 30% of women after DA induced pregnancy (Klibanski 2010; Crosignani et al. 1981).

Table 19.3 Indications for medical/surgical treatment

Surgical therapy	Medical therapy
Mass effects	***Effects of hyperprolactinemia***
Hypopituitarism	Hypogonadism
Visual field defects due to pressure on the optic chiasm	Amenorrhea or oligomenorrhea
Cranial nerve deficits	Infertility
Headaches	Impotence
Other	Osteoporosis or osteopenia
Tumor growth	***Relative indications*:**
Resistance to treatment	Bothersome galactorrhea
Risk of cardiac valvulopathy	Bothersome hirsutism
Expense of lifelong treatment	Headaches

Ref: Gillam and Molitch (2011b); and Klibanski (2010)

In medication induced hyperprolactinemia, particularly when asymptomatic, no treatment is recommended (Melmed et al. 2011). Withdrawal of the offending medication is preferred but an alternate medication may be appropriate. However, treatment for hypogonadal symptoms or low bone mass with estrogen or testosterone therapy may be indicated (Melmed et al. 2011). Likewise, no treatment is indicated in the case of patients with PRL elevations determined to be related to macroprolactins.

Treatment is indicated in the presence of symptoms when other causes have been excluded. The goals of treatment are: normalization of PRL, tumor shrinkage and the relief of symptoms such as headache, visual disturbances, restoration of fertility and hypopituitarism (Romijn 2014; Glezer and Bronstein 2015).

Dopamine agonists are the first line of treatment for prolactinomas. By binding to (Gillam and Molitch 2011a) dopamine receptors sites, DA inhibits the production of PRL from both normal lactotrophs and tumor cells (Romijn 2014). A number of DAs are available including bromocriptine (Parlodel®), lisuride (Dopergine®), quinagolide (Norprolac®), cabergoline (Dostinex®), and pergolide (Permex®) (Chanson et al. 2007a). These are both ergot and non-ergot preparations with ergot drugs being more vasoactive. Pergolide (an ergot) is now considered a second line drug because of its particularly high tendency towards valvular heart disease and quinagolide (a non-ergot) is not available in the USA but is available in Europe (Gillam and Molitch 2011b).

Overall DAs have demonstrated efficacy in meeting all treatment goals. In long-term, largely uncontrolled observational studies, a mean of 68% (20–100%) of patients receiving DA (bro-

mocriptine, cabergoline or quinagolide) normalized PRL and tumor size reduction was achieved in a mean of 62% (20–100%) of cases (Melmed et al. 2011). The majority of patients treated with medical therapy had significant improvement or resolution in: visual field deficiencies 67% (33–100%), amenorrhea 78% (40–100%), infertility 53% (10–100%), sexual dysfunction 67% (6–100%), galactorrhea 86% (33–100%) (Melmed et al. 2011). Interestingly, if PRL remains somewhat elevated after significant improvement, resolution of symptoms, and tumor shrinkage, there is currently no evidence of harm (Klibanski 2010).

DAs differ in their respective dosing profiles, efficacy, and side effects. Bromocriptine has a short elimination half-life of 3.3 h and duration of action of 12–14 h requiring more frequent dosing from 1 to 3 times a day (2.5–15 mg daily) (Romijn 2014). Cabergoline has a longer half-life up to 65 h and duration of action of 7–14 days, allowing a longer dosing interval of 1–2 times weekly, whereas quinagolide with a 22 h half-life and duration of action of 24 h is dosed daily (Barlier and Jaquet 2006). The conventional dose of cabergoline is up to 2 mg/week (Molitch 2017). Drug resistance and intolerance occurs in 10–35% of cases and with higher frequency for those taking bromocriptine (Romijn 2014; Kars et al. 2009). Likewise, cabergoline, which is a more specific D2 receptor agonist, effectively shrinks up to 90% of tumors, compared with 50% in those treated with bromocriptine (Melmed et al. 2011; Romijn 2014; Glezer and Bronstein 2015).

Although side effects of DA are similar for all medications, there are some striking differences. Most common side effects are nausea, vomiting, postural hypotension and dizziness with rare nasal congestion, cramps, psychiatric disorders, and cerebrospinal fluid leaks (Glezer and Bronstein 2015). Cabergoline and quinagolide have been shown to have fewer side effects than bromocriptine (Klibanski 2010; Barlier and Jaquet 2006). Cabergoline and pergolide have been associated with a possible risk of cardiac valvulopathy associated with high doses and long duration of therapy. As ergot alkaloids, these DA may stimulate the serotonin $5HT_{2B}$ receptor activity in cardiac valves, resulting in fibromyoblast proliferation and valvular thickening (Klibanski 2010). Only one study, to date, has shown increased, dose dependent risk of tricuspid regurgitation while several studies have shown no association (Klibanski 2010; Glezer and Bronstein 2015). However, regular monitoring of echocardiogram in patients requiring higher doses of cabergoline is recommended (Molitch 2017).

DA have also been associated with impulse control disorder (ICD) associated with a high affinity for D3 receptors. A dose dependent, anti-anhedonic potency leads to disinhibition of impulse control (Noronha et al. 2016). This includes repetitive and compulsive activities such as shopping, gambling, eating and hypersexuality. A warning to this effect is advised to both patients and families when starting treatment with DA.

Surgical treatment is usually reserved for patients presenting with macroadenomas that continue to grow while on DA and those with, resistance and intolerance to DA (see Chap. 12). Some authors recommend considering surgical intervention to treat severe, unremitting symptoms, when there is a need to "debulk" tumors to improve response to DA, in order to avoid long-term or lifetime treatment with DA or when there is a high risk of cardiac valvular damage or other severe side effects. Radiotherapy is required in <5% of cases for tumor control (Molitch 2017) (see Chap. 13). A single site cost analysis in the USA revealed a significant age based cost and quality-adjusted life years (QALYs) advantage for surgical treatment over long-term medical therapy, but further confirmation of life quality is warranted (Zygourakis et al. 2017).

The duration of therapy continues to be a matter of debate. The current Endocrine Society guidelines (2011) recommend a slow withdrawal of medication while monitoring PRL levels. The most appropriate candidates should have a 2 year history of normal PRL levels and no visible tumor on MRI prior to withdrawal (Melmed et al. 2011). Current studies indicate that approximately 21% of patients have sustained normal PRL after treatment withdrawal (Klibanski 2010).

19.3.3.1.5 Prolactinoma and Pregnancy

Elevated prolactin levels inhibit GnRH release which decreases pituitary LH pulsatility amplitude and subsequently decreases estradiol levels necessary for ovulation resulting in menstrual irregularities and infertility (Cocks Eschler et al. 2018).

Treatment with dopamine agonist (DA) not only aims to reverse hyperprolactinemia and hypogonadism but to restore fertility. Although both cabergoline and bromocriptine can be used when fertility is desired, bromocriptine is the DA of choice. Neither either have been shown to affect fetal development or spontaneous abortions (Melmed et al. 2011; Molitch 2017; Colao et al. 2008). However, quinagolide has been associated with fetal risk and is not recommended in women desiring pregnancy. Regardless, it is recommended that DA be withdrawn as soon as pregnancy is confirmed (Melmed et al. 2011; Molitch 2017; Chanson and Maiter 2017). Successful pregnancy is reported in 75–90% of women treated with DA (Cocks Eschler et al. 2018).

The increased estrogen levels stimulate lactotrophs proliferation and increasing PRL levels during pregnancy and, along with cessation of the DA, there is a risk of tumor growth. In pregnancy there is a physiologic increase in the size of the pituitary gland of up to 136%, reaching maximum size immediately after delivery (Bronstein 2005). In patients with mA, tumor growth is usually minimal (and estimated at 2–3% of cases) and reports up to, and above, 21% for patients with MA (Molitch 2017; Cocks Eschler et al. 2018; Bronstein 2005). Taken together, there is an increased risk to the optic apparatus with a higher risk in patients with MA.

Monitoring during pregnancy is paramount. In the presence of a MA, formal visual field monitoring every 1–3 months is indicated (Klibanski 2010; Bronstein 2005). Measurement of PRL level during pregnancy is not recommended (Melmed et al. 2011). Both imaging and treatment with DA can be resumed during pregnancy only in the presence of signs and symptoms of tumor growth and/or if optic apparatus compression becomes apparent (Glezer and Bronstein 2015; Bronstein 2005). Bromocriptine is frequently recommended over cabergoline during pregnancy, as there is recorded use in over 6000 pregnancies vs 900 women using cabergoline, but both are considered safe (Melmed et al. 2011; Cocks Eschler et al. 2018). Emergent transsphenoidal surgery may be indicated during pregnancy in the case of apoplexy, failed DA therapy or significant visual loss and delivery may be considered if the pregnancy is sufficiently advanced (Glezer and Bronstein 2015; Bronstein 2005).

Re-evaluation for changes in tumor volume and prolactin level is undertaken as soon as is practical postpartum. Although tumor volume may increase during pregnancy, both tumor volume decrease and remission of hyperprolactinemia have been reported in over 10% of patients who normalized PRL level, menses, and ovulation after pregnancy (Cocks Eschler et al. 2018; Glezer and Bronstein 2015). For women with Ma, the basal PRL secretion is reported to be reduced following pregnancy and lactation which may contribute to the resolution of hyperprolactinemia for these women (Bridges 2018).

PRL is high immediately after delivery and slowly returns to normal the week after delivery in non-breastfeeding mothers. Basal levels decrease by about 4–6 weeks postpartum but will sharply increase for short periods with suckling during breastfeeding (Gillam and Molitch 2011b; Bronstein 2005). Intense and frequent suckling inhibits ovulation and menses and has been used as a means of birth control in some settings (Gillam and Molitch 2011b). In the presence of a prolactinoma, levels may remain elevated but there is no evidence of tumor growth during breastfeeding in mothers with either a mA or MA (Bronstein 2005).

Mood shifts postpartum have been associated with changes in PRL levels. High PRL levels have been associated with increased anxiety during gestation and may also be related to postpartum mood changes and depressive-like behaviors (Bridges 2018). Higher PRL has also been implicated in the development of maternal nurturing behaviors (Grattan 2015).

19.3.3.1.6 Prolactin in Males

The actions of prolactin in males remain unclear. Males with prolactinomas usually present after a number of years of impotence and decreased

libido but may also have normal testosterone levels (Ciccarelli et al. 2008). However, infertility is common, as in females, secondary to the suppression of GnRH secretion and decreased pituitary LH/FSH pulsatile secretion and subsequent testosterone production. Gynecomastia and galactorrhea are not common in men (10–20%) and it has been suggested that after long-term hypogonadism, aromatization of testosterone to estrogen and associated mammary gland hyperplasia is no longer apparent (Chanson and Maiter 2017). Additionally, breast stimulation in males does not result in lactation (Grattan 2015). Osteoporosis/osteopenia, anxiety, and depression may be present (Ignacak et al. 2012). Some studies have also reported an association between an increase in PRL level and parental behaviors in men but this remains controversial (Grattan 2015). An association between prostate hypertrophy and hyperprolactinemia has also been found that normalizes after treatment with DA (Ciccarelli et al. 2008).

Headaches and visual changes may be presenting symptoms in men with MA (Ignacak et al. 2012) Males with prolactinomas are on average 10 years older than females. It is unclear if delayed diagnosis accounts for the higher prevalence of MA in men or whether they have, for unknown reasons, more aggressive forms of tumors (giant invasive and malignant). In tumor histopathology, higher cell proliferative indexes (Ki-67, Proliferating Cell Nuclear Antigen) have been found in men (Ciccarelli et al. 2008; Chanson and Maiter 2017). However, some studies have found no gender or difference with respect to response to DA in mA or MA or in dose required for PRL normalization or tumor shrinkage (Ciccarelli et al. 2008; Colao et al. 2003).

Treatment with DA remains first line treatment for males with prolactinomas. Surgery is usually reserved for indications of tumor growth while on DA, DA resistance, apoplexy, acute visual field changes, or when there is a need for histopathology. Although transsphenoidal approach is most common, craniotomy is performed when the lesion is not accessible using the former approach (Chanson and Maiter 2017).

Hypogonadism will usually resolve with the normalization of PRL level (Melmed et al. 2011). Due to PRL action on male germ cells, sperm counts and motility may be low for up to 2 years after PRL normalizes. In up to 20% of patients, sperm counts remain low (Chanson and Maiter 2017). Additionally, in a large UK based retrospective open-cohort study, men with prolactinomas were found to have significantly increased cardiovascular risk compared to a non-affected population, whereas there was no increased risk found for age similar females (Toulis et al. 2018).

19.3.3.1.7 Prolactinoma in Childhood

Prolactinomas are rare in childhood and more likely to occur in adolescence at the beginning of puberty (Hoffmann et al. 2018). Prolactinomas represent about 50% of all pediatric pituitary adenomas but only about 2% of all pediatric intracranial tumors (Hoffmann et al. 2018). Some studies report the prevalence of macroadenomas in children is almost twice that of adults (37.5 vs 19.4%) (Cocks Eschler et al. 2018). Apoplexy in adolescents (14–23 years) with macroprolactinomas may be occur with a similar frequency in adults (approximately 17% vs 20%) (Jankowski et al. 2015; Sarwar et al. 2013).

The clinical presentation and symptoms in children may vary with age, tumor size, and prolactin level (Cocks Eschler et al. 2018). The majority of pediatric prolactinomas (75%) occur in girls who typically present with primary amenorrhea or menstrual disorders (up to 96%), galactorrhea, and headaches associated with mA (Hoffmann et al. 2018; Cocks Eschler et al. 2018; Chanson and Maiter 2017; Catli et al. 2012). Pubertal development may otherwise remain normal in girls, likely related to the higher prevalence of microadenomas (Cocks Eschler et al. 2018). Boys present at an earlier age with headaches, visual changes, delayed pubertal development (50%), and growth retardation (20–25%) with more invasive and aggressive macroadenomas (Hoffmann et al. 2018; Chanson and Maiter 2017; Catli et al. 2013). Other than hypogonadism, panhypopituitarism, thyroid or corticotroph deficiency remains rare in children (Salenave et al. 2015). However, two studies reported that

one-third to one half of patients were obese at diagnosis (Salenave et al. 2015; Catli et al. 2012). In newborns of mothers with high prolactin, the infants PRL will often be markedly elevated until about 3 months of age when it normalizes (Chahal and Schlechte 2008).

Few patients are diagnosed before puberty with several recent studies reporting a mean age at presentation of 14–16.5 years (Salenave et al. 2015; Catli et al. 2012). Basal prolactin levels were significantly higher in boys than girls, likely related to larger tumor size in boys (Salenave et al. 2015; Hoffmann et al. 2018; Catli et al. 2012).

Most prolactinomas in children are thought to result from sporadic genetic mutations. AIP gene mutations are reportedly more frequent in children than adults with prolactinomas, particularly with GH-PRL secreting macroadenomas (Salenave et al. 2015). The possibility of MEN-1 also needs to be evaluated in apparently sporadic pituitary adenomas in children. Salvenave et al. (in a large pediatric cohort, found that patients with DA-resistant tumours were younger, had higher baseline PRL and were more likely to have MEN-1 mutations (Salenave et al. 2015). From the Dutch MEN-1 study of 325 patients >16 years, tumor control was achieved in those with prolactinomas (n = 52) using dopamine agonists (de Laat et al. 2015).

Testing and treatment options are the same for pediatric as in adult patients. Medical therapy with dopamine agonist therapy will normalize PRL levels in approximately 75% of cases (Salenave et al. 2015; Hoffmann et al. 2018; Catli et al. 2012). Few patients require surgical transsphenoidal tumor debulking, usually secondary to visual disorders or loss, DA intolerance or nonadherence. Surgical intervention in order to avoid long-term or lifelong treatment with DAs remains in debate (Chanson and Maiter 2017; Chanson et al. 2007b). However, this may be a cost-effective option given the anticipated length of treatment but the immediate potential operative complications must always be considered (Zygourakis et al. 2017). There are few longitudinal prospective studies regarding the risk of cardiac valvulopathies after long-term treatment with cabergoline from childhood. Avoidance of this risk may be another consideration for surgical intervention in patients requiring large doses of cabergoline. Radiation therapy remains an option in recurrent and aggressive tumors that are unremitted by other therapies, but is limited by concern for hypopituitarism, possibly neurological damage and infertility (Cocks Eschler et al. 2018).

19.4 Tumor Recurrence

Postoperative tumor recurrence in early reports was higher in patients with macroadenoma but some author question the source as new versus "old" or residual tumor (Rodman et al. 1984). Chanson and Maiter highlight the subjective nature of reported data that skews recurrence rates (Spiegel et al. 1994). Some data supports estimates that approximately 75–80% of patients with a history of macroadenoma will require resumption of therapy (Klibanski 2010). Kim et al. (2017) reported a higher frequency of recurrence in males in a median of 8.9±6.6 year follow-up and others have found a higher recurrence with a baseline PRL >200 ng/L (Chanson and Maiter 2017; Kim et al. 2017). Recurrence rates for patients with microadenomas ranges from 10 to 15% postoperatively (Chanson and Maiter 2017). Few patients require radiation treatment for tumor control after failing to respond to DA.

19.5 Quality of Life (QoL)

Few studies of QoL in patients with hyperprolactinemia or prolactinomas were found in a review of the literature. Children treated with DA were found to have no difference in survival or functional capacity compared with long-term survivors of different sellar masses (Hoffmann et al. 2018). Premenopausal women with DA-treated macroprolactinomas had lower physical functioning, physical role and pain scores compared to age matched controls using SF-36 questionnaire (Kim et al. 2017). In other small studies, social functioning and mental health, vitality, role emotion, and mental summary scores were found to be

lower in patients with prolactinoma even after normalization of PRL levels when compared to unaffected controls (Kim et al. 2017; Johnson et al. 2003). Patient scores were not differentiated by tumor size in these studies. There remains no substantial evidence that QoL is changed or improved by treatment or normalization of PRL.

19.6 Nursing Care Summary

19.6.1 Assessment

Assessment at presentation requires the collection of detailed and often sensitive information. Data collected in referral information and patient completed questionnaires requires verification. Patients require assurance of privacy before being comfortable divulging personal information, particularly regarding hypogonadism and sexual activity. The comfort level of the interviewer will often frame the patient's response. In many countries, personal medical information is protected by law unless it is medically necessary to be shared with other medical professionals.

Full disclosure regarding psychiatric history, all medications (including those purchased "over the counter"), other drug use including illicit drugs used by the patient is vital. Direct inquiry may be necessary by the health care provider regarding more sensitive drug use such as alcohol volumes, marihuana, cocaine, and morphine that may decrease or increase PRL levels (Ranganthan et al. 2009; Torre and Falorni 2007). Again, reassurance of confidentiality and information security is needed in order to obtain accurate information for the provision of appropriate care.

Anecdotally, by the time the patient consults in endocrinology, they have many unanswered questions. Initial assessment includes the patients understanding of the reason for the referral and their expectations regarding ongoing evaluation and treatment. Many have little knowledge of the pituitary and its function and may have been told they have a "brain tumor." Connotations of malignancy serve to increase the anxiety of patient and family. Information regarding the benign nature of prolactinomas in 99.8–99.9% of cases is helpful.

Health and illness beliefs and practices vary according to cultures and may need to be made explicit in order for the patient to fully understand the etiology of any pathology and their role in self-care. Identify the key symptoms that the patient wishes to address and clarify these based on known data to support and frame realistic expectations. As with headaches, complete resolution may not be achievable but jointly establish symptom remission goals that would be acceptable and improve his/her quality of life. Coordination and consultation with other services is often necessary.

19.6.2 Diagnosis

Diagnostic testing may be limited to a simple blood draw or may be more extensive and is based on the patient's symptoms. In asymptomatic patients, a macroprolactin level may need to be assessed to determine bioactive PRL levels. If the patient has symptoms and prior PRL levels have been normal, ensuring that a diluted assay has been done may change the course of further evaluation and treatment.

Patient instructions for blood draws should ensure that all medications and drugs that may affect the PRL level have been withdrawn for at least 3–4 days. The patient may need to hold estrogen-based birth control and use other forms of birth control during evaluation. Avoidance of breast stimulation and vigorous exercise before the draw is recommended (Chang et al. 1986). Although midday is usually nadir PRL level, there is no clear recommendations for a specific time of day for samples to be obtained. Nadir levels may vary for shift workers. Repeat samples may be needed prior to a final diagnosis. A pregnancy test may need to be performed simultaneously in woman of child bearing age in order to ensure that an elevated level is not related to an unanticipated pregnancy.

MRI is recommended in symptomatic patients with elevated diluted PRL levels. If the patient is anxious regarding this procedure, pre-treatment with an anxiolytic may be indicated. In the USA, a prior authorization from the patients insurance

is usually required prior to the procedure. Interpretation by an experienced neuroradiologist may be needed to evaluate small mA. Patients with MA that impact the optic apparatus require further evaluation with a formal ophthalmologic exam to identify visual changes and deficits. Both the MRI and ophthalmologic exam will serve as baseline evaluations for comparison after treatment.

Further evaluation of pituitary functions may be needed such as evaluation of cortisol, ACTH levels, thyroid function (TSH/FT4), LH, FSH, testosterone (males) and in addition, renal function. Bone density scanning is recommended to evaluate bone density in patients with prolonged hypogonadism. Males may need further assessment for CVD.

19.6.3 Implementation

With a diagnosis of prolactinoma a detailed patient education is warranted. The goal of patient education is to promote self-care and improve treatment adherence. Visual aids such as the patient's own MRI images are powerful messages and can frame the patient's understanding of the disease. The use of media such as vetted online and YouTube videos and resources such as www.pituitarysociety.org /patient education, the European Society of Endocrinology https://www.ese-hormones.org/for-patients/ and Hormone Health https://www.hormone.org/ that can be readily accessed on mobile devices are valuable educational tools. These resources can be used in an office setting and continue to provide a reference for patients after an introductory discussion. It is important to remember that, under stress, information retention is limited and repetition of material with subsequent visits is essential.

Treatment planning requires patient involvement in decision making. A clear understanding of the risk, benefits, and side effects of each option includes a discussion of the implications for each individual patient. Patient treatment tolerance and adherence may begin with a discussion of coping strategies and practices to minimize the effects of the most common side effects. High risk side effects such as DA behavioral changes and impulse control disorders must be clearly described to the patient and relatives along with a discussion of an effective management plan should these occur. For treatment planning and management of patient pre and post-surgery, see Chap. 23.

Emergency guidelines should be provided in written form and reinforced with each visit. Communicate key events that represent a need for immediate medical intervention and a plan to seek emergency care. These events should include: sudden severe onset of headache, peripheral vision loss, clear nasal drainage usually along with severe headache (cerebrospinal fluid (CSF) leak), and acute psychotic behaviour changes and severe depression with suicidal ideation.

Pregnancy may or may not be a desired outcome but is a risk in sexually active child bearing age women once treatment with DA is initiated and PRL is normalized. If pregnancy is not desired, then a form of birth control should be started concomitantly with DA, particularly when using cabergoline, which can normalize PRL levels quickly. At the confirmation of pregnancy, the DA is withdrawn and the patient is monitored every trimester for compressive symptoms and visual field exams are recommended for patients with MA.

19.6.4 Evaluation

Follow-up may occur in various settings from a general practitioner office to specialty endocrine or pituitary centers or with endocrine consultants and advance practice providers. This may depend on accessibility and convenience for the patient, the complexity of the patient's care needs, and/or the comfort level of the provider. However, the key components of follow-up evaluations include: side effects review, particularly the identification of critical side effects; medication review including usage, dosing interval and timing, consistency and continuity of use; desire for or restoration of fertility; symptom changes or improvement; biochemical assessment; and interval review of MRI (every 6–12 months until stable then every 2 years) (Klibanski 2010). All reviews may require adjustment to a management plan.

Acknowledgement The author acknowledges Mark Molitch MD who is the Professor of Medicine (Endocrinology), Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL USA.

References

Barlier A, Jaquet P. Quinagolide – a valuable treatment option for hyperprolactinaemia. Eur J Endocrinol. 2006;154:187–95.

Bernard V, Young J, Chanson P, Binart N. New insights in prolactin: pathological implications. Nat Rev Endocrinol. 2015;11(5):265–75. https://doi.org/10.1038/nrendo.2015.36. Epub 2015 Mar 17. Review. PMID:25781857

Bridges, RS. Prolactin: Regulation and actions. Neuroscience 2018. Online Jan 2018. https://doi.org/10.1093/acrefore/9780190264086.013.61.

Bronstein MD. Prolactinomas and pregnancy. Pituitary. 2005;8:31–8. https://doi.org/10.1007/s11102-005-5083-4.

Catli G, Abaci A, Altincik A, Demir K, Can S, Buyukgebiz A, Bober E. Hyperprolactinemia in children: clinical features and long-term results. J Pediatr Endocrinol Metab. 2012;25(11–12):1123–8.

Catli G, Abaci A, Bober E, Büyükgebiz A. Clinical and diagnostic characteristics of hyperprolactinemia in childhood and adolescence. J Pediatr Endocrinol Metab. 2013;26(1–2):1–11. https://doi.org/10.1515/jpem-2012-0327.

Chahal J, Schlechte J. Hyperprolactinemia. Pituitary. 2008;11:141. https://doi.org/10.1007/s11102-008-0107-5.

Chang FE, Dodds WG, Sullivan M, Kim MH, Malarkey WB. The acute effects of exercise on prolactin and growth hormone secretion: comparison between sedentary women and women runners with normal and abnormal menstrual cycles. J Clin Endocrinol Metab. 1986 Mar;62(3):551–6.

Chanson P, Maiter D. Prolactinoma. In: Melmed S, editor. The pituitary. 4th ed. London: Elsevier; 2017. p. 467–514.

Chanson P, Borson-Chazot F, Chabre O, Estour B. Drug treatment of hyperprolactinemia. Ann Endocrinol (Paris). 2007a;68(2–3):113–7. Epub 2007 May 29. Review

Chanson P, Borson-Chazot F, Chabre O, Estour B. Drug treatment of hyperprolactinemia. Ann Endocrinol. 2007b;68(2–3):e30–4.

Christensen SE, Jørgensen O, Møller J, Møller N, Orskov H. Body temperature elevation, exercise and serum prolactin concentrations. Acta Endocrinol. 1985;109(4):458–62.

Ciccarelli A, Guerra E, De Rosa M, Milone F, Zarrilli S, Lombardi G. PRL secreting adenomas in male patients. Pituitary. 2008;8:29–32.

Cocks Eschler D, Javanmard P, Cox K, Geer EB. Prolactinoma through the female life cycle. Endocrine. 2018;59:16.

Colao A, Di Sarno A, Cappabianca P, et al. Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J Endocrinol. 2003;148(3):325–31.

Colao A, Abs R, Bárcena DG, Chanson P, Paulus W, Kleinberg DL. Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. Clin Endocrinol. 2008;68:66–71.

Comtois R, Robert F, Hardy J. Immunoradiometric assays may miss high prolactin levels. Ann Intern Med. 1993;119:173.

Crosignani PG, Ferrari C, Scarduelli MC, Picciotti R, Malinverni AC. Spontaneous and induced pregnancies in hyperprolactinemic women. Obstet Gynecol. 1981;58(6):708–13.

Dalzell JR, Jackson E, Gardner RS. An update on peripartum cardiomyopathy. Exp Rev Cariovasc Ther. 2011;9:1155–60. https://doi.org/10.1586/erc.11.121.

de Laat JM, Dekkers OM, Pieterman CR, Kluijfhout WP, Hermus AR, Pereira AM, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, de Herder WW, Valk GD. Long-term natural course of pituitary tumors in patients with MEN1: results from the DutchMEN1 Study Group (DMSG). J Clin Endocrinol Metab. 2015;100(9):3288–96. https://doi.org/10.1210/JC.2015-2015. Epub 2015 Jun 30

Farzami MR, Aliasgharpour M. Chemiluminescence systems; do all lead to same results in prolactin analysis? J Diabetes Metab Disord. 2017;16:24. https://doi.org/10.1186/s40200-017-0305-7. Published online 2017 June 5. PMCID: PMC5460514

Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000;80(4):1523–631.

Gillam M, Molitch M. Prolactin. In: Melmed S, editor. The pituitary. 3rd ed. London: Elsevier; 2011a. p. 119–66. https://doi.org/10.1016/B978-0-12-380926-1.10015-X.

Gillam M, Molitch M. Prolactinoma. In: Melmed S, editor. The pituitary. 3rd ed. London: Elsevier; 2011b. p. 475–531. https://doi.org/10.1016/B978-0-12-380926-1.10015-X.

Glezer A, Bronstein MD. Prolactinoma. Endocrinol Metab Clin N Am. 2015;44:71–8.

Gorvin CM. The prolactin receptor: diverse and emerging roles in pathophysiology. J Clin Translational Endocrinol. 2015;2:85e91.

Grattan D. The hypothalamo-prolactin axis. J Endocrinol. 2015;226:T101–22.

Grossman A, Besser GM. Prolactinomas. Br Med J. 1985;20:182–4.

Hilfiker-Kleiner D, Kaminski D, Podewski E, Bonda T, Schaefer A, Silwa K, Foster O, Quint A, Lanmesser U, Doerries C, et al. A cathespin D-cleaved 16kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2006;128:589–600. https://doi.org/10.1016/j.cell.2016.12.036.

Hilfiker-Kleiner D, Struman I, Hoch M, Podswski E, Silwa K. 16kDa prolactin and bromocriptine in postpartum

cardiomyopathy. Curr Heat Fail Rep. 2012;9:174–82. https://doi.org/10.1007/s11897-012-0095-7.

Hoffmann A, Adelmann S, Lohle K, Claviez C, Müller HL. Pediatric prolactinoma: initial presentation, treatment, and long-term prognosis. Eur J Pediatr. 2018;177:125–32. https://doi.org/10.1007/s00431-017-3042-5.

Horseman ND, Gregerson KA. Prolactin actions. J Mol Endocrinol. 2014;52:R95–R106.

Hu Y, Ding Y, Yang M, et al. Serum prolactin levels across pregnancy and the establishment of reference intervals. Clin Chem Lab Med. 2017;56(5):803–7. https://doi.org/10.1515/cclm-2017-0644. Retrieved 19 Jan 2018

Ignacak A, Kasztelnik M, Sliwa T, Korbut RA, Rajda K, Guzik TJ. Prolactin - not only lactotrophin a "new" view of the "old" hormone. J Physiol Pharmacol. 2012;63(5):435–43.

Ikeda H, Watanabeb K, Tominagac T, Yoshimotoc T. Transsphenoidal microsurgical results of female patients with prolactinomas. Clin Neurol Neurosurg. 2013;115:1621–5.

Jankowski PP, Crawford JR, Khanna P, Malicki DM, Ciacci JD, Levy ML. Pituitary tumor apoplexy in adolescents. World Neurosurg. 2015;83(4):644–51.

Jeffcoate SL, Bacon RRA, beastall GH, Diver MJ, Franks S, Seth J. Assays for prolactin: guidelines for the provision of a clinical biochemistry service. Ann Clin Biochem. 1986;23:638–51.

Jethwa PR, Patel TD, Hajart AF, Eloy JA, Couldwell WT, Liu JK. Surgery versus medical therapy in the management of microprolactinoma in the United States. World Neurosurg. 2016;87:65–76.

Johnson MD, Woodburn CJ, Vance ML. Quality of life in patients with a pituitary adenoma. Pituitary. 2003;6(2):81–7.

Kars M, Pereira AM, Smit JW, Romijn JA. Long-term outcome of patients with macroprolactinomas initially treated with dopamine agonists. Eur J Intern Med. 2009;20:387–93.

Kiive E, Maaroos J, Shlik J, Tõru I, Harro J. Growth hormone, cortisol and prolactin responses to physical exercise: higher prolactin response in depressed patients. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28(6):1007–13.

Kim Y-M, Seo GH, Kim Y-M, Choi J-H, Yoo H-W. Broad clinical spectrum and diverse outcomes of prolactinoma with pediatric onset: medication-resistant and recurrent cases. Endocrine J [Advance publication]. Released December 27, 2017, Online ISSN 1348-4540, Print ISSN 0918-8959. https://doi.org/10.1507/endocrj.EJ17-0268. https://www.jstage.jst.go.jp/article/endocrj/advpub/0/advpub_EJ17-0268/_article/-char/en

Kleinberg DL, Noel GL, Frantz AG. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med. 1977;296(11):589–600.

Klibanski A. Prolactinomas. N Engl J Med. 2010;362(13):1219–26.

Low MJ. Neuroendocrinology. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 13th ed. Philadelphia: ScienceDirect Elsevier; 2016. p. 109–75.

Majumdar A, Mangal NS. Hyperprolactinemia. J Hum Reprod Sci. 2013;6(3):168–75. https://doi.org/10.4103/0974-1208.121400.

Marano RJ, Ben-Jonathan N. Minireview: extrapituitary prolactin: an update on the distribution, regulation, and functions. Mol Endocrinol. 2014;28(5):622–33. https://doi.org/10.1210/me.2013-1349.

Medicines and Healthcare Regulatory Agency. WHO International Standard Prolactin, Human. Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified NIBSC code: 83/573 (Version 5.0, Dated 10/11/2016). http://www.nibsc.org/documents/ifu/83-573.pdf. Accessed 28 Feb 2018.

Melmed S, Felipe F, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, JAH W. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88. https://doi.org/10.1210/jc.2010-1692.

Mitani S, Amano I, Takatsuru Y. High prolactin concentration during lactation period induced disorders of maternal behavioral in offspring. Psychoneuroendocrinology. 2018;88:129–35.

Molitch M. Medication-induced hyperprolactinemia. Mayo Clin Proc. 2005;80(8):1050–7.

Molitch M. Diagnosis and treatment of pituitary adenomas: a review. JAMA. 2017;317(5):516–24. https://doi.org/10.1001/jama.2016.19699.

Noel GL, Suh HK, Stone JG, Frantz AG. Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab. 1972;35(6):840–51. https://doi.org/10.1210/jcem-35-6-840.

Noel GL, Suh HK, Frantz AG. Prolactin release during nursing and breast stimulation in postpartum and non postpartum subjects. J Clin Endocrinol Metab. 1974;38(3):413–23. https://doi.org/10.1210/jcem-38-3-413.

Noronha S, Stokes V, Karavitaki N, Grossman A. Treating prolactinomas with dopamine agonists: always worth the gamble? Endocrine. 2016;51:205–10. https://doi.org/10.1007/s12020-015-0727-2.

Olukoga AO, Kane JW. Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. Clin Endocrinol. 1999;51:119.

Ranganthan M, Braey G, Pittman B, Cooper T, Perry E, Krystan J, D'Souza DC. The effects of cannabinoids on serum cortisol and prolactin in humans. Psychopharmacology. 2009;203(4):737–944. https://doi.org/10.1007/s00213-008-1422-2.

Rodman EF, Molitch ME, Post KD, Biller BJ, Reichlin S. Long-term follow-up of transsphenoidal selective adenomectomy for prolactinoma. JAMA.

1984;252(7):921–4. https://doi.org/10.1001/jama.1984.03350070039020.

Romijn JA. Hyperprolactinemia and prolactinoma. Handb Clin Neurol. 2014;124:185–95. https://doi.org/10.1016/B978-0-444-59602-4.00013-7. Review. PMID: 25248588

Sairenjia TJ, Ikezawaa J, Kanekob R, Masudaa S, Uchidac K, Takanashia Y, Masudaa H, Sairenjid T, Amanoa I, Takatsurua Y, Sayamae K, Haglundf K, Dikicg K, et al. Maternal prolactin during late pregnancy is important in generating nurturing behavior in the offspring. Proc Natl Acad Sci U S A. 2017;114(49):13042–7.

Salenave S, Ancelle D, Bahougne T, Raverot G, Kamenický P, Bouligand J, Guiochon-Mantel A, Linglart A, Souchon P-F, Nicolino M, Young J, Borson-Chazot F, Delemer B, Chanson P. Macroprolactinomas in children and adolescents: factors associated with the response to treatment in 77 patients. J Clin Endocrinol Metab. 2015;100(3):1177–86. https://doi.org/10.1210/jc.2014-3670.

Sarwar KN, Huda MS, Van de Velde V, Hopkins L, Luck S, Preston R, McGowan BM, Carroll PV, Powrie JK. The prevalence and natural history of pituitary hemorrhage in prolactinoma. J Clin Endocrinol Metab. 2013;98(6):2362–7. https://doi.org/10.1210/jc.2013-1249. Epub 2013 Apr 12

Smith TP, Kavanagh L, Healy ML, McKenna TJ. Technology insight: measuring prolactin in clinical samples. Nat Clin Pract Endocrinol Metab. 2007;3(3):279–89.

Spiegel K, Follenius M, Simon C, Saini J, Ehrhart J, Brandenberger G. Prolactin secretion and sleep. Sleep. 1994;17(1):20–7.

Stewart JK, Clifton DK, DJ K, Rogol AD, Jaffe T, Goodner CJ. Pulsatile release of growth hormone and prolactin from the primate pituitary in vitro. Endocrinology. 1985;116(1):1–5.

Torre DL, Falorni A. Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manag. 2007;3(5):929–51.

Toulis KA, Robbins T, Reddy N, Balachandran K, Gokhale K, Wijesinghe H, Cheng KK, Karavitaki N, Wass J, Nirantharakumar K. Males with prolactinoma are at increased risk of incident cardiovascular disease. Clin Endocrinol. 2018;88:71–6. https://doi.org/10.1111/cen.13498.

Zygourakis CC, Imber BS, Chen R, Han SJ, Blevins L, Molinaro A, Kahn JG, Aghi MK. Cost-effectiveness analysis of surgical versus medical treatment of prolactinomas. J Neurol Surg B Skull Base. 2017;78(2):125–31. https://doi.org/10.1055/s-0036-1592193. Epub 2016 Sep 27

Key Reading

1. Melmed S, Felipe F, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, JAH W. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88. https://doi.org/10.1210/jc.2010-1692.
2. Gillam M, Molitch M. Proactin. In: Melmed S, editor. The Pituitary. 3rd ed. London: Elsevier; 2011. p. 119–66. https://doi.org/10.1016/B978-0-12-380926-1.10015-X.
3. Chanson P, Maiter D. Prolactinoma. In: Melmed S, editor. The pituitary. fourth ed. London: Elsevier; 2017. p. 467–514.
4. Glezer A, Bronstein MD. Prolactinoma. Endocrinol Metab Clin N Am. 2015;44:71–8.
5. Romijn JA. Hyperprolactinemia and prolactinoma. Handb Clin Neurol. 2014;124:185–95. https://doi.org/10.1016/B978-0-444-59602-4.00013-7. Review. PMID: 25248588
6. Torre DL, Falorni A. Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manag. 2007;3(5):929–51.

Growth Hormone Producing Adenomas: Acromegaly

20

Karen J. P. Liebert, Daphne T. Adelman, Elisabeth Rutten, and Christine Yedinak

Contents

20.1 **Introduction** 367

20.2 **Epidemiology** 368

20.3 **Pathophysiology** 368

20.4 **Clinical Symptoms** 371

20.5 **Comorbidities** 373
20.5.1 Cardiovascular Comorbidities 373
20.5.2 Metabolic Comorbidities 374
20.5.3 Respiratory Comorbidities 374
20.5.4 Neoplasia and Malignancies 375
20.5.5 Arthropathies 375
20.5.6 Other Comorbidities 376

20.6 **Diagnosis** 376

20.7 **Treatment Options** 376

K. J. P. Liebert (✉)
Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA
e-mail: kpulaski@partners.org

D. T. Adelman
Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: d-adelman@northwestern.edu

E. Rutten
Department of Endocrinology, Ghent University Hospital, Ghent, Belgium
e-mail: els.rutten@uzgent.be

C. Yedinak
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_20

20.7.1 Transsphenoidal Surgery..... 377
20.7.2 Medical Management..... 378
20.7.3 Emerging Therapies..... 380
20.7.4 Radiation Therapy..... 381
20.8 **Quality of Life (QoL)**..... 381
20.9 **Nursing Management Considerations**..... 382
20.10 **Long-Term Management**..... 383
20.11 **Home Care Educational Programme**..... 385
20.11.1 Programme Goals..... 385
20.11.2 Role of the Specialist Endocrine Nurse in Home Care..... 385
20.11.3 Method: A Home Care Programme..... 385
20.11.4 Programme Content..... 386
20.11.5 Programme Conclusion..... 386
20.12 **Conclusions**..... 386
20.13 **Patient Case Studies**..... 386
20.14 **Patient Stories**..... 387
20.15 **Patient Advocacy Groups**..... 388
20.15.1 Best Practice "Bulgarian Association of Patients with Acromegaly"..... 389
References..... 391

Abstract

Acromegaly is a rare disorder characterized by overproduction of growth hormone (GH) predominantly by a pituitary adenoma. Clinical features associated with acromegaly are a result of chronic excess GH and insulin-like growth factor-I (IGF-1) effects on tissue, bone, and other organs.

The disease is associated with increased mortality, chiefly from cardiovascular disease, but morbidity from associated comorbidities is also increased. Adequate control of growth hormone excess is paramount to controlling comorbidities.

The diagnosis is made by the biochemical confirmation of elevated GH and IGF-1 levels, the presence of clinical features, and evidence of a pituitary tumor based on MRI imaging. Transsphenoidal surgery, medical therapies, and radiation therapy are all options for disease control. Patients with acromegaly require long-term health surveillance, despite the fact that they may have normal GH and IGF-1 levels. Patients are monitored lifelong for disease recurrence, management of comorbidities and treatments to improve quality of life.

Keywords

Acromegaly · Growth hormone excess · Pituitary · Pituitary tumor · Insulin-like growth factor-1

Abbreviations

BMI	Body Mass Index
CHD	Congestive heart disease
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DI	Diabetes insipidus
GH	Growth hormone
GHRH	Growth hormone releasing hormone
IGF-1	Insulin-like growth factor-1
OGTT	Oral glucose tolerance test
OSA	Obstructive sleep apnea
SIADH	Syndrome of inappropriate antidiuretic hormone
SRIF	Somatostatin
SSA	Somatostatin analogue
SSRA	Somatostatin receptor analogue

Key Terms

- **Macroadenoma:** pituitary tumour >1.0 cm in any dimension.
- **Gigantism:** growth hormone excess occurring in childhood prior to the fusing of the long bone growth plates.
- **Somatotroph:** growth hormone secreting cell in the anterior pituitary.
- **Somatostatin:** a peptide hormone secreted by the hypothalamus that inhibits the production of growth hormone.
- **Ectopic Acromegaly:** growth hormone-releasing hormone (GHRH) secretion from neoplastic tissue that stimulates pituitary somatotrophs to inappropriately release growth hormone.

Key Points

- Acromegaly is an insidious disease caused by overproduction of growth hormone and insulin-like growth factor-1 (IGF-1) predominantly from a growth hormone producing adenoma in the pituitary gland.
- Hypersecretion of growth hormone may lead to disturbances in the musculoskeletal, cardiovascular, metabolic system as well as have implications for the development of other neoplasms.
- Early diagnosis and prompt treatment can prevent development of comorbidities and improve mortality and morbidity outcomes.
- Diagnosis is based on clinical and biochemical assessments and should include a screening IGF-1 with confirmation of the disease using an oral glucose tolerance test.
- Treatment of acromegaly includes surgery to remove the adenoma, medical therapy, pituitary irradiation, and/or combinations of each therapy.
- Quality of life may be adversely affected in chronic conditions like acromegaly and should be addressed by all care providers.

20.1 Introduction

Acromegaly is a disorder characterized by the overproduction of growth hormone (GH). Acromegaly comes from the Greek words for "extremities" (acro) and "big" (megaly), as one of the hallmark symptoms of this condition is abnormally large hands (Chanson and Salenave 2008). Growth hormone overproduction is usually from a benign tumor found in the pituitary gland. The pituitary gland is located at the base of the brain and directly below the hypothalamus (See Chap. 1).

GH-secreting pituitary adenomas are thought to arise from abnormal changes to somatotroph cells whose primarily role is to secrete GH. Although the reason GH producing tumors occur is unknown, most are the result of a genetic mutation in the replication of somatotroph cells. When GH hypersecretion occurs before the fusion of long bone growth plates in late adolescence, pituitary gigantism results, characterized primarily by excessive vertical growth (Chanson and Salenave 2008).

GH excess occurring during adulthood does not result in abnormal height, but rather is associated with slow insidious changes to the patient's physical appearance and alterations in body physiology. Hence, acromegaly often goes unrecognized in adults for many years. Many patients complain of non-specific symptoms for many years, seeking consultation from a number of medical specialties.

Early recognition of symptoms and treatment is paramount to limiting the impact of GH excess and subsequent comorbidities. A blood test for IGF-1 is recommended as a screening test when a patient presents with signs and symptoms of acromegaly. If elevated, referral to specialty centers versed in the diagnosis and treatment of pituitary diseases is highly recommended. Comprehensive care and access to health care professionals who are devoted to treating this disease is associated with best patient outcomes.

20.2 Epidemiology

Acromegaly is a slow, progressive disease. It may be up to 10 years (or more) before clear features of the disease emerge and are recognized by health care providers, necessitating a referral to an endocrinologist (Chanson et al. 2014; Nachtigall et al. 2008; Galoiu and Poiana 2015). This delay may largely be the result of the rarity of the disease.

Current population prevalence estimates range from 2.8 to 13.7 cases per 100,000 people with a yearly incidence of 0.2–1.1 cases per 100,000 population (Chanson et al. 2014; Gurel et al. 2014; Knutzen and Ezzat 2006; Lavrentaki et al. 2016). This is a significant increase over historical reports and may represent a true reflection of increased disease, increased awareness of the disease and earlier diagnosis, and/or patients more actively seeking medical attention for symptoms, particularly after internet research (Lavrentaki et al. 2016).

The median age of diagnosis is reported to be in the fifth decade of life, between 40.5 and 47 years of life (men: 36.5–48.5, females: 38–56) (Lavrentaki et al. 2016). Acromegaly generally affects both men and women equally. Over 65% of cases are associated with a pituitary macroadenoma at presentation (Nachtigall et al. 2008). If left untreated, disease comorbidities contribute significantly to increased mortality, which is 2–4 times higher than the general population (Beauregard et al. 2003; Colao et al. 2014a; Melmed 2017; Melmed et al. 2005).

Epidemiologic data is sparse regarding young-onset acromegaly, or gigantism, mainly due to the rarity of the cases. Reports indicate that only 2.4% of all cases of acromegaly were found in children between the ages of 0–19 years old (Daly et al. 2006). GH production from an ectopic source is very rare.

20.3 Pathophysiology

Growth hormone is a peptide hormone manufactured and secreted by somatotroph cells located in the anterior pituitary gland. Women secrete more GH than men, and overall GH production decreases with age. Under normal conditions, growth hormone is secreted in an episodic pulsatile manner and has a half-life of 11–19 min (Faria et al. 1989). GH production during the day is relatively low, but secretion and pulsatility increase at night in association with slow wave sleep (Melmed 2017). Approximately 70% of GH is produced at night, beginning within 2 h of the onset of sleep (Fig. 20.1). This circadian pattern is shifted in jet lag, but is unchanged in shift workers (Fig. 20.1) (Morris et al. 2012).

Episodic or pulsatile GH secretion and release is a complex process influenced by many factors. It is primarily under the central neurogenic control of two hormones released by the hypothalamus, growth hormone releasing hormone (GHRH), and somatostatin. GHRH stimulates (positive action) and somatostatin inhibits GH secretion (negative action) (Fig. 20.2). The alternating action of these hormones is largely responsible for GH pulsatility and the regulation of the appropriate concentration of growth hormone in the body (Bonert and Melmed 2017). Ghrelin is a peptide secreted from the gastrointestinal tract and stomach that modulates the release of GH at the levels of the hypothalamus and pituitary gland. GH and ghrelin have been found to be secreted simultaneously in humans with ghrelin amplifying GH pulses (Melmed et al. 2014). Exercise and stress also influences GH secretion (Melmed et al. 2014).

GHRH (positive stimulation) from hypothalamic neurons is released in response to sex steroids, neuropeptides, neurotransmitters, and opiates (Bonert and Melmed 2017). GHRH travels to the pituitary via the infundibulum and attaches to receptors on somatatroph cells. This process results in the synthesis of GH within these cells. GH is then distributed to receptor sites on target tissues throughout the body to affect nerves, muscles, bones, and other organ functions.

GHRH release and GH synthesis are stimulated by many factors. Leptin regulation of fat mass, food intake, and energy expenditure may provide a metabolic signal in fasting states triggering GH secretion in order to maintain meta-

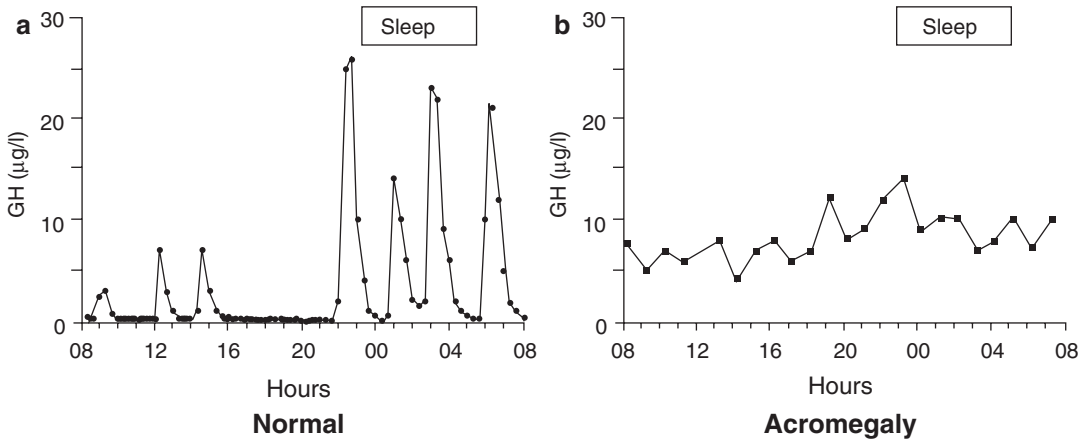


Fig. 20.1 GH circadian pulsatile production. (**a**) Normal subjects circadian pulsatile GH secretion with highest amplitude and frequency of pulses in slow wave sleep. GH levels are undetectable much of the time during the day. (**b**) Acromegaly subjects: Dysregulation of circadian frequency, and amplitude of GH pulses. Elevated baseline GH production. Ref: Chanson P, Salenave S: Acromegaly. Orphanet Journal of Rare Diseases. 3–17 (2008). Reproduced under creative commons license

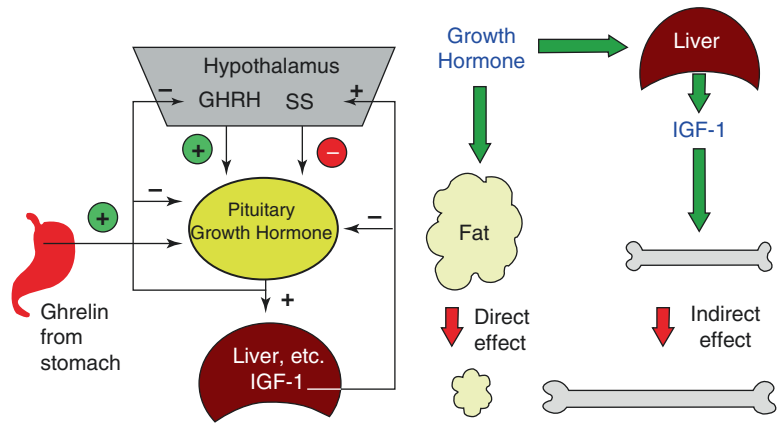


Fig. 20.2 Growth hormone physiology. Growth hormone (GH) or somatotropin secreted by the pituitary gland. Growth hormone releasing hormone (GHRH) stimulates anterior pituitary gland to release GH. The target of growth hormone: adipose tissue, liver, bone, and muscle. GH has direct effects and indirect effects on these targets. Reprinted with permission from http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/gh.html

bolic homeostasis (Bonert and Melmed 2017). Central dopamine and subsequent norepinephrine secretion stimulate GH secretion. Hypoglycemia also increases GH secretion via adrenergic stimulation while cholinergic and serotoninergic neurons have been associated with sleep-induced GH secretion (Bonert and Melmed 2017).

Somatostatin (Somatostatin Receptor Inhibiting Factor or SRIF) is a peptide that blocks GH secretion. SRIF can also inhibit adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), insulin, and glucagon secretion. Synthesized in the hypothalamus, SRIF travels down the infundibulum to the anterior pituitary, where it attaches to somatostatin receptors on somatotroph cells, thereby blocking GH secretion. It has similar actions at somatostatin receptors found throughout the body. Somatostatin attaches to five somatostatin subtype membrane receptors (SSTRs), SSTR 1, 2, 3, 4, and 5 (Bonert and

Melmed 2017). These subtypes have varying affinities for coupling with somatostatin (Bonert and Melmed 2017). SSTR 1, 3, and 5 are found on somatotrophs in the pituitary gland, whereas pituitary tumors express SSTR 1, 2, 3, and 5. These receptors provide a target for treatment of GH excess (Bonert and Melmed 2017). Other adrenergic pathways also inhibit GH release.

Once secreted, GH circulates in the blood stream attaching to peripheral receptors inducing specific cellular changes. In the liver, IGF-1 is synthesized via the JAK/STAT signaling pathway (Morris et al. 2012; Burton et al. 2012). IGF-1 is essential for promoting developmental growth activities, but also provides inhibition of GH and GHRH production via negative feedback mechanisms (Melmed et al. 2014).

GH and IGF-1 excess induces multiple downstream physiologic changes. Bone metabolism is increased with periosteal new bone formation and skeletal overgrowth (Bonert and Melmed 2017). Simultaneously, bone resorption is accelerated, increasing the risk of fracture in the presence of GH excess. There is an associated increase in soft tissue growth, adipose tissue, lipolysis, increased muscle and liver uptake of triglycerides (Bonert and Melmed 2017). GH excess antagonizes both insulin action and carbohydrate metabolism, resulting in hyperglycemia.

Pituitary GH producing adenomas are largely thought to be the result of a genetic mutation leading to autonomous GH secretion and proliferation of somatotroph cells. However, some tumors may also result from GHRH synthesis or secretory dysfunction. Most GH adenomas are monoclonal, leading to abnormal proliferation of cells that only produce GH. However, up to 25% of GH producing tumors contain cells that co-secrete GH and prolactin (Melmed et al. 2014). Rare tumors also contain cells that can produce both GH and prolactin from the same cell (Chanson and Salenave 2008). Familial genetic acromegaly syndromes or familial isolated pituitary adenomas (FIPA) associated with acromegaly are rare and include McCune–Albright syndrome, multiple endocrine neoplasia type 1 (MEN-1), and Carney Complex (Melmed et al. 2014). (See Chap. 9).

Histopathology of GH-secreting tumors demonstrates distinct cell cytoplasmic staining for GH granules and may reflect tumor activity (Melmed 2017). These include: sparsely granulated or rapidly growing tumor cells or densely granulated or slowly growing tumor cells (Melmed 2017). Cell proliferation markers Ki67 (a nuclear protein associated with proliferation) and p53 (a tumour antigen and marker of mitotic activity) are usually quantified are considered of concern if elevated. A Ki67 > 3%, mitotic activity in >10% of cells, and positive nuclear staining for p53 (>10 strongly positive nuclei per 10 high power fields) are indicative of more aggressive tumors (Raverot et al. 2017). Higher expression of SSTR2 and p21 (inhibiting cell proliferation) are associated with lower likelihood of tumor aggression and recurrence (Cuevas-Ramos et al. 2015). Two classification systems have been proposed in an effort for early prediction of treatment response, and/or tumor recurrence or progression. Raverot et al. focused primarily on histopathology and tumor invasion, prospectively evaluating a grading system from 1 to 3 for all pituitary adenomas (Raverot et al. 2017) (Table 20.1). Tumors graded as 2b were found to have a 3.7 times higher risk of recurrence or progression than grade 1 tumors. Others examined clinical, radiologic, histopathologic, and outcome characteristics in order to develop a system of risk specifically for patients with acromegaly (Cuevas-Ramos et al. 2015) (Table 20.2). In this tool, level 1 is considered to have minimal risk of recurrence and is most likely to respond to monotherapy, whereas level 3 characteristics carry a significant risk of recurrence and poorer outcomes. This tool is pending further validation.

Table 20.1 Grading system for prediction of tumour recurrence

Grade	Description
1a	Non-invasive, no or low proliferative indicators
1b	Non-invasive but proliferation
2a	Invasive
2b[a]	Invasive with proliferation
3	Malignant

[a]2b had a 3.7 times higher risk of recurrence or progression over 1a (Raverot et al. 2017)

Table 20.2 Characteristics of aggressive GH producing tumors

Type 1	Older age at diagnosis Longer disease duration before diagnosis (less symptomatology) Nadir GH and IGF-1 lower Smaller tumor volumes but both micro- and macroadenomas Tumors extend toward sphenoid Densely granulated cells on histopathology Ki67 < 3% p16 low or undetectable Highest proportion of cells with SSRT2 staining May respond to dopamine agonists as monotherapy
Type 2	Less symptomatology than type 3 Fewer microadenomas than type 1. Some invasive macroadenomas Higher nadir GH and IGF-1 Invasive macroadenomas Similar proportion of densely and sparsely granulated cells on histopathology KI67 > 3% p16 low or undetectable High p21 immunoreactivity Lower SSRT2 staining More likely to require 2 or more surgeries
Type 3	Younger age at diagnosis Macroadenomas all invasive Nadir GH and IGF-1 higher than type 1 and 2 Higher prolactin levels (p = 0.01) than Most aggressive tumors Sparsely granulated cells Ki67 > 3% p16 low or undetectable Low expression of p21 and alpha subunit Negative or low SSRT2 staining More likely to require 2 or more surgeries More likely to require radiotherapy More commonly require combination medical therapy or modalities for control More likely to be medication resistant

Adapted from Cuevas-Ramos et al. (2015)

20.4 Clinical Symptoms

The presenting manifestations of acromegaly may be a reflection of disease progression and the time to diagnosis. Since the diagnosis is frequently delayed, it may account for the predominance of macroadenomas (tumors >1 cm) found in the majority of patients with acromegaly and the extent of the observed phenotypic changes (Nachtigall et al. 2008).

The most commonly reported symptoms at presentation are headaches, as well as menstrual disturbances in women and hypogonadism in men (Chanson and Salenave 2008; Chanson et al. 2014). The most prominent physical changes in appearance include acral enlargement (78–85%) and course facial features (70%) (Chanson and Salenave 2008; Melmed 2017).

Excess GH and IGF-1 act at multiple receptor sites on body organs, tissues and bone and muscle that ultimately produce the clinical characteristics and morbidity associated with acromegaly. In bone, high levels of IGF-1 increase chondrocyte and osteocyte activity, stimulating excess skeletal bone and cartilage formation (Chanson et al. 2014). Over time, overgrowth of bone and cartilage results in acral changes (enlargement of the hands and feet) and changes in facial features such as frontal bossing and jaw growth. Joint laxity and remodeling is associated with soft tissue changes and boney overgrowth eventually resulting in arthritis and/or joint deterioration (Chanson et al. 2014). Vertebral fractures occur up to 6.9 times more frequently in patients with acromegaly, particularly in association with hypogonadism (Chanson et al. 2014; Mazziotti et al. 2013). Increases in facial soft tissues result in changes in features, such as a bulbous nose, thickened lips, and enlarged tongue. Increases in peripheral tissue and edema result in enlargement of hands (leading to symptoms of carpal tunnel syndrome) and feet. Skin changes, including oily skin with large pores, excessive hair growth, excessive sweating, and skin hyperpigmentation are observed (Chanson and Salenave 2008; Chanson et al. 2014; Melmed 2017; Melmed et al. 2014). Multiple skin tags may be found under arms and on the trunk (Ben-Shlomo and Melmed 2006; Capatina and Wass 2015). Elevated GH levels are also associated with organ tissue hypertrophy and enlargement. This can promote the development of a goiter and colon polyps. Airway obstruction results from tongue enlargement and hypertrophy of pharyngeal tissue leading to sleep apnea and poor oxygenation (Capatina and Wass 2015). IGF-1 production overstimu-

lates myocyte activity, resulting in ventricular hypertrophy, compounding hypertension, cardiomegaly and congestive heart disease (CHD) (Melmed 2017) (Fig. 20.3).

Other pituitary hormonal changes in acromegaly are common and include hyperprolactinemia, which is seen in about 25–30% of patients with acromegaly (Abreu et al. 2016). In the presence of a large tumor, this may be associated with pituitary stalk compression, but co-secretion of prolactin, either from a single cell type or two different cell types, is possible and may be confirmed on histopathology (Melmed 2017). Patients frequently present with symptoms or a history of hypogonadism, menstrual abnormalities, and infertility (Melmed 2017). Hypopituitarism can be due to mass effect on the pituitary, or damage of the pituitary gland from surgical tumor excision or radiotherapy.

On presentation, patient reported symptoms include frontal headaches, increase in ring and shoe size, weight gain, excessive sweating, difficulty with speech, snoring and breathlessness, deepening voice, coarse oily skin, multiple joint pains and carpel tunnel symptoms, hirsutism, fatigue, poor endurance, infertility, plus difficulty

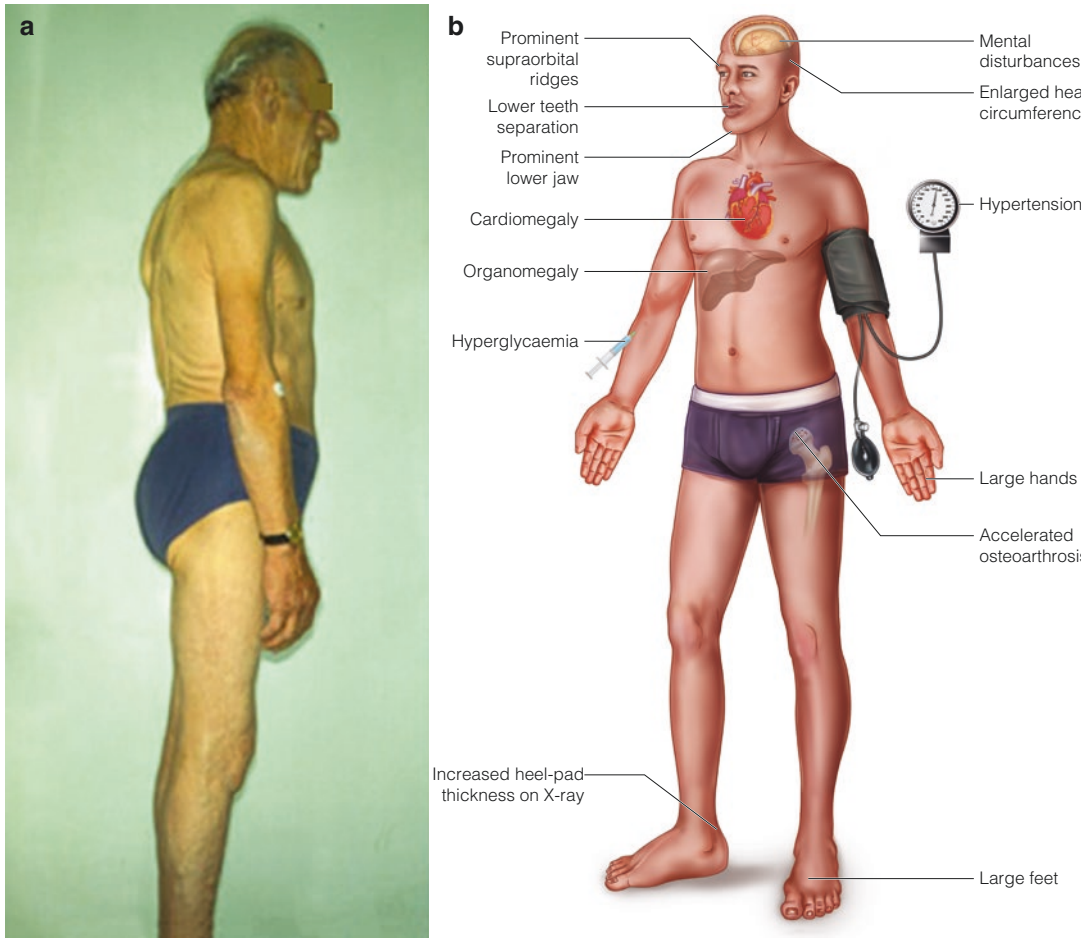


Fig. 20.3 Clinical features of acromegaly. (**a**) Clinical characteristics, (**b**) common morphological changes and comorbities. (**c**) Hand swelling and enlargement (right) (**d**) feet enlargement (left) (**e**) gaps between teeth particularly on mandible (**f**) broadening of nose and jaw enlargement (**g**) frontal bossing and jaw enlargement. Adapted from: Chanson P, Salenave S: Acromegaly. Orphanet J Rare Dis 3, 17 (2008)

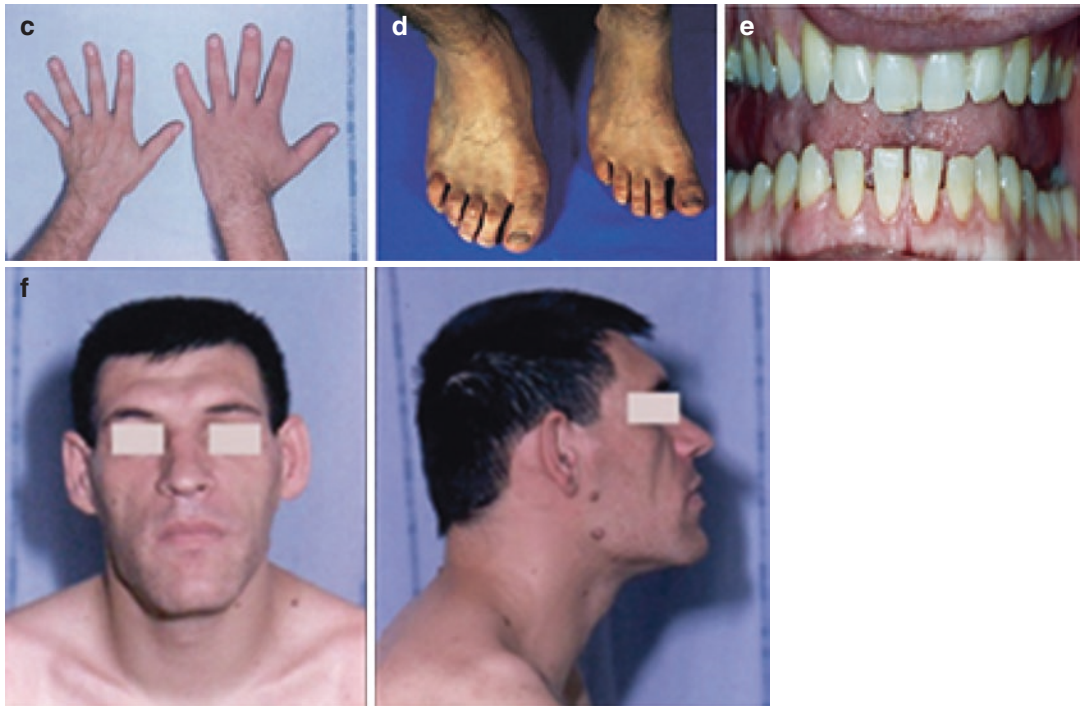


Fig. 20.3 (continued)

with cognition and memory. Patients may also have changes in vision, particularly peripheral vision and acuity when large tumors are present (Chanson and Salenave 2008; Chanson et al. 2014; Melmed 2017).

20.5 Comorbidities

National registries have been created in several countries to track comorbidities and mortality rates and also monitor the effects of treatment. Past reports from registries and other studies have indicated that life expectancy for a patient with untreated acromegaly is reduced by about 10 years compared to the general population. Cardiovascular disease is cited as the leading cause of death. However, in a recent analysis of the French Acromegaly Registry Group, better disease control reduced the incidence of comorbidities, bringing life expectancy close to that of the general population (Maione et al. 2017).

20.5.1 Cardiovascular Comorbidities

Cardiovascular disease (CVD) is the most prevalent comorbidity affecting people with acromegaly. Arrhythmias and sudden cardiac death represent the most common causes of mortality (Colao et al. 1999; Sharma et al. 2017). An increased risk of dilated cardiomyopathy, congestive heart failure (CHF), aortic and mitral valve disease, and coronary artery disease (CAD) are all reported (Sharma et al. 2017). Early studies (published prior to 1995) reported a standardized mortality risk associated with acromegaly of up to 3.31, or over 3 times higher than the general population. However, due to earlier diagnosis and disease control, mortality rates have improved with reported standardized mortality ratio now lower around 2.79 times that of the general population (Esposito et al. 2018). Some studies have found that coronary artery disease (CAD) risk is normalized with disease remission, whereas myocardial fibrosis, valvular dysfunction, and cardiac arrhythmias may be unchanged, despite

treatment for acromegaly (Sharma et al. 2017). CAD (stroke and myocardial infarction) risk remains unclear given concomitant risks from diabetes and hyperlipidemia, confounding morbidity and mortality statistics. However, encouraging data from a large German registry study demonstrated no increased risk of myocardial infarction (MI) or stroke in patients with acromegaly (Schöfl et al. 2017). Regardless, early recognition of CVD, treatment in specialty facilities, and pre-surgical treatment with somatostatin analogues have been shown to improve CVD outcomes (Sharma et al. 2017; Schöfl et al. 2017; Colao 2012).

Hypertension plays a significant role in development of cardiac hypertrophy or thickened heart chamber walls. It has been estimated that the incidence of hypertension in acromegaly is 18–60% and is associated with a significant increase in mortality (Pivonello et al. 2017). Pathogenic mechanisms of hypertension are unclear. However, it is postulated that GH and IGF-1 excess also act directly on the kidneys causing antidiuretic and antinatriuretic effects or by indirectly expanding plasma volume, resulting in increased peripheral resistance. Epithelial sodium channels (ENaC) are found in all cells and play a role in extracellular fluid volume and blood pressure. Excess GH stimulates sodium reabsorption in the distal nephrons, resulting in water retention and volume expansion (Kamenicky et al. 2008). Sleep apnea may also play a role (Sharma et al. 2017). Additionally, chronic GH exposure causes myocardial inflammation and fibrosis, hence tissue hypertrophy and loss of tissue elasticity. Using echocardiography, it has been reported that up to 85% of patients with acromegaly have left ventricular hypertrophy (Sharma et al. 2017). Thus, hypertension in acromegaly is multifactorial.

Cardiomyopathy in acromegaly has been described as occurring in progressive stages (Sharma et al. 2017). Early stages involve increased myocardial performance and decreased peripheral vascular resistance progressing to cardiac hypertrophy associated with myocardial inflammation and fibrosis. These early changes can progress to congestive heart failure, primarily through severe systolic and diastolic dysfunction and increased peripheral vascular resistance (Sharma et al. 2017). Dysfunctional changes in the cardiac valves, particularly in the mitral and aortic valves, are also a common feature in cardiomyopathy (Sharma et al. 2017). All patients presenting with acromegaly should be assessed with echocardiography and referred to cardiology as appropriate.

20.5.2 Metabolic Comorbidities

Disorders of glucose metabolism are frequently reported in patients with acromegaly. IGF-1 regulates carbohydrate metabolism and insulin sensitivity, manifesting in a range of comorbidities such as heart disease, hypertension, and diabetes (Galoiu and Poiana 2015; Melmed 2017). Studies have reported variable rates of impaired glucose tolerance (16–46%) and overt diabetes mellitus type II (19–56%) in patients with acromegaly (Alexopoulou et al. 2013). Chronic GH excess is known to lead to insulin resistance in the liver and peripheral tissues. Impaired beta cell function has also been implicated in hyperglycemia. Severity of impairment in this patient population is also influenced by IGF-1 levels, age, and increased BMI (Alexopoulou et al. 2013) (Fig. 20.4). Links have been shown between glucose intolerance, hypertension, and acromegalic cardiomyopathy (Chanson and Salenave 2008).

20.5.3 Respiratory Comorbidities

The most notable respiratory comorbidity in acromegaly is obstructive sleep apnea syndrome (OSA). Risk factors include: anatomical changes in the craniofacial bones, posterior pharyngeal soft tissue thickening, and soft palate hypertrophy and tongue enlargement. These changes lead to airway impairment (Guo et al. 2018).

Sleep apnea affects up to 80% of patients with acromegaly and is a common cause of daytime sleepiness, snoring, sleep hypoxia, headache, and memory dysfunction (Guo et al. 2018; Attal and Chanson 2018; Grunstein 1991). Obesity, particularly in males over 50 years, is a significant risk factor for OSA. Screening for sleep apnea is

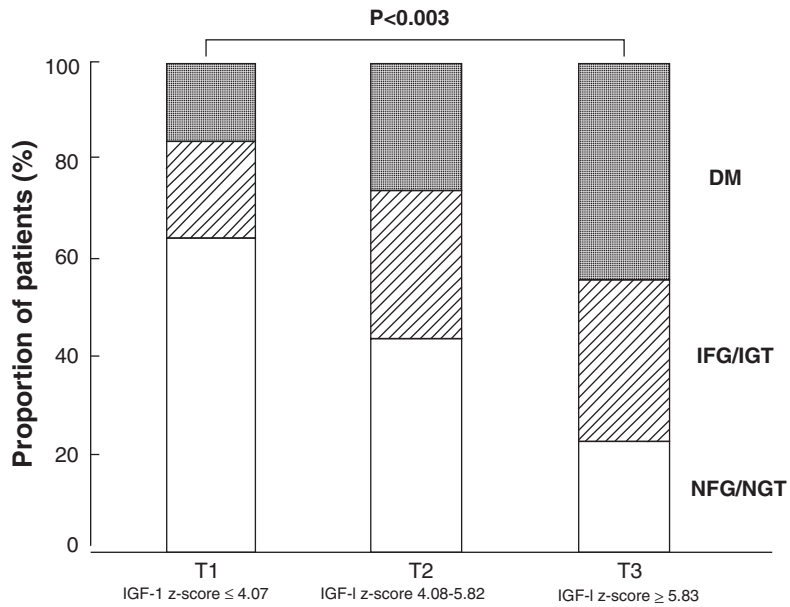


Fig. 20.4 Relationship of acromegaly: Glucose intolerance. Proportion of patients with NFG/NGT, IFG/IGT and DM within groups subdivided according to IGF-I z-score tertiles T1-T3. *NFG* normal fasting glucose, *NGT* normal glucose tolerance, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *DM* diabetes mellitus. Ref: Alexopoulou O, Bex M, Kamenicky P et al. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary 17(1):81–89. Creative commons License with permission

recommended for all patients with active and controlled acromegaly.

Lung function changes are also apparent in acromegaly patients, with rib cage remodeling, changes in cartilage and soft tissue that decrease elasticity and shorten inspiratory time (Chanson and Salenave 2008). Although alveolar volume may be increased, subclinical hypoxemia may be present (Chanson and Salenave 2008).

20.5.4 Neoplasia and Malignancies

Higher risk of developing neoplasms and some forms of cancers has been reported in patients with acromegaly. In a large Italian study, renal, thyroid, and colon cancer risk was significantly higher than in the general population (Terzolo et al. 2017). Pre-cancerous adenomatous colorectal polyps have been reported in upwards of 28% of acromegaly patients (Chanson and Salenave 2008; Abreu et al. 2016). Overexpression of GH in the colon was shown to increased epithelial cell proliferation and decreased apoptosis rates predisposing the development of polyps (Chesnokova et al. 2016). Thyroid nodules appear to be common and are found in up to 90% of patients with acromegaly. These patients have a greater likelihood of developing multinodular goiter when there is a longer interval between onset of symptoms and diagnosis (Chanson and Salenave 2008). However, some studies report the incidence of thyroid cancer does not appear to be different from the general population. A meta-analysis indicated that the overall cancer incidence for acromegaly patients was only slightly higher than the general population particularly for colorectal, breast, urinary, prostate, and hematologic cancers (Dal et al. 2018). No difference was found with respect to lung or gastric cancers. This emphasizes the need for ongoing cancer surveillance in patients diagnosed with acromegaly.

20.5.5 Arthropathies

Arthralgias and myalgias are reportedly experienced by about 70% of patients with acromegaly. Arthropathies develop after an average of 10 years of excess GH exposure, and can affect

all joints, causing progressive pain and dysfunction (Chanson and Salenave 2008; Melmed 2017; Abreu et al. 2016). Carpal tunnel syndrome and hip osteoarthropathy are commonly reported. Range of movement may be limited secondary to mechanical, non-inflammatory etiologies and/or hypermobility and tenderness. On radiographic images, joint spaces are seen to be widened (Melmed 2017). Osteocyte formation and uneven chondrocyte formations are thought to cause joint changes and osteoarthritis. In general, joint degeneration has been found to be irreversible and has been reported to impair activities of daily living and quality of life (Melmed 2017). Neurological conditions in the spine are thought to be associated with neural thickening and nerve entrapment, while disc space widening has been implicated in the development of kyphosis and scoliosis seen in these patients (Melmed 2017). Vertebral fractures have been reported in about 10% of patients (Abreu et al. 2016; Mazziotti et al. 2008).

20.5.6 Other Comorbidities

A higher incidence of asymptomatic cholelithiasis and gallbladder polyps is found in patients with untreated acromegaly (Annamalai et al. 2011; Montini et al. 2010). In addition, the treatment with somatostatins has also been associated with the development of gallstones and gallbladder sludge (Melmed 2017).

20.6 Diagnosis

The diagnosis of acromegaly is made through the clinical assessment of features and the measurement of biochemical parameters. Clinical findings unique to acromegaly, such as changes in facial features, enlarged hands (rings no longer fitting), and an increase in shoe size raise suspicions of acromegaly. Old photographs may be useful in determining changes in facial features (such as a driver's license photograph if taken 5–10 years previously). Other presenting symptoms may include headaches, joint aches or cardiovascular findings and hypogonadism (Chanson and Salenave 2008; Melmed 2017).

Biochemical confirmation of autonomous GH oversecretion is needed to make the diagnosis of acromegaly (Melmed 2017). A screening IGF-1 level should be performed if acromegaly is suspected. An elevated level should prompt a referral to a pituitary specialist or a general endocrinologist if a pituitary specialist is not available. Due to the pulsatile nature of GH secretion, a random GH level to confirm elevated GH is not useful, and is not recommended for diagnosis (Katznelson et al. 2014). According to internationally recognized guidelines, the gold standard test for confirming acromegaly is an oral glucose tolerance test (OGTT/GH suppression test). In this test, an oral glucose load of 75 g is given to the patient and GH levels are monitored every 30 min for 2 h. GH nadir of <1 μg/l (3 mIU/l) at any time point rules out the diagnosis of acromegaly (See Chapter: Provocative Investigations). The diagnosis may be complicated by variability in laboratory assays. Results must be interpreted in the context of the patient's age, BMI, and nutritional status. The presence of diabetes mellitus, renal and liver disease also spuriously alters results (Melmed 2017). Repeat sampling is recommended to confirm biochemical findings (Katznelson et al. 2014).

A pituitary MRI scan should be performed to determine the presence of a pituitary adenoma once an elevated IGF-1/GH is confirmed (Melmed 2017; Katznelson et al. 2014). Given that the majority of GH producing pituitary tumors are macroadenomas (>1 cm) and can impinge on the optic nerves, it is also recommended that these patients undergo ophthalmologic and visual field testing as a component of the initial examination (Katznelson et al. 2014).

20.7 Treatment Options

Treatment goals are to suppress or normalize GH and IGF-1, manage symptoms, and reduce tumor mass without compromising pituitary function (Melmed 2017; Katznelson et al. 2014).

If surgical resection fails to achieve GH control, or if the patient is not a candidate for sur-

gery, medical therapies and/or radiation therapy may be indicated (See Chapter: Pituitary Radiation) (Fig. 20.5).

20.7.1 Transsphenoidal Surgery

First-line treatment where a pituitary tumor is evident on MRI is selective transsphenoidal surgical resection. Success in achieving the aforementioned goals is dependent on a variety of factors, such as tumor size and location and presence of the tumor in the cavernous sinuses (Chanson et al. 2014). If the tumor is a microadenoma (<1.0 cm), surgical remission is achieved in approximately 70% of cases versus <50% for those with macroadenomas (>1.0 cm) (Melmed 2017). The best outcomes are achieved by experienced pituitary neurosurgeons. Both microscopic and endoscopic approaches are currently used, along with sophisticated intraoperative tumor localizing technologies (See Chap. 22).

Post-surgically, new onset hypopituitarism and secondary empty sella may occur (Melmed 2017). Surgical risks and complications include vision loss, cerebral spinal fluid (CSF) leak and epistaxis and hormonal dysfunction. The most common disturbances in hormones following surgery include diabetes insipidus, syndrome of inappropriate antidiuretic hormone (SIADH) and adrenal insufficiency.

Recurrence rates of pituitary tumors postoperatively range from 2 to 8% at 5 years post-op, with reports of up to 10% by 10 years postoperatively (Katznelson et al. 2014; Swearingen et al. 1998). This may be related to residual tumor from incomplete resection with subsequent growth or true recurrence. Re-operation is indicated for patients who experience visual impairment or if there is a high probability for substantial debulking or completely removing

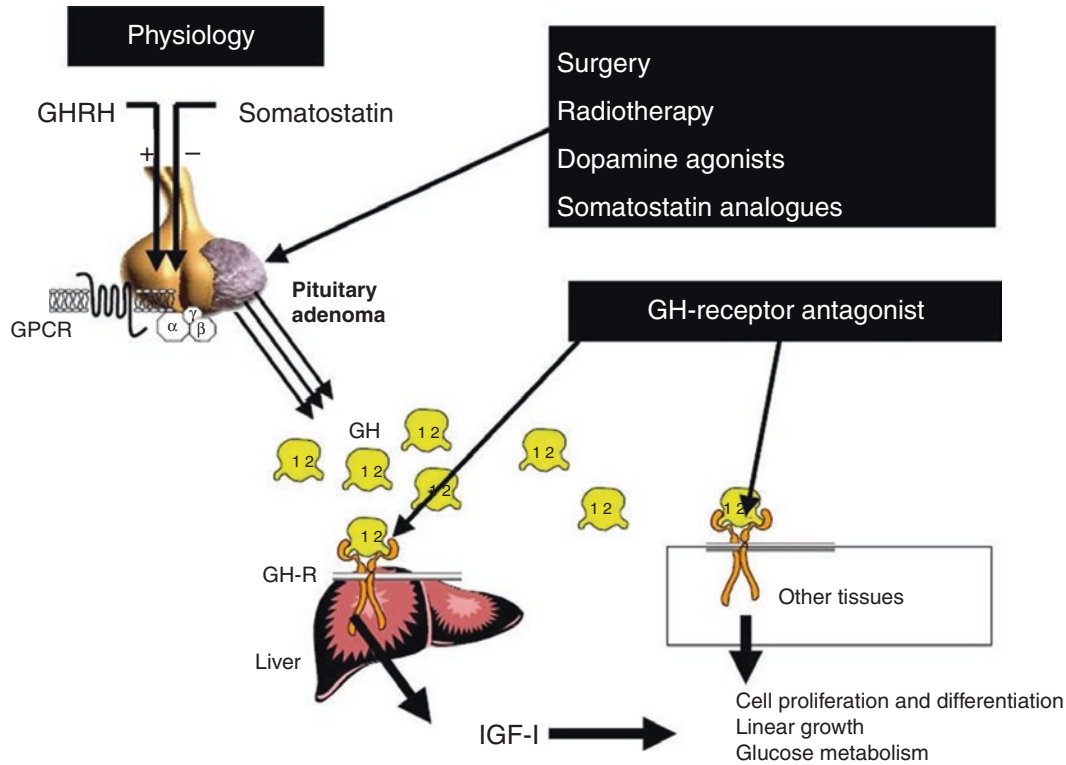


Fig. 20.5 Acromegaly treatments. Chanson P, Salenave S: Acromegaly. Orphanet Journal of Rare Diseases. 3–17 (2008). Reproduced under creative commons license

the tumor. With the potential to either remit disease or lower GH levels, re-operation is thought to be a viable, safe option and may achieve remission in up to 50% of cases (Heringer et al. 2016; Wilson et al. 2013).

20.7.1.1 Nursing Role in Transsphenoidal Surgery (Also See Chap. 23)

Preoperatively, the surgical procedure is reviewed with the patient. Patient needs, tolerance, and desire for specific surgical details vary. An overall description of the procedure itself, the risks, and what is to be expected following surgery are usually included. It is important to review the recommended lifestyle restrictions immediately postoperative, and when it is safe to return work or their previous lifestyle. Depending on the neurosurgeon and the health care system policy, the patient can be expected to stay inpatient for 1–3 days. This may vary based on specific postoperative complications such as CSF leak, diabetes insipidus, or signs of infection.

Immediately postoperatively, patients are monitored for pituitary hormone disturbances, with the most common one being transient diabetes insipidus. Sodium levels will be monitored to detect diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH). Both conditions are usually transient. Discharge instructions may include activity restrictions for 2–4 weeks, with gradual participation in more strenuous activity over the next several months. Lifting is usually restricted and the use of CPAP for sleep apnea is not recommended for the first 2 or more weeks. Surgical and endocrine follow-up is generally performed 2–12 weeks (practice dependent), at which all the pituitary hormones will be evaluated and MRI is performed.

20.7.1.2 Postoperative Testing

There has been some debate as to the definition of "cure" or disease remission. The Endocrine Society guidelines define postoperative "cure" as a suppressed GH level < 1 ng/ml following a glucose load and normalization of IGF-1 levels (Katznelson et al. 2014). A random GH/IGF-1 and oral glucose for GH suppression (OGTT) is recommended at 12 weeks or later postoperatively. MRI to evaluate any residual tumor is also recommended at 12 weeks postoperatively (Katznelson et al. 2014).

If biochemical testing demonstrates the patient has persistent acromegaly, then further therapy is needed. If the MRI scan shows a residual tumor that is surgically approachable, then re-exploration may be considered. If re-exploration is not an option, then the next line of therapy is medical management.

20.7.2 Medical Management

Medical management should be considered for those patients who did not achieve surgical cure, for whom surgery is contraindicated or in patients who elect not to undergo surgery. There are three classes of medical therapy which may be considered: (1) somatostatin analogues, (2) growth hormone receptor antagonist, and (3) dopamine agonists. These medications are used to decrease the production of growth hormone or block the action of growth hormone on target tissues. Patients with microadenomas are more likely to normalize GH and IGF-1 levels than those with macroadenomas (Melmed 2017).

20.7.2.1 Somatostatin Analogues

The native peptide, somatostatin, circulates throughout the body and attaches to one or more of five somatostatin receptor (SSR) sites found in various central and peripheral tissue. This peptide inhibits growth hormone secretion and regulates a number of gastrointestinal secretions and functions (Melmed 2017). Synthetic somatostatin ligands or analogues (SRL) that mimic the effect of native somatostatins have been developed for clinical use. SSR types 2 and 5 are expressed on somatotroph cells, particularly in GH-secreting adenomas. SRLs octreotide and lanreotide bind to somatostatin receptors, which in turn inhibit the production of growth hormone. Downstream effects include decreasing glucagon, increasing insulin secretion, suppressing pancreatic secretions, and increasing gastrointestinal motility

(Melmed 2017). The latter may lead to a side effect of transient diarrhea in some patients.

Octreotide was the first synthetic somatostatin that suppressed GH and decreased GH and IGF-1 levels in up to 90% of patients in clinical trials. Dosing is by subcutaneous injection every 8 h. Subsequently, somatostatin LAR, a long-acting formulation, given intramuscularly in doses of 20–40 mg every 4 weeks, was found to be safe and effective.

Lanreotide autogel (Somatuline) is another SRL, given as a deep subcutaneous injection in doses of 60, 90, or 120 mg every 28 days. It has been shown to be safely administered at home in some cases, and is approved in the USA for an extended dosing interval of up to 8 weeks (Salvatori et al. 2009).

Most patients will have some response to somatostatin analogues, demonstrated by a drop in GH and IGF-1 levels. However, many patients do not achieve normalization of either marker. Overall, the data suggest that approximately 57% of subjects on octreotide LAR normalize GH levels, and 67% normalize IGF-1 levels, but some studies indicate response rates as low as 41%. Similarly, only 44% of subjects on lanreotide may have normalization of IGF-1 levels (Colao et al. 2015). While the efficacy of somatostatin analogues is sub-optimal, an important characteristic of this class of medication is its effect on tumor shrinkage. About 30% of patients had reduction in tumor size by 20–50% (Colao et al. 2015).

Pasireotide is a somatostatin ligand with a broader affinity to the receptor subtypes over octreotide and lanreotide, and maybe slightly more effective in normalizing GH and IGF-1 levels (Colao et al. 2014a). However, in one head to head study, long-acting formulation of pasireotide achieved biochemical control in 31.3% of the patients compared to 19.2% of the patients treated with octreotide LAR (Colao et al. 2014b). Long-acting pasireotide is given as a once a month, intramuscular injection. One drawback of this medication is its impact on glucose metabolism. New onset diabetes was observed in 19–26% of treated patients, as compared to 4–8% of those treated with long-acting octreotide (Colao et al. 2014b).

Owing to the action of SRLs on pancreatic secretions and gastric motility, the most common side effects in more than 50% of patients are loose stools or diarrhea, nausea and abdominal cramping and gas. These side effects generally occur shortly after initial administration of the medication, and are most often transient in nature and gradually diminish or resolve over time. Biliary tract abnormalities including gallstone formation, biliary sludge and cholelithiasis occur in about 30% of patients, although most patients remain asymptomatic (Freda 2002). Abnormalities in glucose metabolism, hypo- and hyperglycemia, occur in about 2% and 15%, respectively, with up to 26% seen with pasireotide. Other less common side effects include hair loss and hypothyroidism. With the depot preparations, injection site reactions are also common (Freda 2002). Lipodystrophy, sterile abscess, and skin irritations have been reported.

20.7.2.2 Growth Hormone Receptor Antagonist

Pegvisomant is a growth hormone receptor antagonist that blocks the activity of growth hormone. By preventing dimerization at the growth hormone receptor, the critical process of transport of GH into the cell is blocked. Without dimerization, the effect of growth hormone on the cell cannot take place. While systemic GH levels remain elevated in the presence of pegvisomant, due to the nature of the compound's actions, IGF-1 levels are lowered. Initial studies demonstrated normalization of IGF-1 levels in 89% of treated patients (Trainer et al. 2000). There has been some concern that tumor growth may occur in 3–5% of the patients, but it is unclear whether this is due to the nature of the tumor, or due to persistent elevation in systemic GH (Frohman and Bonert 2007).

Pegvisomant is self-administered as a daily injection, and its effectiveness is dependent on patient adherence. It is available in 5 mg incremental doses ranging from 10 to 30 mg. Monitoring of biochemical effects is done through IGF-1 testing, as GH values are expected to be elevated and are therefore not informative (Trainer et al. 2000).

Side effects of pegvisomant can include injection site reactions, including local discomfort and reversible lipoatrophy, abnormal liver function tests, fatigue, and headache.

20.7.2.3 Dopamine Agonist

Dopamine agonists bind to dopamine receptor subtypes, D1 and D2 that are widely found throughout the nervous system and gastrointestinal tract. In healthy individuals, binding will result in stimulation of GH secretion (Jaffe and Barkan 1992). However, in individuals with acromegaly, dopamine agonist binding to these receptors results in an inhibition of GH secretion. The advantage of this class of medication is it's oral administration, and it's relatively lower cost. However, efficacy is low, limiting its use as a monotherapy. Data from several studies show that bromocriptine, the first dopamine agonist to be used in acromegaly, is effective in normalizing IGF-1 in only about 10% of patients (Jaffe and Barkan 1992). Newer dopamine agonists, such as cabergoline and quinagolide, have a greater efficacy rate of between 30 and 44% and are often better tolerated (Abs 1998; Sandret et al. 2011). With such low efficacy rates, dopamine agonists may be used in combination with other medicalx therapies for acromegaly or in those patients with modest elevations in GH or IGF-1 levels. Conversely, dopamine agonists have been used successfully in pituitary tumors which oversecrete prolactin (prolactinomas). Therefore, those patients with acromegaly who have a pituitary tumor that co-secretes GH and prolactin may benefit from medical therapy consisting of combination therapy (dopamine agonist and somatostatin analogue or dopamine agonist and pegvisomant) (Jaffe and Barkan 1992).

Side effects of dopamine agonists include gastrointestinal upset, nausea, headache, postural hypotension, fatigue, nasal congestion, and inhibition of impulse control in some cases. High doses of dopamine agonist used for patients with Parkinson's disease have also resulted in cardiac valve abnormalities (Valassi et al. 2010). However, these abnormalities have not been observed in patients where conservative doses of cabergoline have been used (≤2.0 mg/week) (Valassi et al. 2010). Additionally, no increased risk of valve abnormalities was seen in one study of 42 patients with acromegaly treated with cabergoline for a median of 34 months (Maione et al. 2012).

20.7.2.4 Combination Therapy

Combination therapy, although not FDA approved in the USA, has been used in patients who are not responsive to monotherapy. The combination of somatostatin analogues and dopamine agonists is relatively expensive, and recent studies suggest that IGF-1 levels normalized in about 30–40% of patients (Lim and Fleseriu 2016). This combination therapy is appealing for those patients with mild elevations in IGF-1 levels on somatostatin alone. Additionally, combination of a somatostatin analogue and growth hormone receptor antagonist has been reported to normalize IGF-1 levels in 80–97% of previously uncontrolled patients on monotherapy (Lim and Fleseriu 2016). Although this may achieve biochemical control, the cost of this combination therapy is expensive and requires extra monitoring for elevations in liver function.

20.7.3 Emerging Therapies

New formulations of oral octreotide are currently in clinical trials. One formulation is combined with a transient permeability enhancer (TPE) to allow octreotide absorption by temporarily opening the gap junctions in gut epithelial cells (Melmed et al. 2014). Patients must refrain from eating within 2 h of dosing. The most commonly reported side effect is diarrhea that usually resolves within 2 weeks of starting drug therapy. Efficacy is reported as similar to that of subcutaneous injections of octreotide (Melmed et al. 2014). Additionally, just completed phase 1 clinical trials, CRN00808 is an oral octreotide with a half-life of 42–50 h. Efficacy trials are ongoing (clinical trials.gov).

There are several early stage investigations of molecules designed to block the GH receptors (GHr), resulting in lowering of circulating levels of GH and IGF-1 expression. In recently completed phase 2 clinical trials, ATL1103 administered subcutaneously to two cohorts

(once or twice weekly administration) achieved a median fall in IGF-1 of 27.8% from baseline. It was well tolerated in trials with few injection site reactions reported (Trainer et al. 2018). Phase 3 trials are anticipated. Another molecule, ISIS766720 (IONIS GHR-LRX), is an antisense oligonucleotide that also acts to reduce the GHr expression, thus decreasing circulating IGF-1 levels (www.ionispharma.com). Phase 2 studies are planned in patients with acromegaly (clinicaltrials.gov, www.clinicaltrialsregister.eu).

20.7.4 Radiation Therapy

Radiation therapy in acromegaly is primarily used as adjunctive therapy in patients who have not achieved full control through surgical resection, lack of adequate response to medical therapy or with demonstrated tumor growth. Radiation therapy may also be considered to alleviate the burden of lifelong medical therapy (See Chapter: Radiation therapy).

Stereotactic radiotherapy was developed to deliver more focused radiation so as to spare surrounding tissue damage (Minniti et al. 2011). The two types of radiation therapy used to treat acromegaly are conventional fractionated or single dose stereotactic radiosurgery. In conventional fractionated radiation therapy, carefully calculated radiation doses are delivered to a precise area from several angles in divided doses over a period of about 6 weeks (Melmed 2017; Minniti et al. 2011). Patients are usually immobilized in a mask that is placed over the face. GH control is reported in 90% of patients 10 years after treatment. The most rapid decline of around 50% of pre-treatment levels is usually achieved by 2 years after treatment (Minniti et al. 2011). Fractionated treatments are well tolerated and without evidence of cognitive dysfunction, particularly in children after treatment (Minniti et al. 2011). However, there is a risk of optic damage, neurotoxicity, a higher incidence of CVAs, and secondary brain malignancies (2.4% at 20 years) post radiation.

In single dose stereotactic radiosurgery, one high dose is delivered to a single target while the patient is immobilized in a frame. This results in 30–60% of patients achieving remission at 5 years, but may incur a higher risk of radiation-induced side effects (Minniti et al. 2011; Gheorghiu 2017).

It is important to note that patients with active acromegaly continue to require treatment with medical therapy until the radiation takes effect. As GH levels usually fall slowly (over 1–10 years), interim medical therapy is required in over half of post radiation patients (Melmed 2017). Secondary brain neoplasms and radionecrosis may also occur post radiation therapy. Radiation therapy may also be associated with new onset hypopituitarism, requiring ongoing monitoring and initiation of treatment as needed. Regular symptom monitoring, pituitary testing, and MR imaging is indicated post therapy.

20.8 Quality of Life (QoL)

In recent years, the importance of quality of life has become a significant parameter in assessing the overall success in the long-term treatment and management of acromegaly. QoL is recognized by the World Health Organization as one of three patient-related outcome goals along with mortality and morbidity (Geraedts et al. 2017). QoL is multidimensional, comprised of parameters of function such as physical, social, and emotional well-being, and is assessed from the patient perspective. There are multiple general and disease specific tools available for assessment of QOL.

Many studies have demonstrated a decline in QoL in patients with acromegaly despite biochemical disease remission, although results of systematic reviews are inconclusive (Geraedts et al. 2017; Szczesniak et al. 2015; Webb 2006; Webb and Badia 2007). This may be related to factors such as assessments being performed during different stages of the disease, study design, treatment modalities, or differences in parameters assessed. Although drug studies report QoL improvement with currently used medical therapies, significant disease-related decline in QoL

compared to the general population persists (Geraedts et al. 2017; Adelman et al. 2013). Significant treatment burdens remain and include: lifestyle restrictions, pain associated with injections, family issues and high economic burden from loss of wages and productivity, medication and health care insurance costs, in some countries (Liu et al. 2017; Yedinak et al. 2018).

Many structural skeletal changes in acromegaly are permanent. Up to 90% of patients with acromegaly report musculoskeletal pain which has a negative correlation on quality of life (Wassenaar et al. 2010). Decreased mobility from increased joint pain and BMI impacts physical functioning and social activities. BMI and boney changes are also associated with changes in body image, contributing to increased anxiety, depression, decreased motivation, and increased social isolation (Biermasz et al. 2004; Conaglen et al. 2015; Crespo et al. 2016; Pantanetti et al. 2002). Osteoarthritic changes and joint space widening may only be partially improved after treatment, contributing to chronic pain and dysfunction (Claessen et al. 2017). Referrals to, and care coordination with, appropriate specialists such as orthopods, counselors and/or psychiatrists and/or rheumatologists should be encouraged.

Cognitive dysfunction is reported to be more prevalent in patients with acromegaly compared to both those with non-functioning pituitary adenomas and the general population. Executive functions of attention, memory, and new learning are affected, particularly when GH and IGF-1 levels are high and may persist, to some extent, despite treatment (Shan et al. 2017; Yedinak and Fleseriu 2013). Cognitive therapy has been demonstrated to improve associated depression, with concomitant improvement in patients perception of QoL (Kunzler et al. 2018). Long-term outcomes and the impact of more specific cognitive training remain unclear.

Comorbidities also play a role in QoL for this patient population. Headaches may improve after treatment but not resolve and may impact many aspects of functioning (Webb and Badia 2007). Screening for other comorbidities such as oncologic diseases, cardiovascular, respiratory (sleep apnea), metabolic (dyslipidemia and diabetes), osteoarticular, and hypopituitarism is recommended pre and post disease remission (Bernabeu et al. 2018). Some studies have suggested that hypopituitarism does not negatively affect QoL (Geraedts et al. 2017). However, other concomitant diseases may all contribute to a decline in QoL (Fig. 20.6).

20.9 Nursing Management Considerations

In addition to medical assessments, nurses must assess physiological, psychological, sociocultural, spiritual, economic, and lifestyle function. As previously discussed, substantial physiologic changes are usually apparent at the time of presentation, with implications for all functional

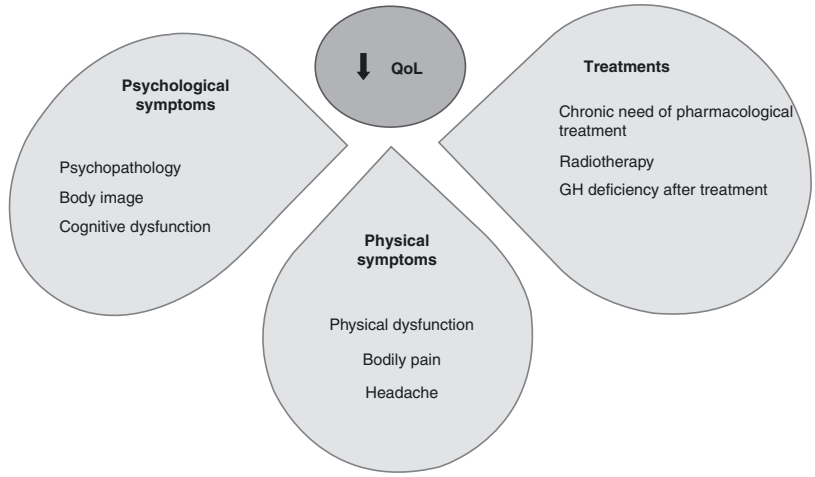


Fig. 20.6 Factors that can affect quality of life (QoL) in patients with acromegaly. From: Crespo, I., Valassi, E. & Webb, S.M. Update on Quality of Life in Patients with Acromegaly. Pituitary (2017) 20: 185. https://doi-org.liboff.ohsu.edu/10.1007/s11102-016-0761-y with permission

domains. Assessment should include family involvement or the patients support structure at diagnosis, as involvement of family/support has shown benefit in treatment adherence and long-term outcomes (Andela et al. 2017; Yedinak 2014). Assessment of memory, coping skills, and mood at baseline can provide direction in the care of these patients. All have been shown to be altered in acromegaly, particularly in the presence of high GH/IGF-1. Baseline assessment alerts the nurse to the potential need for additional resource needs or referrals (Webb and Badia 2007; Yedinak 2014).

Learning styles may also be impacted and require evaluation, although no data was found in the literature in this regard. It is important to note that re-assessment is required as the patient's phase of treatment progresses and life stage needs change.

Medical diagnosis can generate considerable anxiety and relief. Anxiety has been shown to impair memory and patients with acromegaly have also been found to have impaired verbal memory (Crespo et al. 2015). Patients express relief that their symptoms are legitimized with a diagnosis, but the patient may not have realistic posttreatment expectations. Therefore, it is vital to explore the patients' perception of treatment outcomes.

Much disease related information is now freely available on the internet, although not all information is accurate. Determination of the level of patient knowledge and the source of the patient's information can help frame patient and family education needs.

Key issues from patient assessment to address in care planning include: patient and family knowledge regarding acromegaly, the learning style of the patient; how realistic are treatment expectations; resource deficits, particularly with respect to accuracy of information sources; economic and social support; geographic limitations; the patient's level of anxiety and depression; local health care provider availability. Disturbed body image and uncompensated or deficient coping skills will need to be considered in treatment planning.

Care planning is patient centered and goal directed toward self-efficacy. In this model of care, the patient and family are involved in all care decisions. Motivational interviewing is a useful technique when mutually establishing measurable and achievable short- and long-range goals is based on the patient needs assessment. Goals must be meaningful to the patient for best adherence (Hall et al. 2012).

Planning involves multiple phases of care. Beginning with the execution of appropriate testing, preparation for hospitalization progresses through discharge planning and postoperative workup to determine remission versus the need for long-term therapy, medical and or radiologic treatments.

Care planning is complex, requires multidisciplinary collaboration, and must be adaptable. Patient needs change with phase of treatment, age, and life stage, with social and economic changes requiring ongoing adaptation. At each visit it is recommended that the patients' clinical condition, and their geographic, economic, and psychological concerns, treatment expectations and goals be addressed (Plunkett and Barkan 2015). It is estimated that 17–21% of patients with acromegaly are lost to follow-up with around 88% of these patients thought to have uncontrolled disease (Kasuki et al. 2012; Scott et al. 2004). Outcomes must be regularly reviewed and a plan revised to achieve better patient continuity and outcomes.

20.10 Long-Term Management

All patients with a history of acromegaly require periodic evaluations lifelong. The joint European and US Endocrine Societies clinical guidelines recommend a definition of remission as an IGF-1 in normal range for age and gender and a GH of <1 μg/L with glucose suppression. However, an undetectable GH (<0.04 μg/L) along with a normal IGF-1 is thought to be a more rigorous indicator of remission (Katznelson et al. 2014). Using the same GH/IGF-1 assay throughout treatment is advised. Monitoring comorbidities, thyroid studies, and assessment for

hypopituitarism is indicated (Katznelson et al. 2014). Follow-up MRI is the suggested imaging modality, but there is no guideline for follow-up imaging beyond 12 weeks postoperatively. Others recommend varying intervals from 20 to 12 months for the first 5 years and then every 5 years lifelong (Fig. 20.7).

Recurrence rates are low, but may be higher in young patients with larger tumors found to be sparsely granulated on pathology (Melmed 2017; Swearingen et al. 1998). Close and long-term monitoring is necessary. Treatment modalities, particularly transsphenoidal surgery and radiation therapy, may result in damage to the pituitary gland which may lead to the development of hypopituitarism. Hypopituitarism requires frequent biochemical testing and replacement of the missing or decreased pituitary hormones particularly post radiation therapy. Post radiation therapy, ongoing imaging is also recommended for

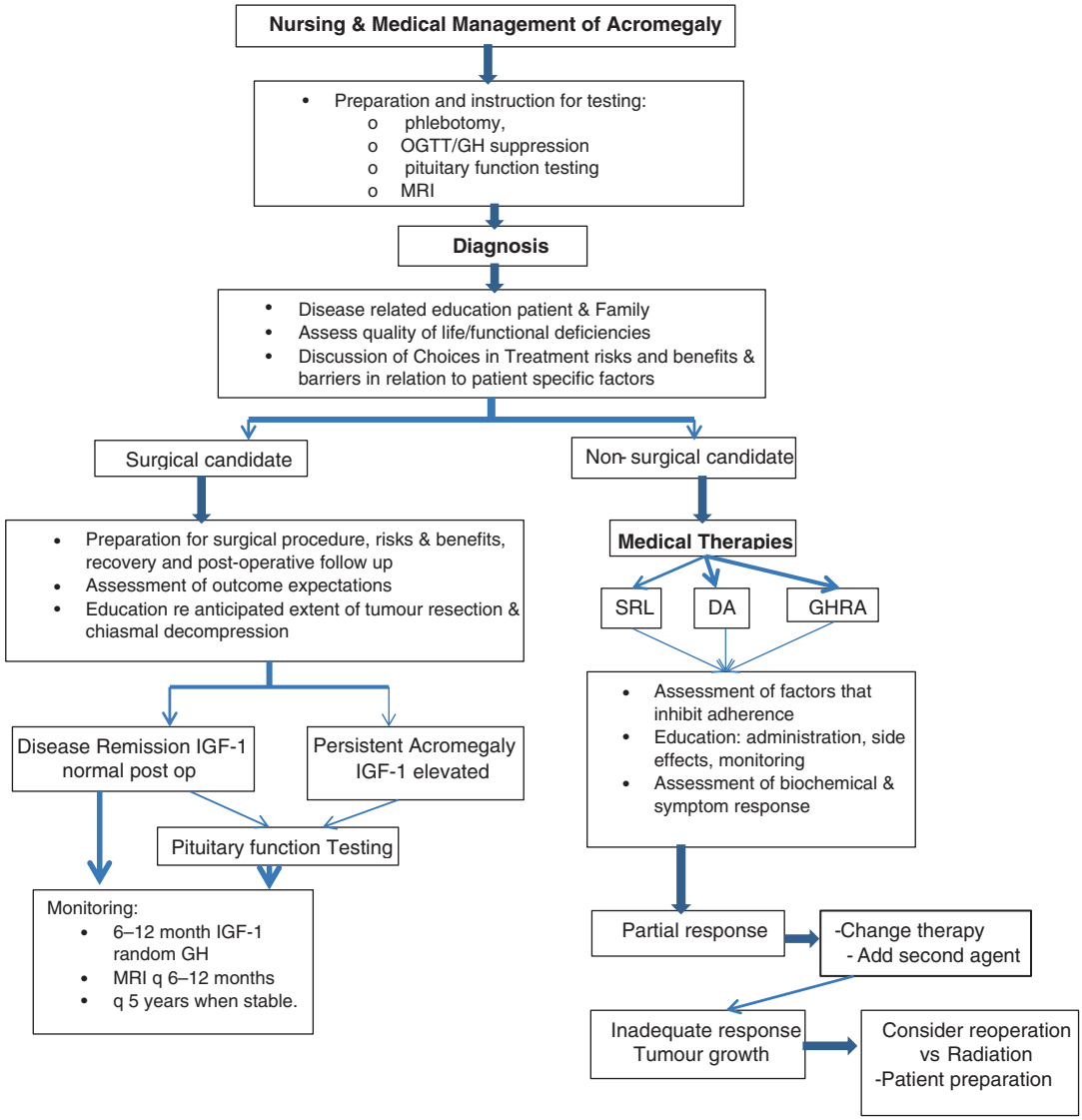


Fig. 20.7 Acromegaly management algorithm. Adapted from: Acromegaly: An Endocrine Society Clinical Practice Guideline J Clin Endocrinol Metab. 2014;99(11):3933–3951. doi:https://doi.org/10.1210/jc.2014-2700. Copyright © 2014 by the Endocrine Society. This article is published under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License (CC-BY-NC-ND; http://creativecommons.org/licenses/by-nc-nd/4.0/)

secondary tumors that may develop in the field of radiation (Minniti et al. 2011).

Guidelines also recommend monitoring for comorbidities, and for the development or worsening of cardiovascular diseases such as coronary artery disease, cardiomyopathy, and hypertension (Katznelson et al. 2014). Respiratory dysfunction and sleep apnea may persist despite disease remission. Since exposure to elevated IGF-1 levels have been implicated in the development of certain malignancies, routine screening tests for the detection of cancer should be performed on a regular basis and should include colonoscopies for the detection of cancerous colon polyps.

Finally, since there are many clinical features of acromegaly that do not improve with remission of the disease, health care providers should not hesitate to refer a patient to a specialist if needed. Many patients will still have clinical conditions associated with changes to bone and cartilage, such as the development of arthritis or joint issues that require referral to appropriate specialists.

20.11 Home Care Educational Programme

Starting a new medicine solicits many questions about the underlying diagnosis, symptoms, complications, and expected outcomes. A new medicine also means another responsibility for the patient, subcutaneous injections that are to be self administered. Patients have high expectations when a new drug has been introduced. However, they lack confidence in using unfamiliar equipment, substances, and techniques. They are particularly concerned about accuracy in drug preparation, administration, and side effects. The home care educational programme was developed to address these questions and concerns.

20.11.1 Programme Goals

(a) Assist the patient to become confident in self-injection technique.
(b) Provide the support of a trained specialist endocrine nurse.
(c) To improve adherence to drug administration schedules.
(d) To support self-care and improve quality of life.
(e) To provide patient focused education, with an emphasis on self-care, tailored to the specific needs of the individual patient.

20.11.2 Role of the Specialist Endocrine Nurse in Home Care

- Highly valued by patients
- Provides support as needed
- Provides personal contact
- Time to listen
- Knowledgeable about acromegaly
- Respects patient autonomy
- Available to answer questions
- Provide consistent follow-up
- Understand the emotional aspects of disease and diagnosis (Scott et al. 2004).
  - Phase 1: first symptoms, patient worried, feel misunderstood, very eager to find a "cure" or an answer. Risk of being lost to follow-up.
  - Phase 2 Diagnosis: patients are relieved when receiving a correct, final diagnosis.
  - Phase 3 Start of treatment: patients are unaware of the complexity of treatment and the implications of the disease.
  - Phase 4 Follow-up: patients accept the situation as it is, yet are sometimes unaware that follow-up and prevention are needed.

20.11.3 Method: A Home Care Programme

This programme is modeled after successful home care programmes for diabetes and CHD (Scott et al. 2004; Corbett 2003). The key to a successful programme is mutual goal setting.

The programme is divided into four face-to-face visits during the first week (day 1–2–3–7), and after 1 month, there are regular phone calls to

answer questions or titrate dose. Visits are scheduled when needed.

20.11.4 Programme Content

Week 1 (Day 1, 2, 3, and 7).

- Explanation of the disease and the chosen medical therapy.
- Description of the importance of adherence to prescription (dose and frequency).
- Outline of possible side effects
- Demonstration of use of injection technique and patient practice manipulating equipment.
- Description of drug dose and titration protocol.
- Day 7 patient reviewed in autonomous drug administration.
- Questions are answered by specialist endocrine nurse as they arise.
- Observations reported to patient's endocrinologist.

20.11.5 Programme Conclusion

This home care programme assigns one nurse who coaches a group of patients for an introductory week and at regular intervals thereafter. The programme improves patient satisfaction, assists patient adherence to treatment, and improves quality of life by attaining rapid IGF-1/GH normalization.

Patient feedback is positive. They are grateful for the education and training, feel independent and motivated by improved biochemical results, and have a sense of security by establishing direct communication with their endocrine team.

A home care programme for patients with acromegaly was initiated in 2011 at the Ghent University Hospital in Belgium. The protocol was approved by the ethical committee. The programme has since been expanded to 20 hospitals in Flanders, Belgium.

20.12 Conclusions

Patients with acromegaly suffer from physical, social, and psychological challenges related to the disease, many of which can persist during and after treatment and significantly modify quality of life. The nurses' role is critical in addressing and managing these issues through collaborative medical management, disease-related education, promotion of treatment adherence and lifestyle modifications, coordination of management of comorbidities and more. Multiple studies have shown that assessing and addressing known quality of life indicators in this population should be incorporated into the regular care of patients with acromegaly for best outcomes.

20.13 Patient Case Studies

Case Study 1

A 59-year-old man was referred for further assessment and treatment of suspected acromegaly. Symptoms include aching in his fingers, shoulders, hips, and knees, as well as snoring. On physical examination, his blood pressure is 150/95 mm Hg, he had acromegalic facies, wide fingers and toes, and crepitation on flexion and extension of both knees. His serum IGF-1 level is 753 ng/mL (98.6 nmol/L), (reference range, 41–279 ng/mL [5.4–36.5 nmol/L]) and his fasting blood glucose level is 142 mg/dL (7.9 mmol/L). His baseline GH is 11.7 ng/ml (11.7 μg/L). MRI was obtained and an 11 mm mass on the right side of the sella was visible. Transsphenoidal surgery is recommended. He asks if any of his abnormalities will persist even if the surgery is successful.

Question: what is this patient's morbidity and mortality risk?

Case Study 2

A 23-year-old man is referred for acromegaly. His height is 74 in. (188 cm), and his weight is 210 lb. (95.5 kg). His hands and feet are enlarged, and he has prognathism. A paternal uncle was thought to have had a pituitary adenoma of uncertain type. There is no known family history of calcium disorders or kidney stones. A random GH level is 33 ng/mL (33 μg/L), and his serum IGF-1 concentration is 811 ng/mL (106.2 nmol/L) (reference range, 147–527 ng/mL [19.3–69.0 nmol/L]). His serum calcium level is nor-

mal. MRI shows a 4.3-cm pituitary adenoma with suprasellar extension.

Question: Does this patient have a genetic risk?

20.14 Patient Stories

Patient 1

In 2014, at the age of 36, I had been having irregular periods. I would alternate having one every other month. Since I had always been regular in the past, I tracked my periods for several months and discussed the pattern with my primary doctor at my annual appointment in December, 2014. Lab work found that my prolactin was high at 59.7 ng/mL (normal 3–13 ng/ml).

She scheduled an MRI with contrast in January 2015, and there was a 1.1 cm tumor on my pituitary. It was assumed to be a prolactinoma. I was referred to an endocrinologist, and in March, 2015, my prolactin was still elevated, but my IGF-1 was also high (432 ng/mL) (reference range 128–291 ng/mL). Looking at the MRI, she said that the tumor was pressing against the pituitary stalk, so the elevated prolactin was likely a product of "stalk effect."

A glucose suppression test in April 2015 showed baseline GH was 1.1 ng/mL, which did not suppress to a level of less than 1.0. This confirmed that I had acromegaly.

I was then referred to a neurologist at the University Pituitary Clinic. Surgery was in June 2015, and the neurosurgeon was fairly sure that she had been able to remove the entire tumor. My prolactin levels immediately went back to normal. About a week after surgery, my sodium levels were low (119 mMol/L). I was readmitted to the hospital and placed on a one liter a day fluid restriction. After 2 days, my sodium levels went back to normal, and I was discharged.

At my 1-month follow-up in July 2015, my IGF-1 was still elevated (403 ng/mL). They decided to re-test in a few months. In September 2015, my IGF-1 had decreased to 346 ng/mL, but was still high. Finally, in November 2015, my IGF-1 had fallen into normal range—283 ng/mL!! What a relief! In December 2015, I repeated the glucose suppression test, and my GH level suppressed to 0.3 ng/mL, indicating remission!

I am happy to report that my IGF-1 levels and MRI results have continued to be normal over the last few years since surgery: September 2016/205 ng/mL, and September 2017/150 ng/mL (range 57–241).

I have noticed a decrease in swelling of my face, hands, and tongue as well as less joint pain since surgery. My cholesterol levels have also improved.

Patient 2

I was diagnosed with acromegaly in October of 2010. My condition, like many, if not most of the stories I read and hear about, was missed for many years. In my case, doctors estimated probably around 30 years.

When I look back, it is difficult to isolate many of the symptoms that now clearly were due to the overproduction of growth hormone. Now, hindsight being 20–20, it all makes sense. I am now 63 years old and was diagnosed with acromegaly at age 56. In retrospect, the signs started in my early to mid-30s. My physical characteristics kept changing. I was getting bigger: my hands, my chest, my muscles, my feet, and even my head was growing. I thought it was the process of aging. It never occurred to me that this was not normal. I clearly remember my dentist noticing bottom teeth separation and my primary care physician noticing my blood pressure was consistently higher than normal. I was put on mild hypertension medication in my late 30s to early 40s. By my mid to late 40s my blood sugars started to rise. Sleep apnea was another tail-tell sign. My wife noticed alarming sings of apneas (breathing stops while at sleep). In my early to mid 40s I started noticing marked pain in my leg joints specifically knees, ankles, and hips as well as a noticeable lack of energy.

I met my endocrinologist and neurosurgeon at the Center for Pituitary Disorders on a dreary, grey, drippy November San Francisco morning. "How fitting," I thought, you're going to get bad news on a miserable day! They were amazingly reassuring, particularly to my wife Carol, who

was very, very worried. After all, it is not every day you are told you have a tumor in your head. For some strange reason, I was as calm as I've ever been. Finally, knowing exactly what had been bothering me for so many years was like a 5000-pound rock lifted off my back. My first thought, as I was listening to their explanations, the surgery, medical treatment steps, and what the future would hold was: "these guys ooze competence." I was reassured with these two doctors and could not wait to get this thing out of my head.

Three months earlier I had gone to an orthopedic surgeon who recommended a hip replacement and, "by the way, I think you have a condition called Acromegaly." He told me what it was and what caused it. I must have looked at him in horror because immediately, he felt compelled to tell me I was not going to die. He had a colleague with acromegaly and a golf-ball-size pituitary tumor was removed.

At home I "googled" "Acromegaly" and THERE IT WAS!!!. "How is this possible" I thought. The screen was filled with people that looked like me. "I have almost every symptom listed" I screamed loud enough for my wife to hear me three rooms away. "You mean to tell me there are other people running around with this?" "I have most of the physical characteristics!", "Andre the Giant has this?. Don't any of these doctors I've been seeing for 30 years know about this?" "My grandmother could have diagnosed me. I could have diagnosed it," I thought angrily. It was so evident to me!

I felt ignorant, then angry, then depressed. But I also realized that as a patient I should have been more aware and perhaps, if I had been more aware of potential pituitary conditions, I could have asked better questions and help the doctors focus on a diagnosis earlier. I knew things would get better, but growing for 30 years had done irreversible damage to my bones and joints. That was the end of some of my favorite things: tennis, backpacking, hiking, even standing and walking for long periods of time. I was going to have to adjust to all of that.

During transsphenoidal surgery 95% of the pituitary adenoma was removed, but my determination to use my skills to help raise awareness of acromegaly and pituitary disorders so that people could be diagnosed early and properly, was peaked. The word about acromegaly is not getting out fast or efficiently enough.

I had developed an admiration and great friendship with my endocrinologist. We decided to move forward on a doctor–patient collaborative approach and communicate, not just the medical and scientific knowledge, but also what it is like to live with the chronic conditions associated with acromegaly. The eNews magazine Pituitary World News was the result.

Pituitary World News is a communication and publishing platform designed to encourage collaborations, innovation and creativity between industry experts, the healthcare community and patients and their families. Through awareness and communication strategies its mission is to reduce the time it take to diagnosis, improve knowledge and quality of life.

Published by permission of the author Jorge D Faccinetti.

20.15 Patient Advocacy Groups

The World Alliance of Pituitary Organizations (WAPO) is a self-governed non-profit organization created in order to unite the international pituitary patient community to push for optimal treatment and care for all patients with pituitary and related conditions worldwide. The goal of this organization is to share information, work together, and support all pituitary patients' advocates all around the world. WAPO believes in the strength of a global network of national pituitary patient organizations, which will lead to better outcomes worldwide (Fig. 20.8). The Acromegaly Community is a patient support and advocacy group for people affected by acromegaly patients,

Fig. 20.8 World Association of Pituitary Organization (WAPO)

their families and friends. Presently, the group has over 2000 members worldwide. They provide an emotional and communal support network for people touched by Acromegaly and offer information on issues of interest to people with the disease and provide a network of emotional support for Acromegaly patients, their friends and their family. The Acromegaly Community Website: https://www.acromegalycommunity.org

20.15.1 Best Practice "Bulgarian Association of Patients with Acromegaly"

One WAPO's member organization is the Bulgarian Association of Patients with Acromegaly (ABAB), who has been raising awareness for acromegaly for more than 7 years. For the last 5 years we have been involved in a court trial regarding "access to radiosurgery" and "parallel export or shortage of medicines." Both campaigns were widely spread by the Bulgarian media over a 5-year period. This amounted to an awareness campaign.

One of the most successful ABAB campaigns is the "Shoe Shop project" (Fig. 20.9). The Patient association contacted two Shoe Shop companies in Bulgaria who were already selling "big size shoes." Only one of the two stores accepted to meet and now supports the "Shoe Shop project." The patient advocacy group prepared information brochures, created from validated information on acromegaly. The brochure invited people to be alert for symptoms and encouraged them to be seen by a specialist. The material was translated and approved by a local endocrinology and used in the ABAB campaign (Acromegaly Shoe Shop Awareness). These brochures were distributed by the shoe shop in the boxes of purchased shoes. The shoe company made special boxes for display with a sign to their clients: "**If your feet and hands are growing, check for *acromegaly.***"

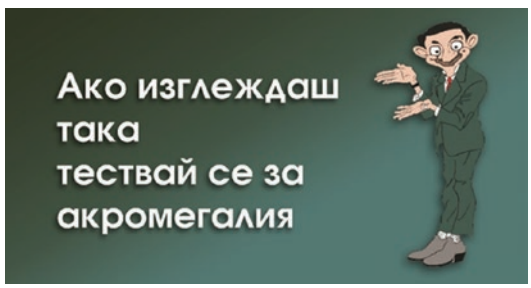


Fig. 20.9 Bulgarian Association of Patients with Acromegaly Email: acromegaly@abv.bgwebsite: http://www.pituitary-bg.com

The shoe shop entrepreneur also donated a pair of shoes to ABAB's tallest member and a journalist wrote an article about the support of the shoe shop, as well as highlighting the awareness campaign.

The next awareness campaigns will focus on access to expert diagnostic centers, medications, and reimbursement for treatment. The only center currently is in the capital city Sofia, and not accessible for rural patients.

As in Bulgaria, pituitary patients encounter similar problems in countries worldwide. The most important is late diagnosis. It takes on average 8–10 years to identify the pituitary diseases since their symptoms are not very specific and the cases are so rare. In some countries the situation is even worse and most patients either don't get treatment at all or get to the neurosurgeon when the adenoma is too large to operate. Even when diagnosed, in many countries, patients do not get appropriate treatment on time. Even when treated, patients still suffer from comorbidities, both physical and psychological.

The number or pituitary patients is relatively small but when they join their voices, they become a real power. To this end, patient groups and organizations appear in most countries. The main goals of a patient group are: (1) to represent patients in communication with health care authorities and policy makers, to advocate for patients, (2) to raise awareness about the pituitary diseases among health care professionals and general public, and (3) to empower patients so that they act in order to improve their own situation, either through better adherence, better communication, lifestyle change, or legal action.

Patient organizations are in most cases not-for-profit organizations acting in the best interest of the patients they represent. To make patient organization's activity most efficient, they try to co-operate with health care authorities, doctors, and nurses. Patient advocates are not doctors and cannot make prescriptions. However, patients tend to trust other patients so patient groups can spread the word about the importance of adherence, about patient rights and duties. Patient groups also raise awareness about the disease, thus improving the chances of undiagnosed patients to be diagnosed. These activities require support from all people involved with pituitary patient care including nurses and doctors.

There are patient groups or patient organizations active in most of the countries in the world. In some countries the organizations are well established, like the UK Pituitary Foundation. They have stable financial support from diverse base of sponsors and many fundraising events. In other countries patient groups are just starting their activities and trying to find their way to sustainability. It is not an easy path. In any case they both are ready to support patients and need your support and active involvement.

Some of the many projects in which member organizations are involved include: Acromegaly Community, US, the Vancouver Acromegaly Support Group, Canada are holding Acromegaly Awareness Days; Velikan, the Russian Pituitary Patient Organization, has launched a program for information and legal support for pituitary patients in Russia; The Spanish Association of People Affected by Acromegaly and the Pituitary Alliance of Latin America, jointly enacted a program of awareness of acromegaly; The dental school of Lima, Peru launched a program to educate dentists in signs an symptoms of acromegaly to promote early diagnosis.

To learn more about patient organizations in your region you can address to WAPO, the World Alliance of Pituitary Organizations (www.wapo.org and facebook.com/wapo.org). WAPO was created in 2016 after a series of annual meetings of patient advocacies from all over the world. The WAPO mission is to identify pituitary organizations, to guide the development of their organization, and to create an active global network (Fig. 20.10).

As of May 2017, WAPO membership included 33 organizations from 24 countries (see the map)

Fig. 20.10 World Membership WAPO

representing 30% of global population of patients with pituitary diseases.

If there is no patient group in your region, maybe you know active people that are ready to create one. Please introduce them to WAPO at mail@wapo.org. In this case WAPO will provide the activists with the best practices collected over the years and all possible support from its members.

Together we can improve the life of pituitary patients worldwide!

Acknowledgement The author acknowledges Shlomo Melmed MB, ChB, FRCP, MACP who is the Professor Cedars-Sinai Medical Center, Dean of the Medical Faculty and Executive Vice President, Chief Academic Officer, Director, Cedars-Sinai Research Institute, Los Angeles, CA, USA.

Special thanks also to Muriël Marks–de Korver, WAPO Executive Director, the World Alliance of Pituitary Organizations (WAPO) (http://www.wapo.org) for her contribution to this chapter with case studies, patient resources, and information on the Patient Advocacy Group

References

Abreu A, Tovar AP, Castellanos R, Valenzuela A, Giraldo CMG, Pinedo AC, et al. Challenges in the diagnosis and management of acromegaly: a focus on comorbidities. Pituitary. 2016;19(4):448–57.

Abs R. Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab. 1998;83(2):374–8.

Adelman D, Liebert N, Lamerson BB. Acromegaly: the disease, its impact on patients, and managing the burden of long-term treatment. Int J Gen Med. 2013;6:31.

Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary. 2013;17(1):81–9.

Andela CD, Tiemensma J, Kaptein AA, Scharloo M, Pereira AM, Kamminga NGA, et al. The partner's perspective of the impact of pituitary disease: looking beyond the patient. J Health Psychol. 2017:135910531769542.

Annamalai AK, Gayton EL, Webb A, Halsall DJ, Rice C, Ibram F, et al. Increased prevalence of gallbladder polyps in acromegaly. J Clin Endocrinol Metab. 2011;96(7):E1120–E5.

Attal P, Chanson P. Screening of acromegaly in adults with obstructive sleep apnea: is it worthwhile? Endocrine. 2018;61(1):4–6.

Beauregard C, Truong U, Hardy J, Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol. 2003;58(1):86–91.

Ben-Shlomo A, Melmed S. Skin manifestations in acromegaly. Clin Dermatol. 2006;24(4):256–9.

Bernabeu I, Aller J, Álvarez-Escolá C, Fajardo-Montañana C, Gálvez-Moreno Á, Guillín-Amarelle C, et al. Criteria for diagnosis and postoperative control of acromegaly, and screening and management of its comorbidities: expert consensus. Endocrinol Diabetes Nutr (English ed). 2018;65(5):297–305.

Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JWA, et al. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab. 2004;89(11):5369–76.

Bonert VS, Melmed S. Growth hormone. In: Melmed S, editor. The pituitary. London: Elsevier; 2017. p. 85–127.

Burton T, Le Nestour E, Bancroft T, Neary M. Real-world comorbidities and treatment patterns of patients with acromegaly in two large US health plan databases. Pituitary. 2012;16(3):354–62.

Capatina C, Wass JAH. 60 YEARS OF NEUROENDOCRINOLOGY: Acromegaly. J Endocrinol. 2015;226(2):T141–T60.

Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3(1):17.

Chanson P, Salenave S, Kamenicky P. Acromegaly. Handb Clin Neurol. 2014;124:197–219. https://doi.org/10.1016/B978-0-444-59602-4.00014-9.

Chesnokova V, Zonis S, Zhou C, Recouvreux MV, Ben-Shlomo A, Araki T, et al. Growth hormone is permissive for neoplastic colon growth. Proc Natl Acad Sci. 2016;113(23):E3250–E9.

Claessen KMJA, Canete AN, de Bruin PW, Pereira AM, Kloppenburg M, Kroon HM, et al. Acromegalic arthropathy in various stages of the disease: an MRI study. Eur J Endocrinol. 2017;176(6):779–90.

Colao A. Improvement of cardiac parameters in patients with acromegaly treated with medical therapies. Pituitary. 2012;15(1):50–8.

Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Morte AMD, et al. Impact of patient's age and disease duration on cardiac performance in acromegaly: a radionuclide angiography study. J Clin Endocrinol Metab. 1999;84(5):1518–23.

Colao A, Vandeva S, Pivonello R, Grasso LFS, Nachev E, Auriemma RS, et al. Could different treatment approaches in acromegaly influence life expectancy? A comparative study between Bulgaria and Campania (Italy). Eur J Endocrinol. 2014a;171(2):263–73.

Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014b;99(3):791–9.

Colao A, Auriemma RS, Pivonello R, Kasuki L, Gadelha MR. Interpreting biochemical control response rates

with first-generation somatostatin analogues in acromegaly. Pituitary. 2015;19(3):235–47.
Conaglen HM, de Jong D, Crawford V, Elston MS, Conaglen JV. Body image disturbance in acromegaly patients compared to nonfunctioning pituitary adenoma patients and controls. Int J Endocrinol. 2015;2015:1–8.
Corbett CF. A randomized pilot study of improving foot care in home health patients with diabetes. Diabetes Educ. 2003;29(2):273–82.
Crespo I, Santos A, Valassi E, Pires P, Webb SM, Resmini E. Impaired decision making and delayed memory are related with anxiety and depressive symptoms in acromegaly. Endocrine. 2015;50(3):756–63.
Crespo I, Valassi E, Webb SM. Update on quality of life in patients with acromegaly. Pituitary. 2016;20(1):185–8.
Cuevas-Ramos D, Carmichael JD, Cooper O, Bonert VS, Gertych A, Mamelak AN, et al. A structural and functional acromegaly classification. J Clin Endocrinol Metab. 2015;100(1):122–31.
Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C, et al. Cancer incidence in patients with acromegaly: a cohort study and meta-analysis of the literature. J Clin Endocrinol Metab. 2018;103(6):2182–8.
Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the Province of Liège, Belgium. J Clin Endocrinol Metab. 2006;91(12):4769–75.
Esposito D, Ragnarsson O, Granfeldt D, Marlow T, Johannsson G, Olsson DS. Decreasing mortality and changes in treatment patterns in patients with acromegaly from a nationwide study. Eur J Endocrinol. 2018;178(5):459–69.
Faria ACS, Veldhuis JD, Thorner MO, Vance ML. Half-time of endogenous growth hormone (GH) disappearance in normal man after stimulation of GH secretion by GH-releasing hormone and suppression with somatostatin. J Clin Endocrinol Metab. 1989;68(3):535–41.
Freda PU. Somatostatin analogs in acromegaly. J Clin Endocrinol Metab. 2002;87(7):3013–8.
Frohman LA, Bonert V. Pituitary tumor enlargement in two patients with acromegaly during pegvisomant therapy. Pituitary. 2007;10(3):283–9.
Galoiu S, Poiana C. Current therapies and mortality in acromegaly. J Med Life. 2015;8(4):411–5.
Geraedts VJ, Andela CD, Stalla GK, Pereira AM, van Furth WR, Sievers C, et al. Predictors of quality of life in acromegaly: no consensus on biochemical parameters. Front Endocrinol (Lausanne). 2017;8:40.
Gheorghiu ML. Updates in outcomes of stereotactic radiation therapy in acromegaly. Pituitary. 2017;20(1):154–68.
Grunstein RR. Sleep apnea in acromegaly. Ann Intern Med. 1991;115(7):527.
Guo X, Zhao Y, Wang M, Gao L, Wang Z, Zhang Z, et al. The posterior pharyngeal wall thickness is associated with OSAHS in patients with acromegaly and correlates with IGF-1 levels. Endocrine. 2018; https://doi.org/10.1007/s12020-018-1631-3.
Gurel MH, Bruening PR, Rhodes C, Lomax KG. Patient perspectives on the impact of acromegaly: results from individual and group interviews. Patient Prefer Adherence. 2014;8:53–62.
Hall K, Gibbie T, Lubman DI. Motivational interviewing techniques - facilitating behaviour change in the general practice setting. Aust Fam Physician. 2012;41(9):660–7.
Heringer LC, de Oliveira MF, Rotta JM, Botelho RV. Effect of repeated transsphenoidal surgery in recurrent or residual pituitary adenomas: a systematic review and meta-analysis. Surg Neurol Int. 2016;7:14.
Jaffe CA, Barkan AL. Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin N Am. 1992;21(3):713–35.
Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M, et al. Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. Endocrinology. 2008;149(7):3294–305.
Kasuki L, Marques NV, Nuez MJBL, Leal VLG, Chinen RN, Gadelha MR. Acromegalic patients lost to follow-up: a pilot study. Pituitary. 2012;16(2):245–50.
Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51.
Knutzen R, Ezzat S. The cost of medical care for the acromegalic patient. Neuroendocrinology. 2006;83(3–4):139–44.
Kunzler LS, Naves LA, Casulari LA. Cognitive-behavioral therapy improves the quality of life of patients with acromegaly. Pituitary. 2018;21(3):323–33.
Lavrentaki A, Paluzzi A, Wass JAH, Karavitaki N. Epidemiology of acromegaly: review of population studies. Pituitary. 2016;20(1):4–9.
Lim DST, Fleseriu M. The role of combination medical therapy in the treatment of acromegaly. Pituitary. 2016;20(1):136–48.
Liu S, Adelman DT, Xu Y, Sisco J, Begelman SM, Webb SM, et al. Patient-centered assessment on disease burden, quality of life, and treatment satisfaction associated with acromegaly. J Investig Med. 2017;66(3):653–60.
Maione L, Garcia C, Bouchachi A, Kallel N, Maison P, Salenave S, et al. No evidence of a detrimental effect of cabergoline therapy on cardiac valves in patients with acromegaly. J Clin Endocrinol Metab. 2012;97(9):E1714–E9.
Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, et al. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. Eur J Endocrinol. 2017;176(5):645–55.
Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A, et al. Prevalence of vertebral fractures

in men with acromegaly. J Clin Endocrinol Metab. 2008;93(12):4649–55.
Mazziotti G, Bianchi A, Porcelli T, Mormando M, Maffezzoni F, Cristiano A, et al. Vertebral fractures in patients with acromegaly: a 3-year prospective study. J Clin Endocrinol Metab. 2013;98(8):3402–10.
Melmed S. Acromegaly. In: Melmed S, editor. The pituitary. London: Elsevier; 2017. p. 423–66.
Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, et al. Consensus statement: medical management of acromegaly. Eur J Endocrinol. 2005;153(6):737–40.
Melmed S, Kleinberg DL, Bonert V, Fleseriu M. Acromegaly: assessing the disorder and navigating therapeutic options for treatment. Endocr Pract. 2014;20(Suppl 1):7–17; quiz 8–20
Minniti G, Scaringi C, Enrici R. Radiation techniques for acromegaly. Radiat Oncol. 2011;6(1):167.
Montini M, Gianola D, Paganl MD, Pedroncelli A, Caldara R, Gherardi F, et al. Cholelithiasis and acromegaly: therapeutic strategies. Clin Endocrinol. 2010;40(3):401–6.
Morris CJ, Aeschbach D, Scheer FAJL. Circadian system, sleep and endocrinology. Mol Cell Endocrinol. 2012;349(1):91–104.
Nachtigall L, Delgado A, Swearingen B, Lee H, Zerikly R, Klibanski A. Changing patterns in diagnosis and therapy of acromegaly over two decades. J Clin Endocrinol Metab. 2008;93(6):2035–41.
Pantanetti P, Sonino N, Arnaldi G, Boscaro M. Self image and quality of life in acromegaly. Pituitary. 2002;5(1):17–9.
Pivonello R, Auriemma RS, Grasso LFS, Pivonello C, Simeoli C, Patalano R, et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary. 2017;20(1):46–62.
Plunkett C, Barkan A. The care continuum in acromegaly: how patients, nurses, and physicians can collaborate for successful treatment experiences. Patient Prefer Adherence. 2015;9:1093.
Raverot G, Dantony E, Beauvy J, Vasiljevic A, Mikolasek S, Borson-Chazot F, et al. Risk of recurrence in pituitary neuroendocrine tumors: a prospective study using a five-tiered classification. J Clin Endocrinol Metab. 2017;102(9):3368–74.
Salvatori R, Nachtigall LB, Cook DM, Bonert V, Molitch ME, Blethen S, et al. Effectiveness of self- or partner-administration of an extended-release aqueous-gel formulation of lanreotide in lanreotide-naïve patients with acromegaly. Pituitary. 2009;13(2):115–22.
Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35.
Schöfl C, Petroff D, Tönjes A, Grussendorf M, Droste M, Stalla G, et al. Incidence of myocardial infarction and stroke in acromegaly patients: results from the German Acromegaly Registry. Pituitary. 2017;20(6):635–42.
Scott L, Setterkline K, Britton A. The effects of nursing interventions to enhance mental health and quality of life among individuals with heart failure. Appl Nurs Res. 2004;17(4):248–56.
Shan S, Fang L, Huang J, Chan RCK, Jia G, Wan W. Evidence of dysexecutive syndrome in patients with acromegaly. Pituitary. 2017;20(6):661–7.
Sharma MD, Nguyen AV, Brown S, Robbins RJ. Cardiovascular disease in acromegaly. Methodist Debakey Cardiovasc J. 2017;13(2):64–7.
Swearingen B, Barker FG, Katznelson L, Biller BMK, Grinspoon S, Klibanski A, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab. 1998;83(10):3419–26.
Szczesniak D, Jawiarczyk-Przybylowska A, Rymaszewska J. The quality of life and psychological, social and cognitive functioning of patients with acromegaly. Adv Clin Exp Med. 2015;24(1):167–72.
Terzolo M, Reimondo G, Berchialla P, Ferrante E, Malchiodi E, De Marinis L, et al. Acromegaly is associated with increased cancer risk: a survey in Italy. Endocr Relat Cancer. 2017;24(9):495–504.
Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7.
Trainer PJ, Newell-Price J, Ayuk J, Aylwin S, Rees DA, Drake W, et al. A randomised, open-label, parallel group phase 2 study of antisense oligonucleotide therapy in acromegaly. Eur J Endocrinol. 2018:EJE-18-0138.
Valassi E, Klibanski A, Biller BMK. Potential cardiac valve effects of dopamine agonists in hyperprolactinemia. J Clin Endocrinol Metab. 2010;95(3):1025–33.
Wassenaar MJE, Biermasz NR, Kloppenburg M, AAvd K, Tiemensma J, Smit JWA, et al. Clinical osteoarthritis predicts physical and psychological QoL in acromegaly patients. Growth Hormon IGF Res. 2010;20(3):226–33.
Webb SM. Quality of life in acromegaly. Neuroendocrinology. 2006;83(3–4):224–9.
Webb SM, Badia X. Quality of life in growth hormone deficiency and acromegaly. Endocrinol Metab Clin N Am. 2007;36(1):221–32.
Wilson TJ, McKean EL, Barkan AL, Chandler WF, Sullivan SE. Repeat endoscopic transsphenoidal surgery for acromegaly: remission and complications. Pituitary. 2013;16(4):459–64.
Yedinak C, editor Prevalence of depression in patients with pituitary tumors: association of depression with perceived social capital. In Sigma Theta Tau International's 25th International Nursing Research Congress; 2014 July 24–28; Hong Kong, China.
Yedinak CG, Fleseriu M. Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: a pilot study. Endocrine. 2013;46(3):585–93.
Yedinak C, Pulaski Liebert KJ, Adelman DT, Williams J. Acromegaly: current therapies benefits and burdens. Clin Pract. 2018;15(2)

Key Reading

1. Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3(1):17.
2. Melmed S, Casanueva F, Cavagnini F, Chanson P, et al. Consensus statement: medical management of acromegaly. Eur J Endocrinol. 2005;153(6):737–40.
3. Melmed S, Kleinberg DL, Bonert V, Fleseriu M. Acromegaly: assessing the disorder and navigating therapeutic options for treatment. Endocr Pract. 2014;20(Suppl 1):7–17; quiz 8–20
4. Plunkett C, Barkan A. The care continuum in acromegaly: how patients, nurses, and physicians can collaborate for successful treatment experiences. Patient Prefer Adherence. 2015;9:1093.

ACTH Producing Adenomas: Cushing's Disease

21

Raven McGlotten, Daphne T. Adelman, and Margaret F. Keil

Contents

21.1 **Introduction to Hypercortisolism** 397
21.1.1 Cushing's Syndrome 397
21.1.2 Cushing's Disease 397

21.2 **Cushing's Disease** 398
21.2.1 Epidemiology and Pathophysiology 398

21.3 **Genetics of Cushing's Disease** 399

21.4 **Morbidity and Mortality** 400

21.5 **Patient Presentation and Assessment** 400

21.6 **Testing and Diagnostic Procedures** 402

21.7 **Treatment Modalities** 404
21.7.1 Surgical Treatment 404
21.7.2 Medical Therapy 406
21.7.3 Bilateral Adrenalectomy 409
21.7.4 Radiation Therapy 409
21.7.5 Other Considerations 409

21.8 **Quality of Life and Patient Education** 410

21.9 **Nursing Considerations** 410

21.10 **Conclusions** 411

References 412

R. McGlotten (✉)
National Institutes of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA
e-mail: mcglottenr@mail.nih.gov

D. T. Adelman
Northwestern University, Chicago, IL, USA
e-mail: d-adelman@northwestern.edu

M. F. Keil
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA
e-mail: keilm@nih.gov

Abstract

Cushing's syndrome is a rare disorder characterized by prolonged exposure to excessive concentrations of glucocorticoids. Endogenous Cushing's syndrome, which will be the focus of this chapter, is usually divided into adrenocorti-

The original version of this chapter was revised. A correction to this chapter can be found at https://doi.org/10.1007/978-3-319-99817-6_70

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_21

cotropic hormone (ACTH)-dependent and ACTH-independent causes. ACTH-dependent Cushing's syndrome accounts for approximately 80–85% of all cases and is primarily due to excess ACTH production from a pituitary adenoma. This is also called Cushing's disease. In Cushing's disease, pituitary adrenocorticotropic hormone (ACTH) oversecretion (from corticotrophs) prompts bilateral adrenocortical hyperplasia, excess production of cortisol, adrenal androgens, and 11-deoxycorticosterone which together cause the clinical and biological features of this disease. The most common clinical features of Cushing's syndrome include central obesity, diabetes, hypertension, moon facies, facial plethora, proximal muscle weakness, and reddish purple striae and in children, impaired growth with concomitant weight gain.

Testing for Cushing's disease first serves to confirm a diagnosis of Cushing's syndrome or hypercortisolemia, then to differentiate the location of the hypersecretory adenoma. Tests used to screen for Cushing's syndrome include measurement of random serum cortisol and ACTH, urine free cortisol, late night salivary cortisol, and a 1 mg dexamethasone suppression test. Tests used to differentiate Cushing's disease from other forms of Cushing's syndrome include an 8 mg high-dose dexamethasone suppression test, a corticotrophin-releasing hormone (CRH) stimulation test, pituitary MRI, and petrosal sinus sampling.

The optimal treatment for Cushing's disease is removal of the culprit pituitary adenoma. However, other treatments exist such as pharmacological therapies. Several medications are available that act at different levels, some on the adenoma itself, others blocking the cortisol receptor sites or inhibiting steroidogenesis at the level of the adrenal glands. In cases of persistent or recurrent Cushing's disease, bilateral adrenalectomy may be performed as a definitive treatment; however, this has long-term implications such as lifelong dependence on replacement glucocorticoids and mineralocorticoids. Pituitary irradiation can be used in cases of recurrent or persistent Cushing's disease.

Cushing's disease is not only associated with increased morbidity and mortality during active disease, but this increased risk may also persist in remission. Cushing's disease is also associated with impaired quality of life, with patients reporting numerous impacts on daily life such as fatigue, interference with family life and relationships with partners, changes in physical appearance, among others. Biochemical remission is typically associated with a small improvement in quality of life impairments when compared to remission of disorders associated with other pituitary adenomas. The nurses' role is vital in the process of patient assessment, postoperative and long-term monitoring and management of these issues.

Keywords

Cushing's syndrome · Cushing's disease · Hypercortisolemia · Adrenocorticotropic hormone · Pituitary adenoma · Glucocorticoid · Cortisol

Abbreviations

ACTH	Adrenocorticotropic hormone
AI	Adrenal insufficiency
CDCS	Cushing's disease
CRH	Corticotrophin-releasing hormone
CS	Cushing's syndrome
CT	Computerized tomography
DST	Dexamethasone suppression test
EAS	Ectopic ACTH syndrome
HPA	Hypothalamic-pituitary-adrenal axis
IPSS	Inferior petrosal sinus sampling
MRI	Magnetic resonance imaging
PCOS	Polycystic ovarian syndrome
PET	Positron emission tomography
TEE	Transsphenoidal endoscopic endonasal surgery
TSS	Transsphenoidal surgery

Key Terms

- **Hypercortisolemia:** A state of excess amount of cortisol in the blood.
- **Cushing's syndrome:** Hallmark symptoms caused by body exposure to high levels of cortisol for an extended period of time. The

source of excess cortisol may be iatrogenic, pituitary, adrenal, or ectopic.

- **Cushing's Disease:** Cushing's disease is a type of Cushing's syndrome caused by excess secretion of adrenocorticotropic hormone (ACTH) from tumorous pituitary cells. Cushing's disease is the most common cause of Cushing's syndrome.
- **Hypothalamic-pituitary-adrenal (HPA) axis:** A system of three endocrine glands (hypothalamus, pituitary gland, adrenal glands) that work in a feedback loop to regulate multiple processes within the body.

Key Points

- Cushing's syndrome is a disorder characterized by excess exposure to glucocorticoids. It can be exogenous (from an outside source), or endogenous (from an internal or tumor source).
- Cushing's disease is a type of Cushing's syndrome caused by excess secretion of adrenocorticotropic hormone (ACTH) from tumorous pituitary cells. Cushing's disease is the most common cause of Cushing's syndrome in children >7 years and in adults.
- The optimal treatment of Cushing's disease is removal of the pituitary adenoma producing excess ACTH; however, pituitary adenomas are most often microadenomas (less than 10 mm in size). In 40–60% of cases, the tumor may be so small that it may not be visualized on magnetic resonance imaging (MRI).
- Symptoms of Cushing's disease at patient presentation largely overlap with a variety of other common disorders and present a diagnostic as well as treatment challenge with severe implications related to quality of life. Nursing assessment should include assessment of the multiple comorbidities associated with Cushing's disease, both physical and psychological.

21.1 Introduction to Hypercortisolism

21.1.1 Cushing's Syndrome

Cushing's syndrome is a rare disorder characterized by prolonged exposure to excessive glucocorticoids. The most common cause of Cushing's syndrome is iatrogenic, or exogenous, caused by the use of exogenous glucocorticoids including topical or inhaled corticosteroids in supraphysiologic doses (such as prednisone or hydrocortisone) (Newell-Price et al. 2006; Sharma et al. 2015a). Endogenous Cushing's syndrome, which will be the focus of this chapter, is usually divided into adrenocorticotropic hormone (ACTH)-dependent causes and ACTH-independent causes (Sharma and Nieman 2011; Findling and Raff 2006). ACTH-independent Cushing's, usually characterized by inappropriately low levels of ACTH, accounts for approximately 15–20% of endogenous Cushing's Syndrome in adults, and is primarily caused by unilateral adrenal tumors (Newell-Price et al. 2006) (see adrenal causes of Cushing's syndrome in Part VI).

21.1.2 Cushing's Disease

ACTH-dependent Cushing's syndrome is typically characterized by elevated or inappropriately normal ACTH levels in the setting of hypercortisolism (Sharma and Nieman 2011). In adults, ACTH-dependent Cushing's syndrome, also called Cushing's disease, accounts for approximately 70–80% of all cases and is primarily due to excess ACTH production from a pituitary adenoma (Newell-Price et al. 2006; Sharma and Nieman 2011). Approximately 15–20% of ACTH-dependent Cushing's syndrome cases are from non-pituitary tumors and include ectopic ACTH syndrome (EAS), and the extremely rare corticotrophin-releasing hormone (CRH) producing tumor (<1% of cases). EAS tumors are most often of neuroendocrine origin (bronchial, thymic, pancreatic, etc.). However, EAS tumors can also be derived from other causes such as pulmonary carcinoids, small cell lung carcinoma, medullary thyroid cancer, pheochromo-

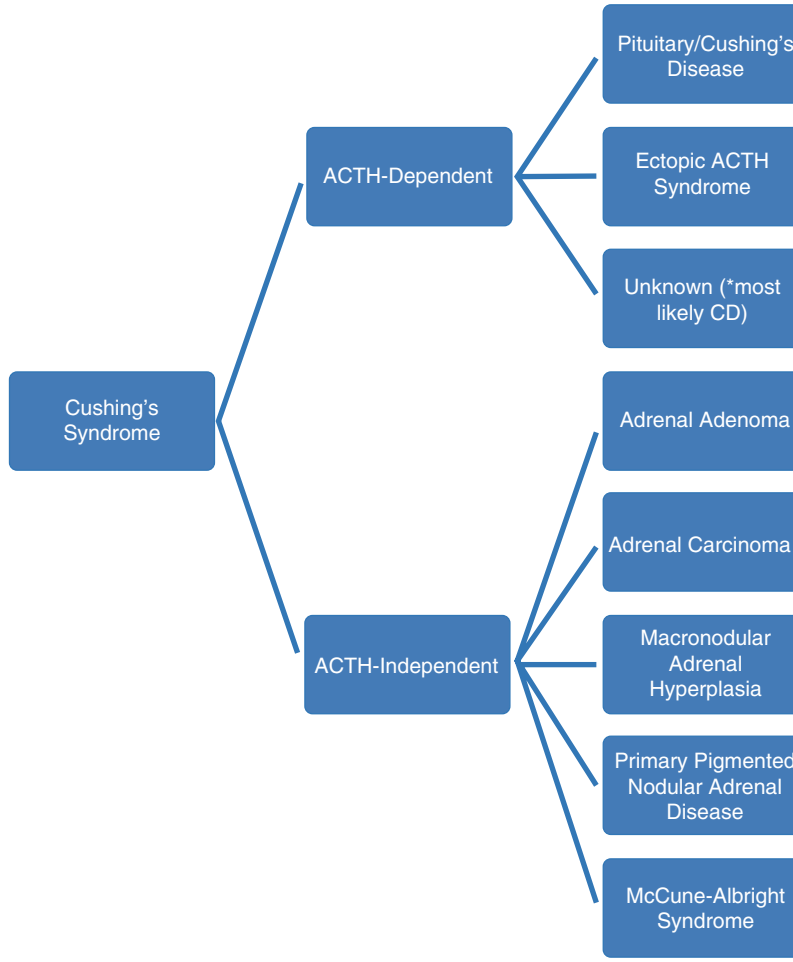


Fig. 21.1 Types and sources of Cushing's syndrome

cytomas, and more (Sharma et al. 2015a; Kamp et al. 2016). In children over the age of 7 years, and in adults an ACTH-secreting pituitary adenoma is the most common cause of CS, and adrenal etiology is the most common in children younger than 7 years. Ectopic causes of CS are extremely rare in children (Magiakou et al. 1994) (Fig. 21.1).

21.2 Cushing's Disease

21.2.1 Epidemiology and Pathophysiology

Cushing's disease (CD) is a pituitary disorder marked by pathologic hypercortisolism resulting from excess secretion of ACTH by tumorous pituitary corticotrophs (anterior pituitary cells). Cushing's disease is the most common cause of endogenous Cushing's syndrome (~70–80% of cases) (Findling and Raff 2006; Cuevas-Ramos and Fleseriu 2014) In Cushing's disease, pituitary adrenocorticotropic hormone (ACTH) oversecretion prompts bilateral adrenocortical hyperplasia with excess production of cortisol, adrenal androgens, and 11-deoxycorticosterone, which together cause the clinical and biological features of this disease (Lindholm et al. 2001).

Ten to 15% of pituitary tumors secrete ACTH, thus causing CD (Newell-Price et al. 2006) In most cases, the tumors are benign and slow growing. Microadenomas (<10 mm in diameter)

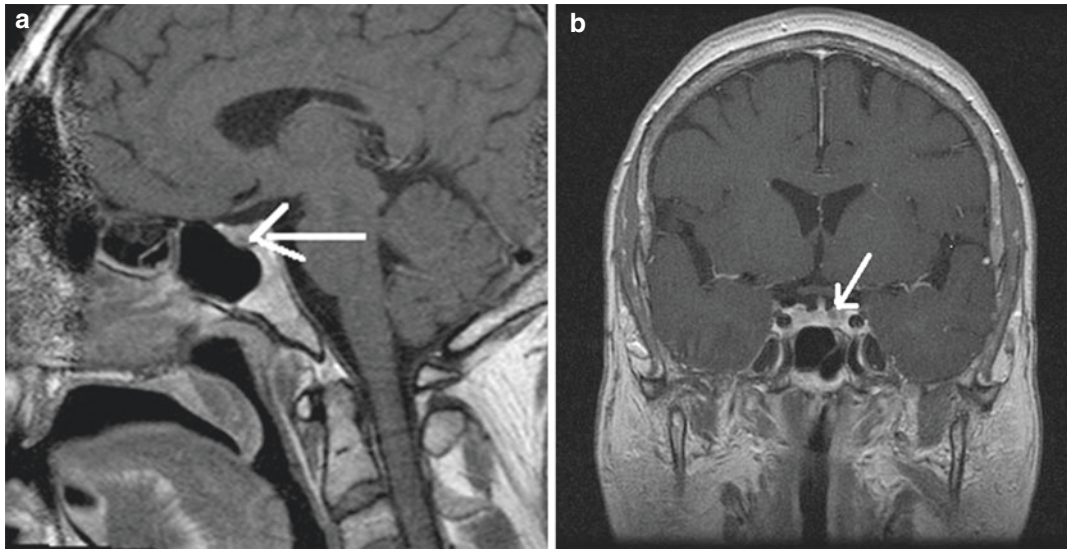


Fig. 21.2 ACTH producing microadenoma of the pituitary. (**a**) Sagittal T1 view, (**b**) Coronal T1 view. Used with permission from Mancini T, Porcelli T, Giustina A. Treatment of Cushing disease: overview and recent findings. Ther Clin Risk Manag. 2010;6:505–16

are found in 90% of cases, whereas macroadenomas (>10 mm in diameter) are less common (10% of cases). ACTH producing pituitary adenomas that cause Cushing's disease are usually well-delineated microadenomas, some as small as 1–2 mm, and most often located in the central wedge of the anterior lobe (see Fig. 21.2). Due to their small size, many ACTH producing tumors are undetectable by MRI and difficult to find at surgery. In some cases, the adenomas are localized to the lateral wings of the pituitary, in the pars intermedia or in the neurohypophysis and, rarely, in the pituitary stalk. The size of the tumor can influence treatment outcome (Newell-Price et al. 2006; Syro et al. 2015) (see Chap. 1).

The overall incidence and prevalence of endogenous Cushing's syndrome is 2–3 per million per year and 30–60 patients per million, respectively (Newell-Price et al. 2006; Syro et al. 2015; Graversen et al. 2012). The average age of onset of Cushing's disease in adults is 36 years (mean of 30.5 years in females, 37.1 years in males) (Newell-Price et al. 2006). Severity of presentation varies widely, but a milder clinical phenotype in a patient presenting with Cushing's syndrome, especially if female, is more likely to be due to Cushing's disease than other etiologies (Sharma and Nieman 2011; Clayton et al. 2011). Cushing's disease also has a definite female preponderance, the female/male ratio ranging between 3:1 and 10:1 (Zilio et al. 2014). Similar to adults, in children there is a female to male predominance that decreases with younger age (see Fig. 21.3) (Magiakou et al. 1994; Nieman et al. 2015).

21.3 Genetics of Cushing's Disease

The majority of ACTH producing pituitary adenomas are the result of sporadic mutations, with most patients reporting no family history of the disease. Since most of these tumors are isolated, this makes hereditary or germ line mutation unlikely. Recent studies have shown that a mutation in a gene known as USP8 is present in approximately one-third of patients with Cushing's disease (Biller et al. 1992; Theodoropoulou et al. 2015). However, the etiology of genetic mutation remains largely unknown.

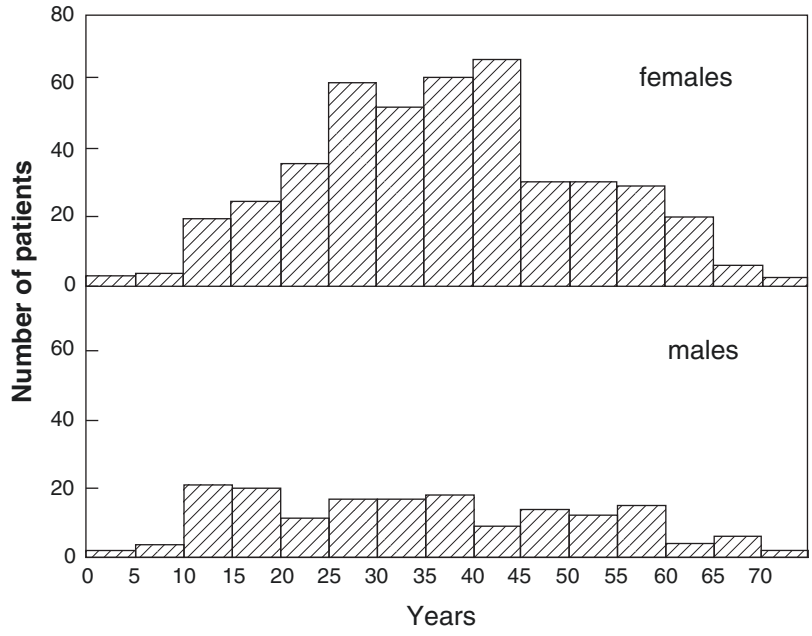


Fig. 21.3 Patient age at the time of diagnosis of Cushing's disease. Melmed S. The pituitary. 3rd ed.:535. https://doi.org/10.1016/B978-0-12-380926-1.10016-1 (Batista et al. 2007)

Childhood corticotropinomas, that occur in the familial setting, most commonly occur in the context of multiple endocrine neoplasia type 1 (MEN 1) and rare *AIP* mutations should be considered (Stratakis et al. 2010).

21.4 Morbidity and Mortality

Cushing's disease is a serious condition associated with significant morbidity and severe impacts on patients' quality of life (Syro et al. 2015; Graversen et al. 2012; Dekkers et al. 2013). Morbidity and mortality associated with Cushing's disease is most often related to cardiac and cerebrovascular events, infections due to immunosuppression, osteoporosis, and diabetes. Untreated, CD has a mortality ratio of approximately of 1.9–4.8 (ratio of CD-associated deaths to expected deaths of general population) (Kamp et al. 2016; Lonser et al. 2017). Importantly, mental health disorders, including suicidal ideation, have been reported in children and adults after disease remission (Keil et al. 2016; Dorn et al. 1995). Overall mortality in Cushing's disease is double that of the general population and up to four times higher than in age- and sex-matched controls (Syro et al. 2015; Graversen et al. 2012; Dekkers et al. 2013). In addition, mortality in patients with Cushing's disease is more than twice that of patients with non-functioning pituitary macroadenomas even when previously treated, implying that even transient cortisol over-exposure contributes to the increase in mortality risk (Clayton et al. 2011).

21.5 Patient Presentation and Assessment

Prolonged exposure to excessive cortisol levels results in multiple signs and symptoms affecting various body systems. Although the tumor causing the disease tends to be slow growing, the excess secretion of ACTH means that clinical features can manifest before the tumor has grown large or large enough to be detected. Although Cushing's disease may be more easily identifiable when severe, the signs and symptoms remain broad and may be difficult to distinguish from other disorders such as metabolic syndrome or polycystic ovarian disease (Nieman et al. 2008). The most common clinical features in adults include central obesity, diabetes, hypertension, moon facies, and facial plethora (Lonser et al. 2017; Nieman

Table 21.1 Clinical features of Cushing's syndrome

Clinical features—more specific to Cushing's syndrome	
More common	Less common
Easy bruising	Striae
Facial plethora	
Proximal muscle weakness	
In children, weight gain and decreased linear growth	
Clinical features less discriminatory for Cushing's syndrome or common in the general population	
More common	Less common
Obesity/weight gain	Acne
Depression	Recurrent infections
Lethargy/fatigue	Nephrolithiasis
Hypertension[a]	Female balding
Menstrual changes	Osteopenia or fracture[a]
Hirsutism	
Abnormal glucose tolerance[a]	
Round face	
Decreased libido	
Thin skin[a]	

This table made with data from: Newell-Price et al. (2006), Sharma et al. (2015a), Neiman et al. (2008), Neiman (2015).
[a]Nieman (2015)

et al. 2008) (see Table 21.1). Some symptoms are more unique to Cushing's syndrome and can be helpful in differential diagnosis such as reddish purple striae, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis, often with a history of one or more fractures (Nieman et al. 2008). In most children, the onset of Cushing's syndrome is somewhat insidious (Magiakou et al. 1994). Lack of height gain concomitant with persistent weight gain is the most common presentation of Cushing's syndrome in childhood, as depicted in a typical growth chart for a child with Cushing's syndrome shown in Fig. 21.4. Other common problems reported in children include facial plethora, headaches, hypertension, hirsutism, amenorrhea, skin fungal infections, and delayed sexual development (Magiakou et al. 1994). Pubertal children may present with virilization. Glucose intolerance and diabetes, fractures, and kidney stones are also associated presenting symptoms. In comparison to adult patients with Cushing's syndrome, symptoms that are less commonly seen in children include sleep disruption, muscular weakness, and problems with memory dysfunction (Magiakou et al. 1994).

Physical characteristics can also include dorsocervical fat pad (buffalo hump), thinning hair, thin skin, striae (most often on the abdomen), purpura, and skin ulcers due to poor wound healing. In addition, other features may manifest, including severe fatigue, hypokalemia, hypertension, depression, cognitive impairment, hyperpigmentation, sexual/menstrual dysfunction, hirsutism, acne, bone fractures, kidney stones, and susceptibility to opportunistic infections (Lonser et al. 2017; Nieman et al. 2008). Patients presenting with pituitary adenomas frequently experience impairment of the gonadotropic axis resulting in amenorrhea in females and impaired fertility (Graversen et al. 2012). Furthermore, the effects of Cushing's disease include cardiovascular complications, as well as metabolic disturbances that can result in fat tissue redistribution and obesity, often most severe in the abdomen (Lonser et al. 2017; Nieman et al. 2008) (see Fig. 21.5).

Although Cushing's disease is less frequent in males, the presentation tends to be more florid with higher cortisol levels and severity of complications (Zilio et al. 2014). Average time from initiation of symptoms to diagnosis ranges from 2 to 3 years in adult males but can be significantly longer in females. Before puberty, the prevalence

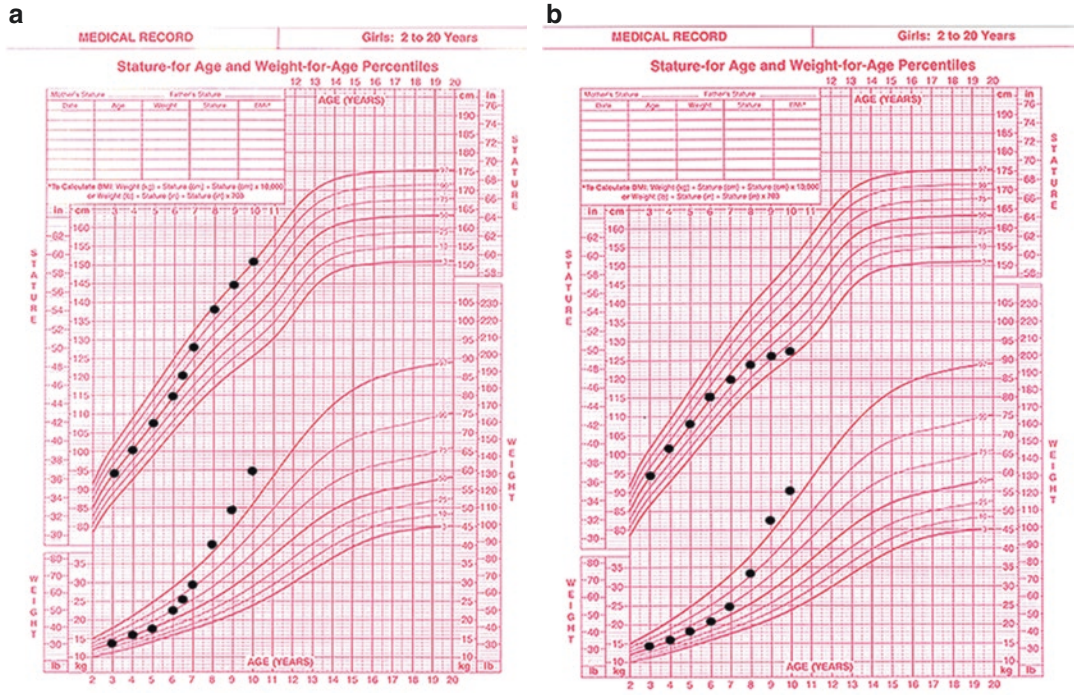


Fig. 21.4 Growth in children with Cushing's disease. (**a**) Obsese child, (**b**) Child with Cushing's disease

of CD is similar in both genders versus in adult cases when females are more frequently affected than males (3:1 vs 5:1, respectively) (Lonser et al. 2017). Few of the symptoms of CD are unique, and many have strong overlap of symptoms with other disorders and in some cases with the general population, presenting challenges in identifying the disorder based on clinical presentation alone (Nieman et al. 2008).

While many physical symptoms of Cushing's syndrome are not completely indicative of the disorder, many other disorders, such as those causing pseudo-Cushing's syndrome (PCS), also present a challenge in the diagnosis of Cushing's syndrome. PCS cases present with a similar clinical phenotype including obesity, diabetes, hypertension, moon face, buffalo hump, striae as well as mild hypercortisolemia. Disorders associated with PCS include chronic alcoholism, psychiatric disorders, severe obesity, poorly controlled diabetes, and extreme physical and psychological stress. Polycystic Ovarian Syndrome (PCOS) can also present with a similar phenotype in women of reproductive age. Metabolic syndrome described in overweight or obese individuals with comorbidities such as hypertension, diabetes, and dyslipidemia can also mimic Cushing's due to its similar phenotype. Additionally, small elevations in cortisol can contribute to obesity and metabolic syndrome. Treatment of these underlying conditions will lead to resolution of these Cushingoid symptoms, differentiating them from Cushing's syndrome (Alwani et al. 2014; Friedman and Yanovski 1995; Brzana et al. 2014).

21.6 Testing and Diagnostic Procedures

Diagnostic testing for Cushing's disease serves to not only confirm the presence of hypercortisolemia, but to differentiate its cause as ACTH dependent or independent. In ACTH-dependent Cushing's, the next step is to confirm a pituitary source of excess ACTH.

Patients who present with features of Cushing's who are not taking exogenous glucocorticoids (iatrogenic Cushing's syndrome) should first be screened for Cushing's syndrome or the presence of hypercortisolism. The initial screening tests are

measurement of urine free cortisol over 24 h, and late night salivary cortisol collected before bedtime to check for inappropriately elevated cortisol (see circadian rhythm, Chap. 1). Multiple measurements should be done to ensure that results are not falsely positive or falsely negative. A 1 mg overnight dexamethasone suppression test (DST) and the longer 2 day or high-dose DST (over 48 h) are also used. Normal subjects without Cushing's will have suppression of cortisol levels when given one or more dose(s) of exogenous steroids (dexamethasone) due to the HPA axis feedback loop (see Fig. 21.6), but those with Cushing's syndrome and excess cortisol production will not. A longer low-dose DST, over 48 h, is sometimes performed instead of the 1 mg or overnight DST due to increased specificity of this test and may be also be combined with corticotrophin-releasing hormone (CRH) stimulation to increase the test reliability. The normal variability of random serum cortisol or plasma ACTH levels makes these measures unreliable for a diagnosis of Cushing's syndrome (Nieman et al. 2008).

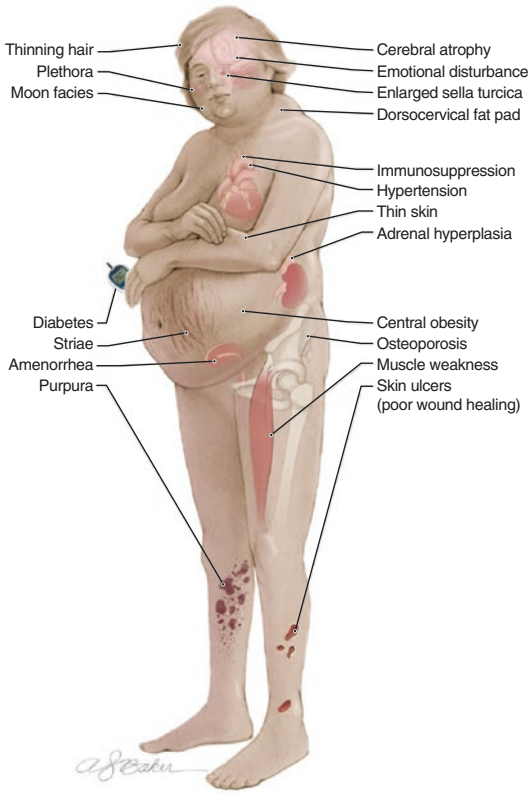


Fig. 21.5 Clinical features of Cushing's syndrome. Used with permission from Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and management. J Neurosurg. 2017;126(2):404–17

If after screening Cushing's syndrome is confirmed, a basal ACTH level can be used to help differentiate ACTH-dependent from independent Cushing's syndrome. Suppressed plasma ACTH indicates an adrenal or ACTH-independent cause, while inappropriately elevated ACTH levels are consistent with an ACTH-dependent cause (Lonser et al. 2017; Lindsay and Nieman 2005). It is important to measure on several occasions to ensure accuracy.

Multiple dynamic tests are usually conducted to differentiate Cushing's disease from ectopic ACTH-secreting tumors. The high-dose dexamethasone suppression test relies on the concept that pituitary tumor cells retain sensitivity to glucocorticoid feedback effects similar to that of normal pituitary cells. After administration of 8 mg of dexamethasone, if there is a suppression of serum cortisol Cushing's disease should be suspected (Lonser et al. 2017; Lindsay and Nieman 2005). Sensitivity of this test for CD

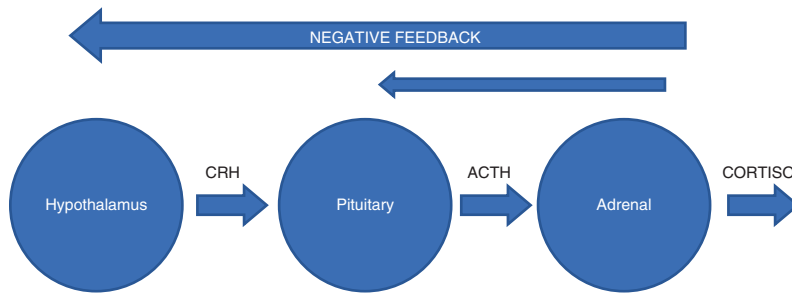


Fig. 21.6 HPA axis feedback loop

varies from 65 to 100%, increasing with degree of cortisol suppression (Lindsay and Nieman 2005). The corticotrophin-releasing hormone (CRH) stimulation test again relies on pituitary tumor cells responding to CRH stimulation. When CRH is given, if cortisol and ACTH rise from basal levels Cushing's disease should be suspected, whereas ectopic tumors generally do not respond to CRH (Lonser et al. 2017; Lindsay and Nieman 2005). A combination of a positive response to CRH and suppression on DST makes CD more likely (Clayton et al. 2011), so the use of multiple biochemical tests is often encouraged.

Less common tests include the metyrapone and desmopressin tests. These have little efficacy when used alone and are not typically recommended for diagnostic purposes (Lindsay and Nieman 2005). It is also important to note that Cushing's syndrome can be cyclic, characterized by fluctuations in, or periods of hypercortisolism, although this is extremely rare (Colao et al. 2014). Because of this, to ensure accuracy of testing, hypercortisolism must be confirmed before undergoing any differential diagnostic testing for Cushing's disease. There is also no widely accepted consensus regarding diagnostic cut-offs related to these tests, therefore ranges may vary by institution and laboratory assays. Specificity among the various diagnostic tests is also variable, and it is recommended that multiple tests are conducted to increase specificity and confirm a diagnosis (Colao et al. 2014).

Diagnosis can be further supported by presence of pituitary adenoma on imaging. However, in 40–60% of cases, microadenomas cannot be detected on MRI (Lonser et al. 2017; Colao et al. 2014). Petrosal sinus sampling, while more invasive, can help with a more definitive diagnosis of Cushing's disease when other results and features are unclear (Colao et al. 2014). Computed tomography (CT) (more preferable than MRI) of the adrenal glands is useful in the distinction between Cushing's disease and adrenal causes of Cushing's syndrome, usually caused by a unilateral adrenal tumor. The distinction is harder in the presence of micronodular forms of bilateral adrenal hyperplasia (BAH) (such as primary pigmented nodular adrenocortical disease (PPNAD)) or the rare case of bilateral adrenal carcinoma. Most patients with Cushing's disease have ACTH-driven bilateral hyperplasia, and both adrenal glands will appear enlarged and nodular on CT or MRI (Tsigos and Chrousos 1996; Batista et al. 2007).

Testing for the differential diagnosis of ectopic ACTH syndrome is similar to the testing for Cushing's disease and is dependent on the correct interpretation of the results. This includes confirmation of hypercortisolism, the high-dose dexamethasone suppression test, pituitary imaging (for absence of pituitary adenoma), and petrosal sinus sampling. Structural (CT and MRI) and functional imaging such as positron emission tomography (PET) scans are also vital in the identification of the source of EAS (Sharma et al. 2015a; Sharma and Nieman 2011; Kamp et al. 2016) (See Fig. 21.7). (See Part VI for detailed information on EAS and ACTH independent Cushing's disease).

For more details on dynamic testing, endocrine testing, and patient instructions, see Chap. 15.

21.7 Treatment Modalities

21.7.1 Surgical Treatment

The optimal treatment for Cushing's disease is the successful removal of the culprit pituitary adenoma by a surgical, selective adenomectomy (removal of the tumor while preserving pituitary tissue). This will immediately eliminate the excess cortisol production with the goal of preserving normal pituitary function (Lonser et al. 2017). Surgical access to the pituitary gland, also known as transsphenoidal surgery (TSS), has multiple approaches. These can be sub-labial, endonasal, endoscopic, and/or microscopic (Lonser et al. 2017). Pituitary adenomectomy generally leads to remission rates of 65–90% of cases in the hands of an experienced neurosurgeon with a higher likelihood of remission for those with microadenomas versus macroadenomas (Lonser et al. 2017; Mancini et al. 2010; Vilar et al. 2015). However, the lifetime recurrence rate after

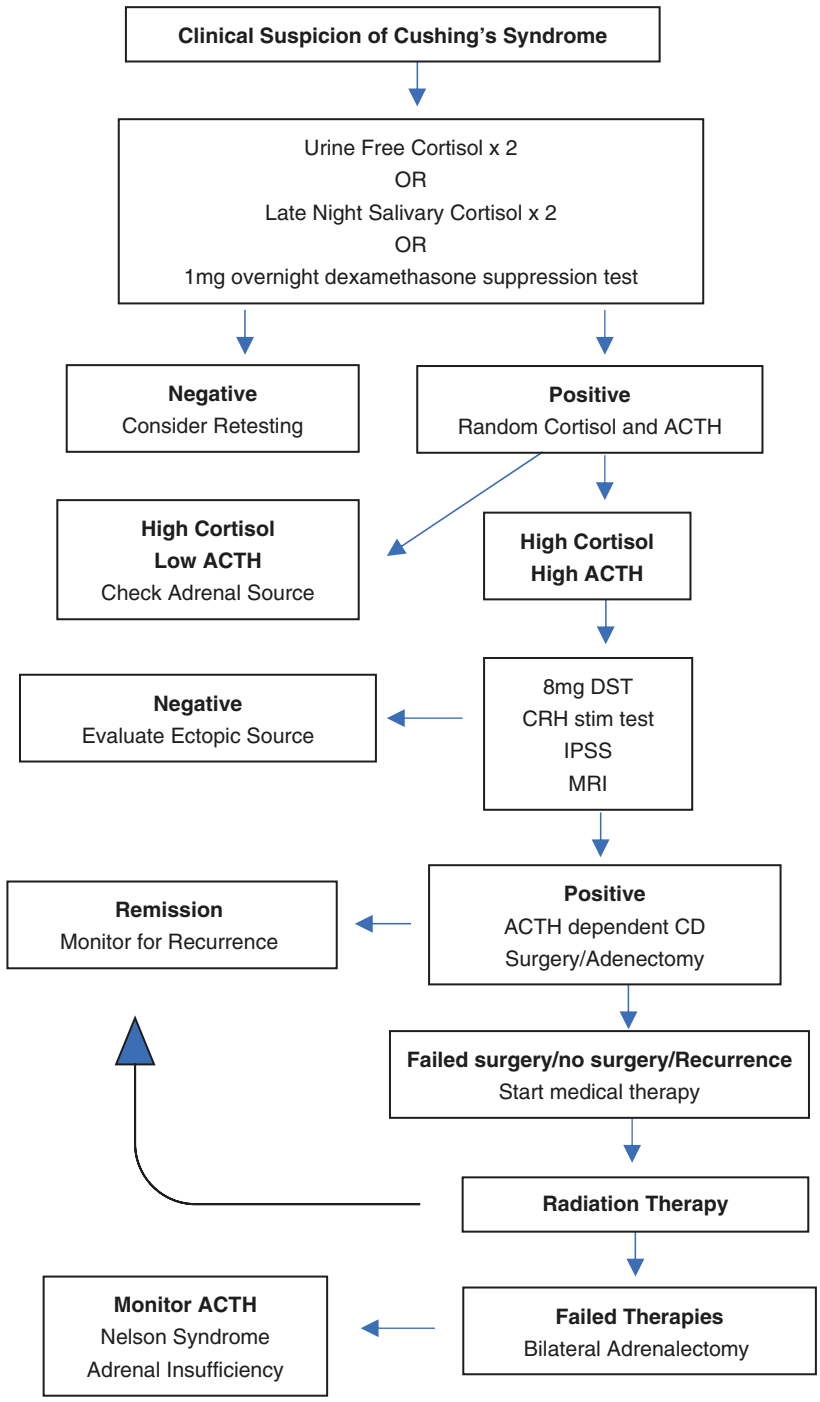


Fig. 21.7 An algorithm for the assessment and treatment of Cushing's disease. Derived from Neiman et al. 2008; Lonser et al. 2017; Dekkers et al. 2013

surgical remission is reported as 10–35% (Lonser et al. 2017; Vilar et al. 2015) (See Chap. 11).

Multiple factors influence successful surgical outcome. Magnetic resonance imaging (MRI) is most helpful in localizing the offending tumor; however, 40–60% of microadenomas (diameter of 6 mm or below) will not be clearly detected (Lonser et al. 2017; Mehta and Lonser 2017).

Lateralization of ACTH secretion using IPSS is also helpful to direct the surgeon to the corticotroph tumor. When the adenoma is seen on MRI, it directs surgical exploration to the adenoma within the gland, increasing chances of identifying the adenoma. Adenomas found to be at least 3 mm are not only easier to identify on MRI, but may develop a histological pseudocapsule, or tissue envelope around its rim. Using this capsule to remove an adenoma can improve remission rates to 97% in adults or 98% in children, again, in the hands of an experienced neurosurgeon (Lonser et al. 2017). Adenomas can also be found to invade the dura or surrounding tissue. Macroadenomas often invade into the cavernous sinus, which makes curative surgery unlikely. In such cases, a portion of the tumor cannot be surgically removed safely without significant risk to structure in the area such as the internal carotid arteries or cranial nerves 11-V1 (Lonser et al. 2017) (See Chap. 22).

While many adenomas not seen on MRI can later be identified during pituitary exploration, some may still be too small to be located. In these cases a portion of the pituitary gland, or a partial hypophysectomy, of the anterior lobe may be performed. Partial and total hypophysectomies have remission rates similar to that of selective adenomectomy (60–80%) but result in significant pituitary hormone deficiencies or panhypopituitarism (Lonser et al. 2017).

The risks of surgery, although not common, include: vision loss, cranial nerve injury, loss of pituitary function, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), pituitary apoplexy, delayed hemorrhage, cerebrospinal fluid leakage, infection (meningitis), and very rarely, death (<1%) (Lonser et al. 2017). For more information on pituitary surgery, see Chap. 22. Remission is confirmed by absence of hypercortisolism, and pathologic findings. Typically, biochemical remission is considered achieved when a 24–48 h postsurgical morning serum cortisol level is below 5 mg/dL (90 mmol/L) after glucocorticoids have been withheld for 24 h (Mehta and Lonser 2017).

21.7.1.1 Postsurgical Hypopituitarism and Adrenal Insufficiency

After successful surgery to remove a pituitary adenoma, normal corticotrophs are typically suppressed, causing a temporary secondary adrenal insufficiency. Glucocorticoid replacement is required until the HPA axis recovers, typically for 6–12 months following resection of ACTH producing pituitary tumors or longer. Patients are usually treated with hydrocortisone, prednisone, or dexamethasone using a physiologic dose (usually 15–30 mg of hydrocortisone daily for adults and 10–12 mg/m^2 in children or adults) until laboratory testing reveals a functional HPA axis (via serum cortisol and ACTH level, or dynamic ACTH stimulation test) (Nieman et al. 2015). Higher doses may be required immediately postoperatively to avoid symptoms of adrenal insufficiency. These doses are usually tapered to physiologic dose based on body surface area to avoid acute symptoms of secondary adrenal insufficiency. There is still no general consensus regarding steroid dosing or tapering technique during this time period. Once on a physiologic dose, further dynamic testing to ensure HPA axis is functional is usually undertaken prior to discontinuing glucocorticoids.

It is vital that patients are educated on the signs and symptoms of acute adrenal insufficiency, adrenal crisis, as well as stress dose requirements. An adrenal crisis occurs when a patient with adrenal insufficiency is challenged by severe illness or stressor but unable to meet the demand or increased need of cortisol. Insufficient cortisol coverage during periods of illness (such as infections) is linked to increased morbidity and mortality risk (van der Meij et al. 2016; Johannsson et al. 2015) (see adrenal insufficiency, Chaps. 22, 23, 62, and Part XII).

21.7.2 Medical Therapy

Medical therapy is recommended as a second-line treatment or alternative approach of patients with CD who cannot undergo surgery, who have

not achieved remission after surgery, or those who are not candidates for a repeat surgical procedure in the case of recurrence (Mancini et al. 2010; Mehta and Lonser 2017). However, medical therapy can also be used preoperatively to control the metabolic effects of severe hypercortisolism, to reduce surgical and anesthesia risk, or while waiting for the effects of pituitary radiotherapy to manifest (Mancini et al. 2010; Vilar et al. 2015). Types of medical therapy include corticotroph or pituitary directed agents or steroidogenesis (adrenal) inhibitors or glucocorticoid antagonists.

Pituitary directed medical treatments are centrally acting and work to inhibit ACTH secretion from corticotroph tumor cells (Nieman et al. 2015; Vilar et al. 2015; Mehta and Lonser 2017). Somatostatin is a primary neuromodulating hormone that is produced in the hypothalamus and affects the production of ACTH from corticotroph cells. The drug pasireotide binds with four of the five known somatostatin receptor types but with a high affinity for subtype 5 and subsequently inhibits the secretion of ACTH from corticotroph cells and corticotroph tumor cells expressing somatostatin receptors (Johannsson et al. 2015). Dopamine agonists have a similar, but weaker, effect on the dopamine receptors, subsequently inhibiting ACTH.

Although the ideal therapy would be directed at the pituitary adenoma itself, steroidogenesis inhibitors were the first therapies used in the treatment of CD and remain among the most common therapies (Cuevas-Ramos and Fleseriu 2014). Steroidogenesis inhibitors or adrenal enzyme inhibitors, lower serum cortisol levels by blocking one or several steps in the biosynthesis of cortisol from the adrenal cortex (Vilar et al. 2015). Close monitoring of the HPA axis and patient symptoms is required during therapy to avoid the development of adrenal insufficiency.

Glucocorticoid antagonists, such as mifepristone, block systemic effects of hypercortisolism but do not lower serum cortisol (Mehta and Lonser 2017). Therefore, serum cortisol levels and hence urine free cortisol levels will rise but the tissue and end organ effects of cortisol are blocked.

Mitotane, an adrenocorticolytic drug that causes necrosis of adrenocortical cells, is reserved for patients with persistent or recurrent Cushing's disease who cannot undergo bilateral adrenalectomy, due to its severe side effects and high cost (Abdel Mannan et al. 2010). Intravenous etomidate inhibits 11β-hydroxylase and is used for emergent control of severe hypercortisolism, but is used rarely due to its need for intensive care monitoring due to its sedative hypnotic effect and need for airway support (Mehta and Lonser 2017) (Fig. 21.8).

Combination medical therapy with multiple drug classes is a treatment option gaining popularity. While there are still no guidelines or treatment strategies, utilization of multiple therapies may increase efficacy, decrease drug doses, and possibly result in fewer adverse effects (Cuevas-Ramos and Fleseriu 2014) (Table 21.2).

In the USA, only a few medications effective in the medical management of hypercotisolism are FDA approved for use in CS, several are used off-label such as ketoconazole (Vilar et al. 2015). The use and availability of medical therapies for CS varies from country to country.

Each medication comes with multiple side effects, and patients should be closely monitored. With any of the medical therapies, there is a risk of overtreatment that could lead to adrenal insufficiency (Sharma et al. 2015a). Therefore, medical therapy can be used to either block cortisol production to achieve normal levels, or by blocking cortisol production completely, which would require glucocorticoid replacement (Sharma et al. 2015a). Somatostatin analogues also inhibit gut cholecystokinin release affecting gallbladder contractility and may result in gallstone formation. Decreased digestive enzymes result in abdominal bloating and diarrhea (Bertagna et al. 2011). All patients on medical therapy, post-surgery, and post-radiation should be educated regarding therapy side effects and the signs, symptoms, and management of adrenal insufficiency (see Tables 21.2 and 21.3).

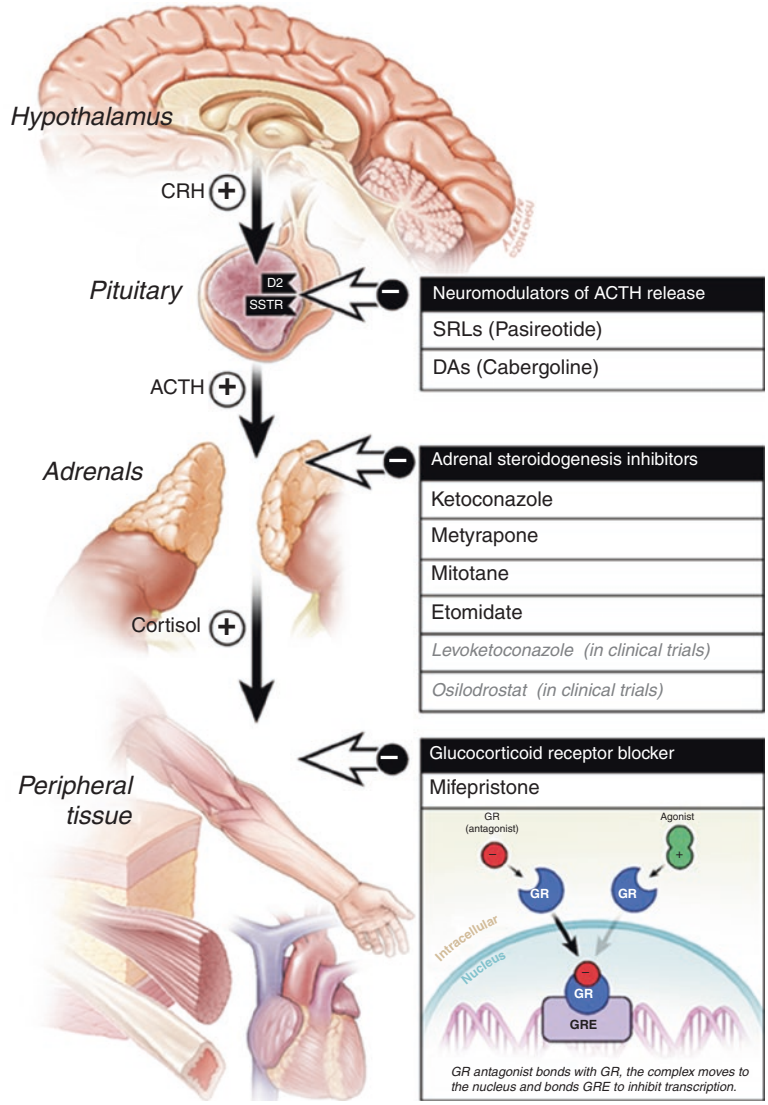


Fig. 21.8 Medications and their level of action in Cushing's disease. Fleseriu M. Medical management of persistent and recurrent Cushing disease. Neurosurg Clin N Am. 2012;23(4):653–68. Reproduced with permission from Fleseriu 2012

Table 21.2 Medications and side effects

Class	Drug name	Common side effects/considerations
Steroidogenesis inhibitors	Ketoconazole	Hepatitis, gastrointestinal disturbance, gynecomastia, male hypogonadism, adrenal insufficiency
	Fluconazole	Similar to ketoconazole
	Metyrapone	Hypertension, adrenal insufficiency, hirsutism, acne, hypokalemia, edema, gastritis, nausea, accessibility variable across countries
	Etomidate (IV)	Somnolence, nausea, vomiting, adrenal insufficiency (*often require intensive care monitoring—quick onset of action)
	Mitotane	Gastrointestinal disturbance, hepatitis, neurologic disturbance, neutropenia, adrenal insufficiency, slow onset of action
Dopamine agonist	Cabergoline	Headache, nausea, dizziness
Somatostatin receptor binding	Pasireotide	Hyperglycemia, diabetes, diarrhea, nausea, QT prolongation
GR antagonist	Mifepristone	Nausea, fatigue, headache, hypertension, hypokalemia, endometrial thickening, vaginal bleeding, adrenal insufficiency, difficult to titrate (no biomarker)

Table 21.3 Patient education topics

Symptom start/diagnosis	Testing/treatment	Recovery
• Weight management • Fatigue/sleep • Management of comorbidities (diabetes, hypertension, etc.) • Fertility/menstrual cycle/libido • Self-perception/self-esteem	• Dynamic testing • Treatment options • Management of comorbidities (diabetes, hypertension, etc.) • Pre- and postsurgical care and restrictions • Medical therapy	• Fatigue/sleep • Weight management • Returning to work • Self-perception/ self-esteem • Support groups • Physical activity/ physical therapy • Long-term follow-up

21.7.3 Bilateral Adrenalectomy

As a definitive treatment, a bilateral adrenalectomy (BLA) may be considered. BLA is most often used in cases of refractory Cushing's Disease as last resort (Sharma et al. 2015a; Colao et al. 2014; Mancini et al. 2010). The adrenal glands are the target organs of ACTH and in a hypersecretory state this upregulates the production of cortisol from the adrenal cortex leading to hypercortisolism. Bilateral adrenalectomy leads to immediate resolution of hypercortisolism; however, the patient subsequently will require lifelong glucocorticoid and mineralocorticoid replacement (Sharma et al. 2015a). Education of patients to treat illness and injury by increasing glucocorticoids and in the use and administration of emergency stress doses of intramuscular glucocorticoids may be lifesaving. It is recommended that all patients obtain medic alert jewelry and/or carry a card identifying their surgical absence of adrenal glands, risk of adrenal insufficiency and clearly state their need for IM/IV glucocorticoids, fluid resuscitation, and monitoring of electrolytes in emergent situations (van der Meij et al. 2016).

Long-term clinical, serum ACTH level monitoring, and brain imaging is recommended to evaluate for tumor growth and the development of Nelson's syndrome after BLA. Nelson's syndrome is a potentially life-threatening syndrome that occurs in the presence of residual corticotroph pituitary tumor. ACTH levels may continue to climb secondary to the lack of cortisol opposition and tumor growth (Barber et al. 2010). The incidence of this syndrome is as high as 8–43% in adults and 25–66% in children and has been reported to occur up to 24 years after BLA (Barber et al. 2010). BLA at a younger age is more predictive of the development of Nelson's syndrome with children being at increased risk. Patients may present with compressive symptoms such as visual field deficits, and skin hyperpigmentation that may first become apparent in axillae, hand, and knuckle creases and then become generalized. Treatment with adequate suppressive doses of glucocorticoid may be adequate but first-line therapy is usually redo surgical resection of the pituitary tumor and radiotherapy may be necessary to achieve tumor control (Barber et al. 2010).

21.7.4 Radiation Therapy

In cases of persistent disease post TSS, pituitary radiotherapy can be used to control hypercortisolism. Pituitary irradiation is also an option for those who are poor surgical candidates, patients with residual tumors, and patients with surgically inaccessible tumors (Abdel Mannan et al. 2010). Fractionated external beam radiation and stereotactic radiosurgery have remission rates of approximately 50–60%, but require long-term follow-up to monitor for both initial response and recurrence. Risks of radiation are similar to that of TSS surgery, but also include potential for radiation damage and higher risk of secondary malignancies (Mancini et al., 2010) (see radiotherapy, Chap. 12).

21.7.5 Other Considerations

21.7.5.1 Management of Concomitant Diseases

While it is important to manage the cause of Cushing's disease with surgery or medications, it

is also vital to manage comorbidities. After treatment, management of comorbidities remains an important goal as there is a persistently increased cardiovascular risk despite remission (Sharma et al. 2015b). Those patients who experience immediate improvement in comorbidities, such as diabetes and hypertension, require regular monitoring for down-titration of associated medications; however, some comorbidities persist long-term. In many patients, diabetes, hypertension, obesity, hyperlipidemia, osteoporosis or osteopenia, compromised final height (children and adolescents), as well as psychological and cognitive issues can persist after remission. Patients in remission of Cushing's disease overall remain at an increased risk of mortality (Sharma et al. 2015b; Espinosa-de-Los-Monteros et al. 2013; Clayton et al. 2016).

21.8 Quality of Life and Patient Education

Patients with Cushing's disease suffer from multiple health and psychological issues related to the disease, many of which can endure during and after treatment. Health related quality of life (HRQoL) is significantly impaired in patients with active Cushing's disease, and this often remains impaired even after remission is achieved. In a recent analysis of a large cohort of patients treated for CD drawn from a European registry, HRQoL remained lower than patients in remission from adrenal Cushing's syndrome 1 year later (Valassi et al. 2018). All patient scores showed lower HRQoL than normal subjects at baseline. Those patients with CD and baseline depression and patients diagnosed with CD at a younger age also had worse HRQoL scores 1 year after remission (Valassi et al. 2018). In terms of disease impact on daily life, CS patients most commonly report fatigue, weakness, interference with family life and relationships with partners, changes in physical appearance and body image issues, among others. Despite biochemical remission, quality of life measures also remain lower in children when compared to the treatment of other pituitary adenomas (Lonser et al. 2017; Johannsson et al. 2015; Keil et al. 2009). Younger children with CS are also more likely to experience negative cognitive changes (Keil et al. 2009).

Current research using modified glucocorticoid release formulae or delivery methods for glucocorticoid-dependent patients are showing some promise with respect to stabilizing or improving HRQoL, BMI, and blood sugar (Quinkler et al. 2015). Comprehensive education has also been shown to impact HRQoL. A study of 61 Cushing's syndrome patients randomly assigned to a structured nurse directed education program for patients with Cushing's syndrome over a period of 9 months versus no education found statistically significant improvement in physical activity, healthy lifestyle, better sleep patterns, and reduced pain in CS patients (Martinez-Momblan et al. 2016). The program both influenced HRQoL and reduced consumption of health resources.

21.9 Nursing Considerations

The nurses' role is vital in all phases of patient management and in particular patient education. Healthcare programs to address quality of life indicators in this population are lacking. Educational programs and use of support resources can lead to clinical improvement, reduced hospital admissions or visits, and improved overall quality of life (Martinez-Momblan et al. 2016).

Additional quality of life topics that should be addressed include fertility issues, sleep dysfunction, emotional instability, depression, cognitive impairments, among others (Feelders et al. 2012) (Table 21.3).

Advocating for psychological support, family support, and cognitive therapies may be useful to help patients and families negotiate changes during treatment. Referrals and care coordination with other disciplines regarding the assessment and management of comorbidities such as sleep dysfunction, weight management, nutrition, and physical therapies etc. may assist to improve patient outcomes and HRQoL. However, more evidence is needed to support these assumptions. Consideration should be given to the specific

needs of the patient's stage of life, functional needs, and economic support.

Patients will require long-term follow-up and monitoring and perhaps a transition plan for all, or a component of, care to be provided at a convenient location in order to ensure ongoing follow-up.

21.10 Conclusions

Hypercortisolemia caused by an ACTH producing pituitary adenoma or Cushing's disease incurs a high mortality risk if not treated. It is a complex disease often with a significant delay in diagnosis. This delay results from the numerous non-specific symptoms that overlap with other disorders such as PCOS and metabolic syndrome. Diagnosis requires multiple test modalities and frequently the resources of a specialty center. The first-line treatment is surgical excision of the causative pituitary adenoma with the best chance of remission achieved by a neurosurgeon who is experienced in removing pituitary tumors.

Although remission rates are higher when surgery is performed in major centers, those patients not in remission with recurrent disease or with large or inaccessible tumors will require medical therapies and/or radiation therapy to control disease. Bilateral adrenalectomy is a definitive cure for CD but risks the development of Nelson's syndrome with high levels of ACTH.

All patients will require long-term management and support from all disciplines. Although quality of life may remain lower than that of the average population, the best patient outcomes are more achievable with collaboration of endocrine physicians and nurses and the involvement and coordination of all axillary services available to meet the patient's needs.

Patient Case Study

Background:

- A 46-year-old female presented to the hospital ER for a non-healing wound on her right foot after an insect bite. She was found to be hypertensive (180/102), hypokalemic (potassium 2.0 nmol/L), and hyperglycemic (300 mg/dL), leading to new diagnoses of diabetes and hypertension. Patient was referred to endocrinology for diabetic management.
- Patient also reported a plethora of symptoms beginning approximately 6 months prior: excessive facial hair, easy bruisability, depression with severe mood swings, weakness, difficulty climbing stairs, and weight gain of approximately 15 lb (6.8 kg).
- On exam the patient was noted to have central obesity purple striae on her abdomen and an unhealed purulent foot wound. A 24 h urine free cortisol was collected due to suspicion for Cushing's syndrome and the patient was referred to specialty center for further diagnostic testing.

Laboratory Results:

24 h urine free cortisol 1505 mcg/24 h (ref 3.5–45)

8 mg DSST pre-dexamethasone dose cortisol: 29.3 mcg/dL, post-dexamethasone dose cortisol: 2 mcg/dL (93.2% suppression)

CRH stimulation test

	−5 min	0	+15 min	+30 min	+45 min	% change?
Cortisol (5–25 mcg/dL)	20.4	20.5	24	28.9	30.8	46%
ACTH (5–46 pg/mL)	97.7	109	294	311	318	193%

MRI pituitary: no clear adenoma identified. Ill-defined area of decreased enhancement in the left half of the pituitary gland, possible adenoma.

With unclear pituitary MRI, IPSS was completed with CRH stimulation.

ACTH (ref 5–46 pg/mL)	Right petrosal	Left petrosal	Peripheral	RP/P ratio	LP/P ratio
−5	850	1148	86.6	9.8	13.3
0	812	1029	83.3	9.7	12.4
+3 min	925	1255	91.7	10.1	13.7
+5 min	865	1211	93.6	9.2	12.9
+10 min	803	1176	113	7.1	10.4

- The samples drawn from the petrosal sinuses, particularly on the left, were significantly higher than those drawn from a peripheral site, supporting a diagnosis of Cushing's disease. Patient underwent a transsphenoidal surgery for resection of a 12 mm × 10 mm × 8 mm pituitary adenoma on the left aspect of the anterior pituitary gland. Pathology showed loss of reticulin fibers, as well as positive staining for ACTH.
- By postoperative day 3, morning serum cortisol level was 1 mcg/dL, ACTH undetectable, and patient was started on 25 mg of hydrocortisone daily, divided into two doses.
- At 6 month follow-up, patient reported a 20 lb (9.1 kg) weight loss, but persistent depressive symptoms. ACTH stim test was conducted with a normal adrenal response (up to 18.7 ug/dL/516 nmol/L), and hydrocortisone was discontinued.
- At 1 year follow-up, patient reports continued improvement in energy levels, as well as continued weight loss. Diabetes and hypertension were also resolved, with patient no longer requiring medical management.

Questions:

1. Outline a potential education programme for this patient.
2. Describe other services that this patient may require to achieve best outcomes.
3. Consider other evidence that may need to be obtained for best practice in the care of this patient.

References

Abdel Mannan D, Selman WR, Arafah BM. Peri-operative management of Cushing's disease. Rev Endocr Metab Disord. 2010;11(2):127–34. https://doi.org/10.1007/s11154-010-9140-6.

Alwani RA, et al. Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests. Eur J Endocrinol. 2014;170(4):477–86.

Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N, Wass JAH. Nelson's syndrome. Eur J Endocrinol. 2010;163:495–507.

Batista DL, Riar J, Keil M, Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. Pediatrics. 2007;120(3):e575–86.

Bertagna X, Guignat L, Raux-Demay MC, Guilhaume B, Girad F. Cushings disease. In: Melmed S, editor. The pituitary. 3rd ed. Amsterdam: Elsevier; 2011. https://doi.org/10.1016/B978-0-12-380926-1.10016-1.

Biller BM, Alexander JM, Zervas NT, Hedley-Whyte ET, Arnold A, Klibanski A. Clonal origins of adrenocorticotropin-secreting pituitary tissue in Cushing's disease. J Clin Endocrinol Metab. 1992;75(5):1303–9. https://doi.org/10.1210/jcem.75.5.1358909.

Brzana J, Yedinak CG, Hameed N, Plesiu A, McCartney S, Fleseriu M. Polycystic ovarian syndrome and Cushing's syndrome: a persistent diagnostic quandary. Eur J Obstet Gynecol Reprod Biol. 2014;175:145–8.

Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab. 2011;96(3):632–42. https://doi.org/10.1210/jc.2010-1942.

Clayton RN, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol. 2016;4(7):569–76.

Colao A, Boscaro M, Ferone D, Casanueva FF. Managing Cushing's disease: the state of the art. Endocrine. 2014;47(1):9–20. https://doi.org/10.1007/s12020-013-0129-2.

Cuevas-Ramos D, Fleseriu M. Treatment of Cushing's disease: a mechanistic update. J Endocrinol. 2014;223(2):R19–39. https://doi.org/10.1530/JOE-14-0300.

Cuevas-Ramos D, et al. Update on medical treatment for Cushing's disease. Clin Diabetes Endocrinol. 2016;2:16.

Dekkers OM, Horvath-Puho E, Jorgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab. 2013;98(6):2277–84. https://doi.org/10.1210/jc.2012-3582.

Dorn LD, Burgess ES, Dubbert B, et al. Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. Clin Endocrinol. 1995;43:433–42.

Espinosa-de-Los-Monteros AL, et al. Persistence of Cushing's disease symptoms and comorbidities after surgical cure: a long-term, integral evaluation. Endocr Pract. 2013;19(2):252–8.

Feelders RA, Pulgar SJ, Kempel A, Pereira AM. The burden of Cushing's disease: clinical and health-related quality of life aspects. Eur J Endocrinol. 2012;167(3):311–26. https://doi.org/10.1530/EJE-11-1095.

Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. J Clin Endocrinol Metab. 2006;91(10):3746–53. https://doi.org/10.1210/jc.2006-0997.

Fleseriu M. Medical management of persistent and recurrent Cushing disease. Neurosurg Clin N Am. 2012;23(4):653–68.

Friedman TC, Yanovski JA. Morning plasma free cortisol: inability to distinguish patients with mild Cushing syndrome from patients with pseudo-Cushing states. J Endocrinol Invest. 1995;18(9):696–701.

Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jorgensen JO. Mortality in Cushing's syndrome: a systematic review and meta-analysis. Eur J Intern Med. 2012;23(3):278–82. https://doi.org/10.1016/j.ejim.2011.10.013.

Johannsson G, et al. Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy. Clin Endocrinol. 2015;82(1):2–11.

Kamp K, Alwani RA, Korpershoek E, Franssen GJ, de Herder WW, Feelders RA. Prevalence and clinical features of the ectopic ACTH syndrome in patients with gastroenteropancreatic and thoracic neuroendocrine tumours. Eur J Endocrinol. 2016;174(3):271–80. https://doi.org/10.1530/EJE-15-0968.

Keil MF, Merke DP, Gandhi R, Wiggs EA, Obunse K, Stratakis CA. Quality of life in children and adolescents 1-year after cure of Cushing syndrome: a prospective study. Clin Endocrinol. 2009;71(3):326–33.

Keil MF, Zametkin A, Ryder C, Lodish M, Stratakis CA. Cases of psychiatric morbidity in pediatric patients after remission of Cushing syndrome. Pediatrics. 2016;137(4). Epub 2016/03/31.

Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001;86(1):117–23. https://doi.org/10.1210/jcem.86.1.7093.

Lindsay JR, Nieman LK. Differential diagnosis and imaging in Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34(2):403–21., x. https://doi.org/10.1016/j.ecl.2005.01.009.

Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and management. J Neurosurg. 2017;126(2):404–17. https://doi.org/10.3171/2016.1.JNS152119.

Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB Jr, et al. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med. 1994;331(10):629–36.

Mancini T, Porcelli T, Giustina A. Treatment of Cushing disease: overview and recent findings. Ther Clin Risk Manag. 2010;6:505–16. https://doi.org/10.2147/TCRM.S12952.

Martinez-Momblan MA, Gomez C, Santos A, Porta N, Esteve J, Ubeda I, Webb S, Resmini E. A specific nursing educational program in patients with Cushing's syndrome. Endocrine. 2016;53(1):199–209. https://doi.org/10.1007/s12020-015-0737-0.

Mehta GU, Lonser RR. Management of hormone-secreting pituitary adenomas. Neuro Oncol. 2017;19(6):762–73. https://doi.org/10.1093/neuonc/now130.

Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367(9522):1605–17. https://doi.org/10.1016/S0140-6736(06)68699-6.

Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40. https://doi.org/10.1210/jc.2008-0125.

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818.

Quinkler M, Miodini Nilsen R, Zopf K, Ventz M, Øksnes M. Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. Eur J Endocrinol. 2015;172:619–26.

Sharma ST, Nieman LK. Cushing's syndrome: all variants, detection, and treatment. Endocrinol Metab Clin North Am. 2011;40(2):379–91., viii–ix. https://doi.org/10.1016/j.ecl.2011.01.006.

Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. Clin Epidemiol. 2015a;7:281–93. https://doi.org/10.2147/CLEP.S44336.

Sharma ST, Nieman LK, Feelders RA. Comorbidities in Cushing's disease. Pituitary. 2015b;18(2):188–94. https://doi.org/10.1007/s11102-015-0645-6.

Stratakis CA, Tichomirowa MA, Boikos S, Azevedo MF, Lodish M, Martari M, et al. The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. Clin Genet. 2010;78(5):457–63.

Syro LV, Rotondo F, Cusimano MD, Di Ieva A, Horvath E, Restrepo LM, et al. Current status on histological classification in Cushing's disease. Pituitary. 2015;18(2):217–24. https://doi.org/10.1007/s11102-014-0619-0.

Theodoropoulou M, Reincke M, Fassnacht M, Komada M. Decoding the genetic basis of Cushing's disease: USP8 in the spotlight. Eur J Endocrinol. 2015;173(4):M73–83. https://doi.org/10.1530/EJE-15-0320.

Tsigos C, Chrousos GP. Differential diagnosis and management of Cushing's syndrome. Annu Rev Med. 1996;47:443–61.

Valassi E, Feelders R, Maiter D, Chanson P, Yaneva M, Reincke M, Krsek M, Tóth M, Webb SM, Santos A, Paiva I, Komerdus I, Droste M, Tabarin A, Strasburger CJ, Franz H, Trainer PJ, Newell-Price J, Wass JA, Papakokkinou E, Ragnarsson O. Worse health-related quality of life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN. Clin Endocrinol. 2018;88(6):787–98. https://doi.org/10.1111/cen.13600.

van der Meij NT, et al. Self-management support in patients with adrenal insufficiency. Clin Endocrinol. 2016;85(4):652–9.

Vilar L, Naves LA, Machado MC, Bronstein MD. Medical combination therapies in Cushing's disease. Pituitary. 2015;18(2):253–62. https://doi.org/10.1007/s11102-015-0641-x.

Zilio M, Barbot M, Ceccato F, Camozzi V, Bilora F, Casonato A, et al. Diagnosis and complications of Cushing's disease: gender-related differences. Clin Endocrinol. 2014;80(3):403–10. https://doi.org/10.1111/cen.12299.

Key Reading

1. Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and management. J Neurosurg. 2017;126(2):404–17. https://doi.org/10.3171/2016.1.JNS152119.
2. Feelders RA, Pulgar SJ, Kempel A, Pereira AM. The burden of Cushing's disease: clinical and health-related quality of life aspects. Eur J Endocrinol. 2012;167(3):311–26. https://doi.org/10.1530/EJE-11-1095.
3. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367(9522):1605–17. https://doi.org/10.1016/S0140-6736(06)68699-6.
4. Martinez-Momblan MA, Gomez C, Santos A, Porta N, Esteve J, Ubeda I, et al. A specific nursing educational program in patients with Cushing's syndrome. Endocrine. 2016;53(1):199–209. https://doi.org/10.1007/s12020-015-0737-0.

Pituitary Surgery

22

Jürgen Honegger

Contents

22.1 **Transsphenoidal Surgery** 417
22.1.1 History of Transsphenoidal Surgery 417
22.1.2 The Microscopic Transsphenoidal Approach 418
22.1.3 The Endoscopic Transsphenoidal Approach 418
22.1.4 Tumour Removal in Transsphenoidal Surgery 420
22.1.5 Risk of Transsphenoidal Surgery 420
22.1.6 Special Considerations and Outcome in Different Adenoma Types 420
22.1.7 Modern Technologies in Transsphenoidal Surgery 423

22.2 **Perioperative and Postoperative Care** 423
22.2.1 Perioperative and Postoperative Care: Endocrinological 423
22.2.2 Postoperative Care: Neurosurgical 426
22.2.3 Further Early Postoperative Care 426

22.3 **Transcranial Surgery** 427
22.3.1 Indications for Transcranial Surgery 427
22.3.2 Transcranial Approach and Tumour Removal 427
22.3.3 Risk of Transcranial Surgery 427

22.4 **Surgery for Non-adenomatous Pituitary Lesions** 428
22.4.1 Other Pathologies 428
22.4.2 Surgery for Craniopharyngiomas 428

22.5 **Recommendations for Radiotherapy Postoperatively** 428
22.5.1 Indications for Radiotherapy in Pituitary Tumours 428
22.5.2 Tumour Control and Remission Rates with Radiotherapy 430

References 430

J. Honegger (✉)
Department of Neurosurgery, University of Tuebingen, Tuebingen, Germany
e-mail: Juergen.Honegger@med.uni-tuebingen.de

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_22

Abstract

Today, more than 95% of pituitary adenomas are removed using transsphenoidal surgery. The complication rates both for the traditional microscopic technique and for the more recently introduced endoscopic technique are comparably low. In acromegaly, the overall surgical cure rate of the transsphenoidal operation is approximately 50% in experienced hands. In Cushing's disease, the cure rate is high if an adenoma is visible on MRI. In prolactinomas, surgery should be preferentially offered to patients with microadenomas (<10 mm) as their chance of surgical cure is >90%.

Adequate perioperative endocrinological management is pivotal. Replacement therapy for adrenal insufficiency must be adapted to the perioperative demand. Diabetes insipidus (DI) with impaired ADH secretion is encountered frequently on days 1–5 after surgery while the opposing syndrome of inappropriate antidiuretic hormone secretion (SIADH) with excessive ADH release typically presents on days 3–10. Thorough surveillance of water and electrolyte balance in the postoperative course is paramount for early detection and treatment of these typical postoperative dysregulations of the posterior pituitary lobe. Postoperative endocrine care includes early assessment of remission status and pituitary function. It is recommended that neuro-endocrine and neurosurgical follow-up appointments be scheduled prior to discharge to guarantee professional ongoing follow-up.

For non-functioning pituitary adenomas (NFPA), radiotherapy (RT) may be considered for invasive residual tumour after surgery. The timing of radiotherapy is still a subject of controversy. For functioning adenomas, radiotherapy is indicated if surgery and medical therapy cannot control hormonal oversecretion. Fractionated radiotherapy (fRT) is used for large adenoma volumes to minimize secondary injury to surrounding structures. Stereotactic radiosurgery (SRS) is used for small target volumes with a sufficient distance from the optic apparatus. These two principle techniques have different risk profiles. Both fRT and SRS are highly effective in preventing further adenoma growth. Biochemical cure is less frequent. Reportedly, the biochemical cure rates are slightly higher for Cushing's disease than for acromegaly and are least favourable in prolactinomas. Biochemical remission is often delayed and the cure rates increase over the years after RT.

Keywords

Pituitary surgery · Pituitary adenoma · Transsphenoidal · Microscopic · Endoscopic · Fractionated radiotherapy · Radiosurgery

Abbreviations

ACTH	Adreno-corticotrophic hormone
ADH	Antidiuretic hormone
CD	Cushing's disease
CS	Cushing's syndrome
CSF	Cerebro-spinal fluid
DA	Dopamine-agonist
DI	Diabetes insipidus
fRT	Fractionated radiotherapy
GH	Growth hormone
GKRS	Gamma-knife radiosurgery
Gy	Gray
IGF-1	Insulin-like growth factor 1
LINAC	Linear accelerator based radiosurgery
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
RT	Radiotherapy
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SRS	Stereotactic radiosurgery

Key Terms

- **Transsphenoidal:** Surgery is performed through the nose and the sphenoid sinus.
- **Transcranial:** Surgery is performed by removing a piece of skull bone.
- **Microscopic:** The surgeon looks through a microscope during transsphenoidal surgery.
- **Endoscopic:** The surgeon uses an endoscope to visualize during transsphenoidal surgery.

Key Points

- More than 95% of pituitary adenomas are removed through the transsphenoidal route. The complication rates both for the traditional microscopic technique and for the more recently introduced endoscopic technique are comparably low.
- Pituitary surgery is the first line of treatment for large non-functioning adenomas and in functioning adenomas causing Cushing's disease or acromegaly. Prolactinomas, by contrast, are primarily treated with dopamine-agonists (DAs). Transsphenoidal surgery, however, is an accepted alternative for small prolactinomas as cure rates greater than 90% can be achieved.
- Adequate perioperative endocrinological management is pivotal. It includes perioperative hormonal replacement therapy, thorough surveillance of water and electrolyte balance, and assessment of postoperative remission status.
- Radiotherapy is indicated if adenoma growth or hormonal hypersecretion is not controlled by surgery and/or medical therapy. Fractionated radiotherapy (fRT) is used for large adenoma volumes while stereotactic radiosurgery (SRS) is indicated for small target volumes with a sufficient distance from the optic nerves and chiasm.
- Both fRT and SRS are effective in preventing further adenoma growth. Biochemical cure rates are slightly higher for Cushing's disease than for acromegaly and are least favourable in prolactinomas.

22.1 Transsphenoidal Surgery

22.1.1 History of Transsphenoidal Surgery

The first successful operation for a pituitary tumour was performed by Victor Horsley in 1904 at Queen Square in London using a transcranial approach. Only a few years later, Hermann Schloffer, at University Clinic in Innsbruck, performed the very first transsphenoidal operation in 1907 (Schloffer 1907). He approached the sphenoid sinus and sella through an invasive rhinotomy incision along the lateral aspect of the nose (Fig. 22.1a). The nose was reflected to the side and the septum, medial wall of the orbit and portions of the maxillary sinus wall were removed. In the following years,

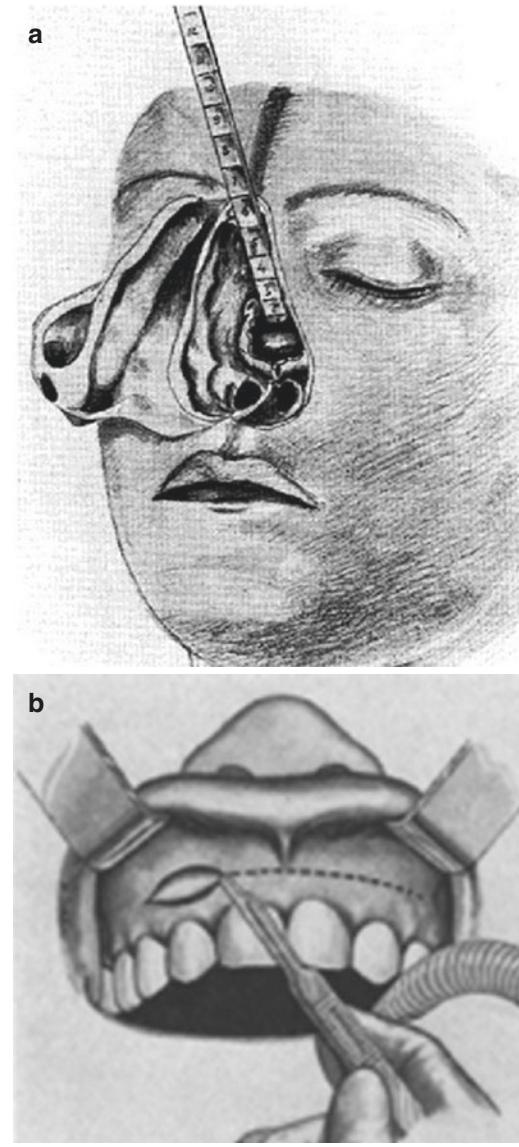


Fig. 22.1 (**a**) First transsphenoidal surgery using rhinotomy (Courtesy of the National Library of Medicine). (**b**) Translabial approach (Courtesy of the National Library of Medicine)

transsphenoidal surgery was refined. Inferior nasal approaches were established with the advantage of less disfigurement and a better suprasellar view. The transnasal and sublabial approaches avoided an external incision (Fig. 22.1b). A major pioneer of transsphenoidal surgery was Harvey Cushing who performed 231 transsphenoidal operations in Boston between 1910 and 1925 with a mortality rate of 5.6%. However, he abandoned the transsphenoidal approach in the late 1920s because of the better results of transcranial surgery at that time. One must bear in mind that, at that time, imaging techniques were poor and it was impossible to know the true size and extent of pituitary tumours into the suprasellar space, making transsphenoidal surgery hazardous. Jules Hardy from Montreal who worked together with Gérard Guiot in Paris introduced the operating microscope for transsphenoidal surgery in the late 1960s (Hardy 1969). It offered two major advances that made the approach safer and more effective: First, it allowed better illumination of the operative field in the depth through a narrow approach. Second, selective adenomectomy with preservation of the pituitary gland and identification of small microadenomas became possible with magnification under the microscope. With the introduction of microscopy, the surgical morbidity and mortality of transsphenoidal surgery were significantly reduced and lead to worldwide recognition and adoption.

As early as in 1963, Gérard Guiot suggested the use of the endoscope at the end of a transsphenoidal operation for visualization. In the 1990s, Hae Dong Jho introduced the concept of pure endoscopic transnasal surgery (Jho et al. 1997). In the last two decades, endoscopy has become a generally accepted alternative to microscopy in pituitary surgery.

Today, the transsphenoidal approach is used in 96–99% of the patients for removal of pituitary adenomas (Honegger et al. 2007).

22.1.2 The Microscopic Transsphenoidal Approach

The preferred microscopic approach to the pituitary is the so-called “septum-pushover technique”. This technique is a uninostril-endonasal approach to the sphenoid sinus. The mucosa is incised over the nasal septum in the depth in front of the sphenoid sinus. The nasal septum is disconnected from the rostrum of the sphenoid sinus and displaced to the opposite side with the nasal speculum (Griffith and Veerapen 1987). At the end of the operation, the septum is brought back to the midline. The “septum-pushover technique” is a minimally invasive technique that is performed quickly and causes minimal postoperative discomfort and pain. In particular, the patients appreciate that no nasal packing is required and nasal breathing is possible immediately after surgery.

The microscopic approach (Figs. 22.2a, 22.3) offers the advantage of a 3-dimensional view. A speculum is necessary for visualization of the operative field, because the optic system is outside the nose. On the other hand, surgical manoeuvres are fast and straight-forward because the access to the operative field is held open by the speculum.

22.1.3 The Endoscopic Transsphenoidal Approach

For the endoscopic approach (Figs. 22.2b and 22.4), a binostril or uninostril approach is used to access the sphenoidal sinus (Juraschka et al. 2014). Endoscopic surgery is mostly performed in a “four-hand technique” where one surgeon performs the operation and the other surgeon holds and guides the endoscope. Once the sphenoid sinus is sufficiently opened, the endoscope is positioned in the sphenoid sinus. The position of the optic system inside offers the advantage of a panoramic view. In particular, lateral and suprasellar tumours can be directly visualized which can increase the extent of surgical resection.

One has to bear in mind that the microscope and endoscope are only instruments for visualization. The experience of the surgeon is most important for the success of surgery and not whether a microscopic or endoscopic technique is used.

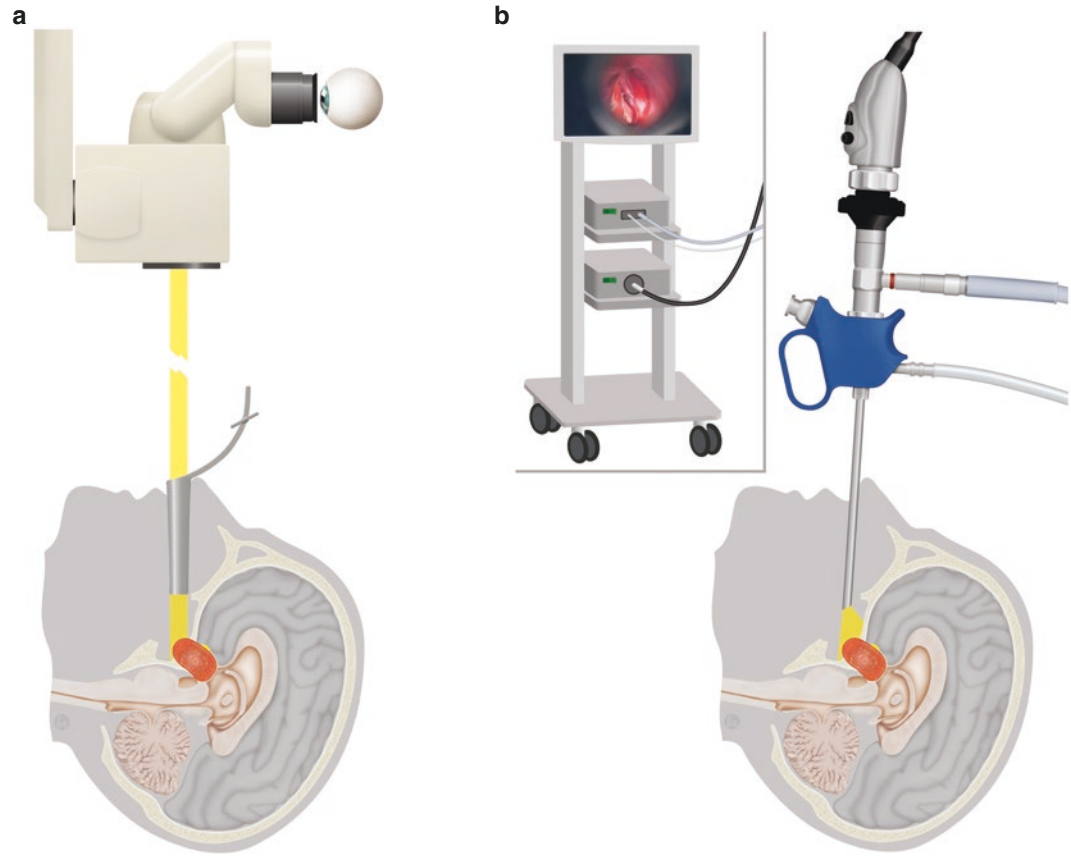


Fig. 22.2 Schematic drawing of the microscopic and endoscopic setting. (**a**) Microscopy. The surgeon visualizes the surgical field through the microscope. The surgical corridor is held open by the nasal speculum. (**b**) Endoscopy. The endoscope is positioned inside the surgical corridor. The surgical field is visualized on the monitor. Copyright: Universitätsklinikum Tübingen

Fig. 22.3 Microscopic transsphenoidal approach. With the microscope, the surgeon has a 3-dimensional view of the surgical field. Additionally, the operation is shown on the screen in the operating theater

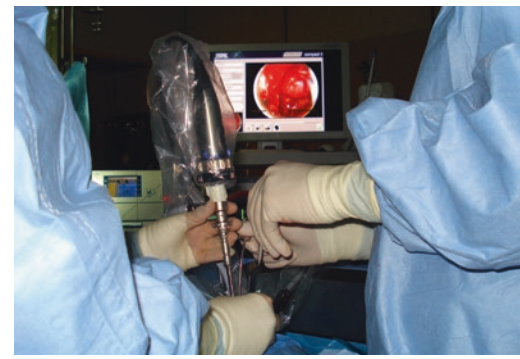


Fig. 22.4 Endoscopic transsphenoidal surgery: four-hand techique of the endoscopic procedure is shown

22.1.4 Tumour Removal in Transsphenoidal Surgery

Once the anterior wall of the sphenoid sinus has been opened, the pituitary fossa becomes visible. The bony floor of the pituitary fossa is removed. For this surgical step, we use a diamond drill and punches. The next anatomical structure which lines the floor of the sella is the basal dura. Once this is opened in a Y-shaped manner, the pituitary adenoma is exposed. The adenoma is then removed with microinstruments. As adenomas are often soft, curettes are mostly used for adenomectomy. Once the intrasellar tumour is removed, the suprasellar portion can descend into the pituitary fossa and can be resected (Fatemi et al. 2008).

Approximately one-third of surgically treated pituitary adenomas show an invasive character. This means that the adenoma grows into the adjacent anatomical structures. The most frequent site of invasion is the cavernous sinus. Some soft adenomas may be removed from within the cavernous sinus without undue morbidity. However, invasion is clearly an adverse factor for complete resection and incurs risk to cranial nerves III, IV, VI, trigeminal nerve V2 (maxillary branch) and the internal carotid artery that traverse this area.

Under microscopic or endoscopic view, the pituitary gland can be differentiated from the adenoma and then preserved. With large adenomas, the gland has become flattened and displaced and lines the resection cavity.

The diaphragma sellae is the upper border of the pituitary fossa and protects the fossa from the cerebro-spinal fluid (CSF) space. Particularly in large adenomas, the diaphragma is thin and intraoperative CSF rhinorrhea can occur, requiring repair. For closure of a CSF leak, various techniques are used. Repair may be with autologous material from the patient (e.g. fascia late, abdominal fat) or with dural substitutes or both. For large CSF leaks, a vascularized naso-septal flat is often placed over the skull base defect (Hadad et al. 2006). If a large intraoperative leak occurs, an additional prophylactic postoperative lumbar drainage for 5–7 days may be placed to prevent formation of a nasal CSF fistula by lowering the intracranial pressure.

22.1.5 Risk of Transsphenoidal Surgery

The complication rate in transsphenoidal surgery for pituitary adenomas is relatively low. In a recent meta-analysis (Ammirati et al. 2013), the risk of a CSF leak was 6–7%. Meningitis occurred in 1–2% of cases. The frequency of these typical complications was similar if microscopic and endoscopic series were compared. The risk of death was 0.5% for microscopy and 1.58% for endoscopy. Only for vascular injury, was a significant difference between microscopy (0.23%) and endoscopy (0.49%) found.

Of course, the experience of the surgeons has major influence on the complication rates. In experienced hands, a risk of CSF leak requiring operative repair can be below 1%.

The risk of new postoperative hypopituitarism is about 10%. It is significantly correlated to adenoma size. On the other hand, the chance of postoperative improvement of pituitary function is 30–40%. While transient diabetes insipidus is frequently observed, the rate of permanent diabetes insipidus is only about 1% (Ammirati et al. 2013).

Postoperative deterioration of visual function and visual fields is rare (Fig. 22.5). It can be caused by postoperative bleeding. On the other hand, preoperative visual deficits often recover after surgery. The risk that chiasmal syndrome does not improve postoperatively is particularly high if preoperative deficits were long-standing and pronounced.

22.1.6 Special Considerations and Outcome in Different Adenoma Types

Pituitary adenomas are either non-functioning or hormone-secreting. The most frequent types of

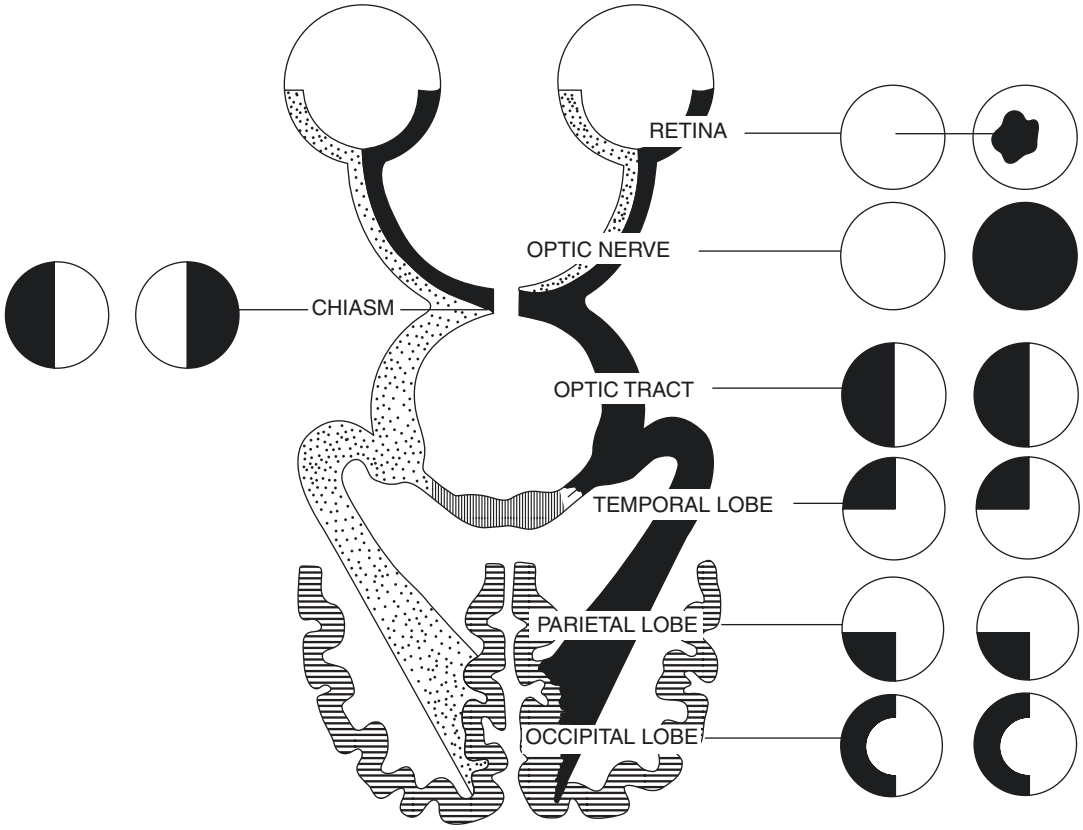


Fig. 22.5 The visual pathway and the visual defects that occur depending on the site of a lesion. A pituitary adenoma typically causes midline compression of the optic chiasm from below that results in bitemporal visual field defects

hormone-secreting adenomas are GH-secreting adenomas causing acromegaly or gigantism, ACTH-secreting adenomas causing Cushing's disease and prolactin-secreting adenomas, which are called prolactinomas. In the following, the special surgical considerations and the surgical outcome of these frequent adenoma types are described.

22.1.6.1 Transsphenoidal Surgery for Non-functioning Pituitary Adenomas (NFPA)

NFPA only become symptomatic if they cause local symptoms due to a space-occupying lesion. Visual deficits and hypopituitarism prevail and represent the indication for surgery. On the other hand, NFPA are often diagnosed incidentally during cranial imaging for other reasons (such as on evaluation of headaches or head injuries). The indication for treatment of asymptomatic adenomas is relative. Surgery is usually performed if the adenoma size is larger than 2 cm or some degree of chiasmal compression is found on MRI.

Despite their large size, more than 90% of NFPA can be removed by a transsphenoidal approach. Figure 22.6 shows the MRI of a large NFPA before and after transsphenoidal removal. If complete removal of a NFPA has been confirmed by MRI, the risk of recurrence is low (Chang et al. 2010). In contrast, residues of NFPA are at high risk for re-growth. Due to the low growth velocity of many pituitary adenomas, re-growth may be detected only after several years of observation.

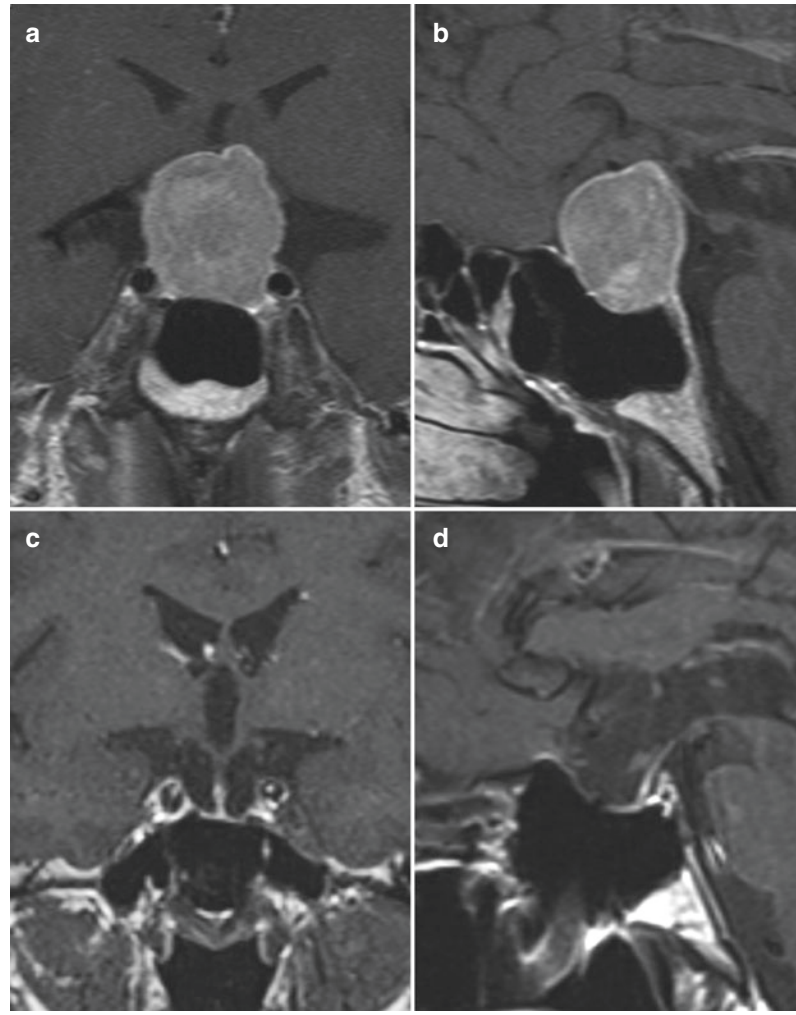


Fig. 22.6 (**a**) coronal view and (**b**) sagittal view: Preoperative MRI shows a large non-functioning pituitary adenoma causing visual field defects. (**c**) coronal view and (**d**) sagittal view: Postoperative MRI confirms complete adenoma removal

22.1.6.2 Transsphenoidal Surgery and Outcome in Acromegaly

Transsphenoidal surgery is the first choice of treatment in acromegaly.

The anaesthetist must be prepared, as intubation might be difficult. Intubation can be hampered by macroglossia, goitre and spinal kyphosis.

The surgeon must be prepared that the nasal anatomy can be distorted due to overgrowth of the anatomical structures. The nasal septum is often deviated. An extra long nasal speculum may be needed because the approach can be abnormally deep in acromegaly.

Criteria for cure are normalized insulin-like growth factor 1 (IGF-1), normal basal growth hormone (GH) and adequate suppression of GH during an oral glucose tolerance test.

Strong adverse prognostic factors in terms of cure are large adenoma size, invasive character and high preoperative GH and IGF-1 levels. The data of the German Acromegaly Register showed a long-term cure rate of 38.8%, others report lower or similar remission rates (Schöfl et al. 2013; Minniti et al. 2003). In centres with a high case-load of acromegalic patients, the cure rate was 49.8–51% (Mortini et al. 2018). In those patients without complete surgical cure, a significant reduction of GH excess by surgery will improve the success rate of postoperative medical treatment or radiotherapy.

22.1.6.3 Transsphenoidal Surgery and Outcome in Cushing's Disease

Cushing's disease (CD) is a life-threatening disease that is mostly caused by microadenomas. CD is unique in that 30% of microadenomas are so small that they are not detected even with modern MRI of the pituitary.

Endocrinological diagnostics prove the pituitary origin and differentiate CD from ectopic and adrenal Cushing's syndrome (CS). If the pituitary origin is unclear, inferior petrosal sinus sampling (IPSS) is performed as the pituitary blood is drained into the inferior petrosal sinus. Higher ACTH values in the petrosal sinus compared to ACTH in the peripheral vein confirm the pituitary origin. For prediction of the laterality of a microadenoma within the gland, IPSS only has a poor positive predictive value.

Transsphenoidal surgery is the treatment of first choice in CD. If no adenoma is detected by MRI, the pituitary gland is systematically explored by micro-incisions. A special small ultrasound probe for intraoperative detection of minute microadenomas is used in some specialized centres.

In large series with transsphenoidal surgery for microadenomas, postoperative remission rates in the range of 59–98% have been reported (Chandler et al. 2016). The cure rate is clearly superior if a microadenoma has been detected on preoperative MRI.

22.1.6.4 Transsphenoidal Surgery and Outcome in Prolactinomas

In prolactinomas, medical treatment with dopamine-agonists (DAs) is the first choice. However, a re-increase of prolactin occurs in 79% of prolactinomas after withdrawal of DA.

Transsphenoidal surgery is a second choice treatment for prolactinomas. The classical indications for surgery are resistance to DA or intolerable side-effects of DA. Further indications for surgery have emerged: The guidelines of the Pituitary Society from 2006 describe that the possibility of cure by surgery versus long-term DA therapy should be discussed with the patient, and patient preference is an indication for surgery (Casanueva et al. 2006). Surgery may be preferentially offered in microadenomas where the surgical cure rate is >90% (Casanueva et al. 2006; Kreutzer et al. 2008). The chance of prolactin normalization is still good in circumscribed intrasellar macroprolactinomas. Transsphenoidal surgery is usually not offered in large or invasive prolactinomas because postoperative normoprolactinaemia is unlikely. The risk of cardiac valvulopathy under DA is also a concern. Therefore, young patient age is an argument for surgery in order to avoid long-term DA. If acute visual loss occurs, it should not be hesitated to perform acute surgical decompression instead of awaiting the effect of DA (Kreutzer et al. 2008).

22.1.7 Modern Technologies in Transsphenoidal Surgery

Intraoperative MRI is available in some neurosurgical centres. The completeness of resection can be controlled intraoperatively. Identified residual adenoma can be removed during the same procedure avoiding a second operation.

Today, neuronavigation systems are widely used in neurosurgery and also in pituitary surgery. With neuronavigation, intraoperative tumour and major structure positions can be compared with the preoperative imaging data. With neuronavigation, the location of risk structures (i.e. carotid arteries) and the extent of resection can be verified intraoperatively.

22.2 Perioperative and Postoperative Care

22.2.1 Perioperative and Postoperative Care: Endocrinological

The postoperative endocrine care is demanding. Adequate management of postoperative endocrinological peculiarities is pivotal for the success of surgical treatment.

The details of postoperative management vary between different centres. The practices and therapeutic schemes that are provided in this section only have an exemplary nature.

22.2.1.1 Postoperative Dysregulation of Water and Electrolyte Balance

Disturbances of water and electrolyte balance are frequently encountered during the early postoperative period due to dysregulation of the posterior pituitary lobe. The two major postoperative dysregulations are diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion (SIADH) which are opposing problems. Diabetes insipidus is caused by impaired secretion of antidiuretic hormone (ADH) from the posterior pituitary lobe. In contrast, SIADH is caused by postoperative degeneration of some ADH-secreting neurons with excessive release of ADH.

Surveillance of water and electrolyte balance plays a central role in postoperative management. (see Chap. 23: Pituitary Surgery: Part 2 Nursing Care) Monitoring incudes:

- Balancing of daily fluid intake and output.
- Specific gravity of every urine portion.
- Daily measurement of serum sodium level.
- Daily measurement of body weight.

22.2.1.2 Diagnosis and Treatment of Postoperative Diabetes Insipidus

Impaired ADH secretion of the posterior lobe results in diabetes insipidus which is frequently encountered in the first days after surgery:

- 40% of patients have polyuria (>2.5 l/24 h) at the first postoperative day after transsphenoidal surgery for a pituitary adenoma.
- 5% suffer from polyuria at the fifth postoperative day.
- Permanent diabetes insipidus is only found in 1% of cases postoperatively.

Algorithm for the Management of Diabetes Insipidus: A Single Centre Protocol

Diagnosis

- Fluid intake and output exceeds 3500 mL in 24 h.
- Urine output exceeds 400 mL within 2 h.
- Serum sodium above upper limit of normal.

Treatment

- Desmopressin 2 μg subcutaneous or intramuscular after transsphenoidal surgery during the first postoperative days (because of reduced nasal uptake following transsphenoidal surgery).
- Nasal application of desmopressin spray 1 puff can be commenced from postoperative day 6 onward.
- Desmopressin tablets are also recommended for cases of mild or partial diabetes insipidus.

22.2.1.3 Diagnosis and Treatment of Postoperative Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH usually occurs between postoperative day 3 and day 10 and is a potential life-threatening complication. This is reported in up to 30% of cases. SIADH results in hyponatremia. Therefore, our protocol is to regularly measure serum sodium level until postoperative day 10 but protocols may be site specific.

Asymptomatic SIADH can be treated with restriction of fluid intake to 1 L per day. In symptomatic SIADH, hyperosmolar sodium infusion is often required in addition to fluid restriction. Recently, the vasopressin antagonist tolvaptan became available. It allows efficient treatment of SIADH without fluid restriction. We start with a single dose of tolvaptan 7.5 mg. Mostly, a second dose is necessary 1–2 days later.

It is imperative that an unduly rapid correction of hyponatremia is avoided. A rapid correction can cause damage to the myelin sheath of the nerve cells in the brainstem called central pontine myelinolysis which is a severe neurological disorder with poor prognosis.

Signs and Symptoms of SIADH

- Headache
- Malaise
- Agitation
- Tiredness
- Poor Concentration
- Nausea and vomiting
- Mental state changes and confusion
- Epileptic seizure

22.2.1.4 Perioperative Replacement Therapy of Adrenal Insufficiency

Replacement therapy for adrenal insufficiency is of vital importance. A higher demand of cortisone is required during the stressful event of an operation. Two principle perioperative strategies can be pursued:

(a) Replacement in every patient undergoing pituitary surgery.
(b) Replacement only if:
    - Preoperative adrenal insufficiency exists or
    - Adrenal function is unknown (for example in emergency cases) or
    - New adrenal failure is anticipated based on intraoperative findings.

Table 22.1 shows our regime if glucocorticoid replacement is required during the perioperative period. Physiological doses are continued at discharge as indicated after assessment of HPA axis (Table 22.1).

In some countries, an emergency card is available or provided to the patient if postoperative adrenal insufficiency is found or if adrenal function is equivocal.

Table 22.1 Hydrocortisone Replacement Regime: a single centre protocol

Day of surgery	100 mg hydrocortisone intraoperatively (intravenous) 100 mg hydrocortisone until the next morning (intravenous)
First postop day	50 mg hydrocortisone (oral)
Second postop day	40 mg hydrocortisone (oral)
Third postop day	30 mg hydrocortisone (oral)
Forth postop day	30 mg hydrocortisone (oral)
From fifth postop day onward	20 mg hydrocortisone (oral) (maintenance dose)

22.2.1.5 Early Postoperative Assessment of Remission Status

In functioning adenomas, postoperative assessment of the oversecreted hormone provides important information about the success of the surgery. Re-assessment should be performed as early as possible because the result is not only important for further treatment but also urgently awaited by the patient.

In *prolactinomas*, prolactin can be assessed on the first postoperative day. In *acromegaly*, we also assess GH on the first postoperative day. However, IGF-1 decline is delayed. Both prolactin and GH are peptide hormones with a short half-life period. Their measurement at the first postoperative day provides valuable information of surgical success regarding correction of the oversecreted hormone (see specific chapters for more information).

In *Cushing's disease*, different methods for early assessment of the remission status are in use: Some centres withhold perioperative hydrocortisone replacement and measure cortisol daily after surgery. A drop in serum cortisol into the hypocortisolemic range indicates remission. As soon as remission is documented or the patient shows clinical signs of adrenal insufficiency, hydrocortisone replacement therapy must be commenced.

This regimen allows for the earliest possible detection of remission. However, continuous clinical surveillance for symptoms of adrenal insufficiency is paramount to avoid adrenal crisis.

Other centres use perioperative hydrocortisone replacement and withdraw hydrocortisone some days after surgery for assessment of the remission status.

22.2.1.6 Early Postoperative Assessment of Anterior Pituitary Function

The regimen of postoperative endocrine reassessment of pituitary function differs between centres. An orienting status of pituitary hormones prior to discharge should be the minimal standard.

22.2.2 Postoperative Care: Neurosurgical

22.2.2.1 Surveillance of Vision

The optic chiasm is in close proximity to the pituitary gland. Patients with pituitary tumours may suffer from chiasmal syndrome preoperatively. Assessment of visual acuity and visual fields is mandatory immediately and regularly postoperatively. Visual fields are tested with finger perimetry.

Knowledge of preoperative vision and visual fields is important for proper judgement of the postoperative state. Furthermore, the nurse must have information from the surgeon about which patients are at risk for visual deterioration.

Visual failure may indicate postoperative bleeding. The risk of bleeding is particularly high during the first postoperative day. On the other hand, improvement of preoperative visual deficits can often be detected immediately after surgery but may also be delayed. Formal ophthalmological re-assessment can be done 1 week after surgery.

Furthermore, optomotor nerves run lateral to the pituitary fossa within the cavernous sinus. Postoperative care includes alertness for double vision and ptosis.

22.2.2.2 Nasal Care After Transsphenoidal Surgery

Regular nasal application of decongestant nose drops enhances nasal breathing and avoids troublesome nasal secretion or painful retention of secretion in the paranasal sinuses. Some centres use xylometazoline 0.1% nasal spray or drops. This shrinks the swollen nasal mucosa via vasoconstriction. It is applied after transnasal surgery until there are minimal secretions and free ventilation is restored which is usually the case after 7–14 days. Other centres use sterile saline spray multiple times daily to achieve a similar outcome.

Medication for nasal pain is not routinely administered. Nonsteroidal anti-inflammatory drugs can be given if required. However, acetylsalicylic acid should be avoided during the first 10 postoperative days because of the anticoagulant effects.

It may be difficult to differentiate nasal secretion from cerebro-spinal fluid (CSF) rhinorrhea. No laboratory test is absolutely reliable. Measurement of glucose in nasal fluid is not helpful after transnasal surgery. Mucosal fluid is a hint for nasal secretion while clear fluid like water is suspicious of CSF. CSF rhinorrhea can be provoked if the patient is brought into a sitting position and the head bend forward.

The nasal conditions must be closely supervised. If CSF rhinorrhea occurs, lumbar drainage or operative repair in a timely fashion is indicated to avoid further complications such as meningitis.

22.2.3 Further Early Postoperative Care

The timing of discharge from the neurosurgical unit varies between centres. The postoperative stay is usually between 3 and 6 days. In some centres, the patients are transferred to the endocrine unit during the postoperative hospital stay. Prior to discharge, the patient is given both verbal and written instructions regarding postoperative home care. After transsphenoidal surgery, an increase of intracranial pressure must be avoided for a period of at least 4 weeks (Knappe et al. 2018). For that time, physical strain, sports activities, steam baths, saunas, and blowing the nose must be avoided. After 4 weeks, physical activities can be slowly resumed. Patients are advised to sneeze with an open mouth to avoid Valsalva pressure. The use of continuous positive airway pressure (CPAP) devices is not recommended

immediately postoperatively and patients may need supplemental oxygen. Review with the Ear Nose and Throat (ENT) specialist 2–4 weeks postoperatively is recommended.

The patient's case is booked for the tumour board where decisions of further management (for example requirement of postoperative medical treatment or radiotherapy) are made.

Most importantly, an appointment with the endocrinologist must be arranged prior to postoperative discharge. An exact date for the appointment is strongly recommended to guarantee an endocrinological follow-up. A first re-assessment by the endocrinologist is usually recommended 2–3 weeks after surgery. Some endocrinologists see their patients as early as 1 day after discharge from the neurosurgical unit.

Similarly, a neurosurgical follow-up appointment is mandatory. The first appointment at the neurosurgical outpatient department is usually scheduled 3–6 months postoperatively. The patient is instructed to bring along a recent postoperative MRI or is scheduled the same day for a postoperative MRI. Postoperative endocrine re-assessment may be scheduled simultaneously or independently and these results should be available to the neurosurgery at the time of this appointment. If the adenoma had suprasellar extension or the patient had suffered from chiasmal syndrome, an ophthalmological report should also be presented at the neurosurgical follow-up appointment.

22.3 Transcranial Surgery

22.3.1 Indications for Transcranial Surgery

Transcranial surgery is only required if a pituitary adenoma is not sufficiently accessible by a transsphenoidal operation. The decision for the appropriate approach depends on adenoma size and location. A multilobulated suprasellar extension points to a perforated diaphragm sellae. It means that the adenoma has grown out of the confines of the pituitary fossa into the intracranial (intradural) space. Under these circumstances, the risk of transsphenoidal surgery might be too high because it does not provide adequate control of intracranial neurovascular structures. Transcranial surgery is necessary in some of these adenomas. A predominant suprasellar adenoma with a small pituitary fossa, an eccentric suprasellar extension or a dumbbell shaped adenoma also hamper transsphenoidal resection and are reasons for transcranial surgery (Buchfelder and Kreutzer 2008). Today, less than 5% of pituitary adenomas require a transcranial operation.

22.3.2 Transcranial Approach and Tumour Removal

For a transcranial approach, the skin incision is made fronto-temporal behind the hairline to avoid an externally visible scar. The pterional approach and the fronto-lateral approach are most frequently used. The pterional approach exposes the Sylvian fissure between the frontal and temporal lobes. The arachnoid of the Sylvian fissure is opened for exposure of the adenoma. The adenoma can be visualized and removed through the prechiasmatic space or through the space between the optic nerve and carotid artery (so-called "optico-carotid triangle"). The fronto-lateral approach provides a more anterior view. It is less invasive but the lateral view through the optico-carotid triangle is limited.

22.3.3 Risk of Transcranial Surgery

The reported morbidity and mortality of transcranial surgery is certainly higher than of transsphenoidal surgery. However, one has to keep in mind a selection bias because the difficult adenomas with major intracranial, suprasellar extension require a transcranial operation. The mortality rate of transcranial surgery is approximately 2% (Buchfelder and Kreutzer 2008). Transcranial operations carry a particularly high risk of rebleeding into the tumour bed. Another specific risk is hypothalamic dysfunction which may be caused by damage to small perforating arteries.

The risk of visual deterioration following transcranial surgery is approximately 15–22%. On the other hand, the chance that a pre-existing visual deficit improves after surgery is 50% (Bulters et al. 2009). In large adenomas with eccentric lateral extension, a significant risk of an oculomotor nerve palsy with ptosis and double vision exists.

The risk of postoperative hypopituitarism and diabetes insipidus is also higher in transcranial surgery than in transsphenoidal surgery and the chance of postoperative recovery of pre-existing endocrine deficits is low (Buchfelder and Kreutzer 2008).

As the adenomas requiring craniotomy are typically large and show invasive character, a gross total resection is mostly not feasible.

22.4 Surgery for Non-adenomatous Pituitary Lesions

22.4.1 Other Pathologies

The vast majority of surgically treated lesions of the pituitary area are adenomas. However, numerous other pathologies of the pituitary, pituitary stalk and hypothalamus are encountered (see Chap. 14). The appropriate surgical approach for other pituitary pathologies also depends on their location.

Among non-adenomatous lesions, tumours of neighbourhood origin that secondarily encroach upon the pituitary such as chordomas, chondosarcomas or perisellar meningiomas must also be considered.

22.4.2 Surgery for Craniopharyngiomas

The second most frequent pathology of pituitary or hypothalamic origin is the craniopharyngioma. In contrast to pituitary adenomas, only 30% of craniopharyngiomas show major intrasellar involvement allowing transsphenoidal surgery (Honegger and Tatagiba 2008). Many craniopharyngiomas are not confined to the pituitary fossa and grow in the suprasellar intradural space above the diaphragm sellae requiring craniotomy. Various transcranial approaches have to be considered as craniopharyngiomas may involve several intracranial compartments. Large craniopharyngioma cysts can be decompressed by stereotactic cyst puncture.

Recently, extended transsphenoidal operations have been suggested for purely suprasellar craniopharyngiomas (Kim et al. 2011) and other suprasellar tumours. The major disadvantage of such extended approaches is the large defect in the skull base and intraoperative CSF leak which is necessary for tumour exposure. It carries a high risk of a postoperative CSF fistula. Whether purely suprasellar tumours should be operated by craniotomy or extended transsphenoidal surgery is still a matter of debate (Jeswani et al. 2016).

Gross total resection of craniopharyngiomas offers a high chance of recurrence-free long-term survival. Some neurosurgeons recommend an attempt at total removal so long as there is no risk of hypothalamic damage (Honegger and Tatagiba 2008). Other surgeons recommend conservative resection (biopsy or partial resection) followed by radiotherapy. However, the tumour burden remains with this policy and the therapeutic options in the case of re-growth are limited.

22.5 Recommendations for Radiotherapy Postoperatively

22.5.1 Indications for Radiotherapy in Pituitary Tumours

22.5.1.1 Indications for Radiotherapy in Non-functioning Pituitary Adenomas (NFPA)

In NFPA, radiotherapy is indicated for postoperative adenoma remnants with invasive character that are not accessible surgically. The typical indication is a residual adenoma within the cavernous sinus (Fig. 22.7). The timing of radiation for NFPA is a current subject of controversy. Some radiotherapists recommend radiotherapy

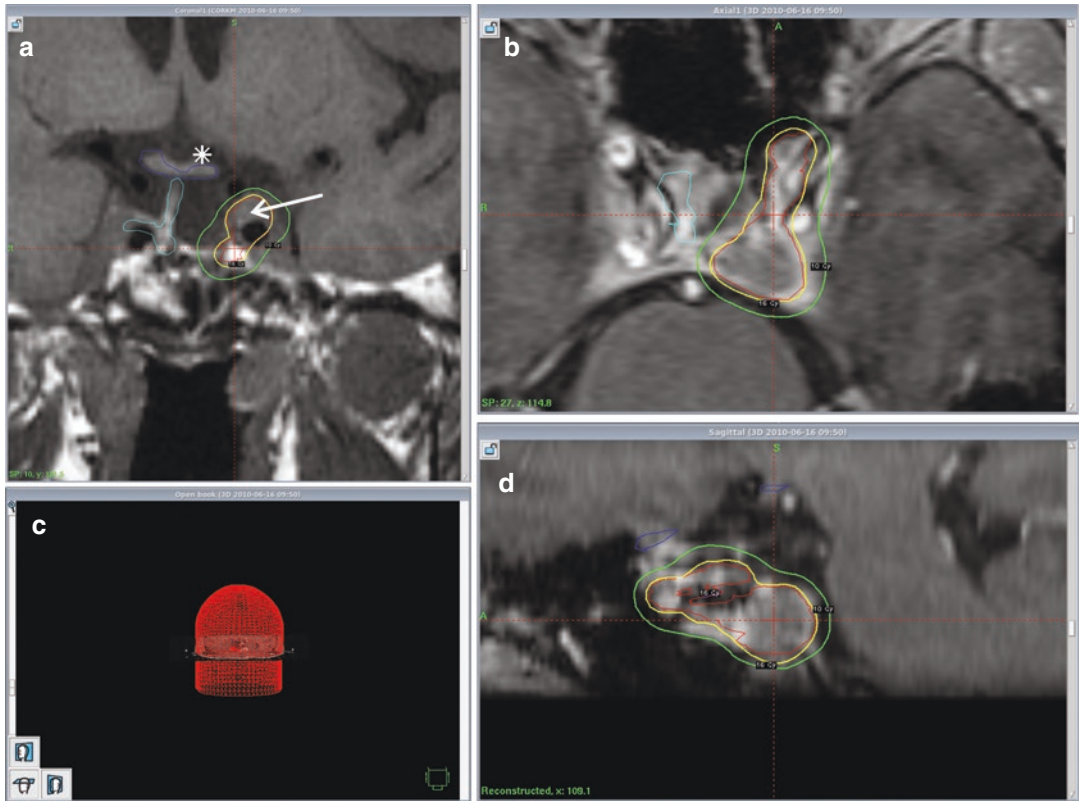


Fig. 22.7 Planning for stereotactic radiosurgery (SRS) with Gamma Knife of a left parasellar residual adenoma (arrow in **a**) within the cavernous sinus following transsphenoidal surgery. (**a**) Coronal view, (**b**) axial view, (**c**) 3D, (**d**) sagittal view. Yellow: 16 Gy isodose of the target volume; Green: 10 Gy isodose of the target volume. Blue: Optic chiasm (asterisk in **a**). Cyan: pituitary stalk and gland. The target volume has a sufficient distance to the optic chiasm to avoid visual compromise. Courtesy by Dr. G.A. Horstmann, Gamma Knife Centre, Krefeld, Germany

after initial surgery. Others use radiotherapy only if further growth of the residual adenoma is observed (Fig. 22.7).

22.5.1.2 Indications for Radiotherapy in Cushing's Disease

Radiotherapy (RT) is a second treatment option in CD. Radiotherapy is indicated if CD persists after pituitary surgery. This can be the case after negative sellar exploration(s) or for non-resectable invasive residual adenoma within the cavernous sinus. RT is also an option for recurrent CD (Estrada et al. 1997).

Other second-line options are medical treatment or bilateral adrenalectomy. The treatment decision in the second-line therapy is usually made on an individual basis. Medical treatment might be required while awaiting the delayed effect of radiotherapy.

22.5.1.3 Indications for Radiotherapy in Acromegaly

In acromegaly, RT competes with medical treatment as the second-line treatment. However, medical treatment is favoured in some countries for second-line treatment and RT is used if GH hypersecretion cannot be controlled by surgery and medical treatment.

22.5.1.4 Indications for Radiotherapy in Prolactinomas

In prolactinomas, RT is used if hyperprolactinaemia persists under dopamine-agonist (DA) treatment and surgery is not successful or not

indicated because of invasive adenoma extension. Radiotherapy is rarely used in prolactinomas because of the high efficacy of DAs.

22.5.1.5 Indications for Radiotherapy in Craniopharyngiomas

RT is indicated for residual or recurrent craniopharyngiomas. The ideal timing of RT is yet to be determined. An ongoing study in childhood craniopharyngiomas investigates whether adjunctive RT immediately after incomplete resection or salvage RT upon re-growth is superior.

22.5.2 Tumour Control and Remission Rates with Radiotherapy

Radiation techniques are explained in Chapter 24: Radiotherapy.

22.5.2.1 Tumour Control Rates in Non-functioning Pituitary Adenomas (NFPA)

The goal of radiotherapy in NFPA is tumour control which means that the adenoma remains stable in size or shrinks.

According to the literature, 80–98% of patients with NFPA are recurrence-free after *fRT*. The reported studies of *SRS* for NFPA showed tumour control rates of 83–100% (Sheehan et al. 2012) (Fig. 22.7). On average, the tumour control rate was 96%. However, long-term follow-up was not available in most of the studies on SRS.

22.5.2.2 Remission Rates in Cushing's Disease

With *fRT*, the reported remission rates with complete reversal of ACTH- and cortisol-oversecretion were between 46% and 100% (Estrada et al. 1997).

In published series of *SRS* with more than ten cases, the remission rates were highly variable with a range from 17% to 83%. Recent studies provide evidence that remission rates of 60–80% can be achieved today (Marek et al. 2015).

22.5.2.3 Remission Rates in Acromegaly

In the retrospective data collection of *fRT* for acromegaly from 14 centres throughout the United Kingdom, normalization of IGF-1 was achieved in 63% of the patients at 10 years (Jenkins et al. 2006).

The remission rates of *SRS* in acromegaly reported in the literature are heterogeneous. On average, a remission was achieved in approximately 50% of the patients (Pollock et al. 2008). Recent studies suggest that higher remission rates can be achieved today (Lee et al. 2015).

22.5.2.4 Remission and Control Rates in Prolactinomas

Both with *fRT* and with *SRS*, further tumour growth can be prevented in the vast majority of cases. However, remission with normal prolactin off dopamine-agonist treatment is only achieved in a minority of cases. Evidently, remission in prolactinomas is less frequent than in Cushing's disease and acromegaly (Tanaka et al. 2010).

22.5.2.5 Control Rates in Craniopharyngiomas

In the main published studies on *fRT*, control rates at 10 years after RT were 56.5–100% (Minniti et al. 2009). Long-term results of SRS are still sparse. In the main published studies on *SRS* with mean follow-up periods between 16 months and 17 years, control rates of SRS were 34–88% (Minniti et al. 2009).

Acknowledgement The editors acknowledge manuscript review by Justin Cetas MD who is the Associate Professor of Department of Neurosurgery, Oregon Health & Sciences University, Portland, Oregon, USA.

References

Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2013;84:843–9.

Buchfelder M, Kreutzer J. Transcranial surgery for pituitary adenomas. Pituitary. 2008;11:375–84.

Bulters DO, Shenouda E, Evans BT, et al. Visual recovery following optic nerve decompression for chronic compressive neuropathy. Acta Neurochir. 2009;151:325.

Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JAH, Giustina A. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol. 2006;65:265–73.

Chandler WF, Barkan AL, Hollon T, Sakharova A, Sack J, Brahma B, Schteingart DE. Outcome of transsphenoidal surgery for Cushing disease: a single-center experience over 32 years. Neurosurgery. 2016;78:216–23.

Chang EF, Sughrue ME, Zada G, Wilson CB, Blevins LS, Kunwar S. Long term outcome following repeat transsphenoidal surgery for recurrent endocrine-inactive pituitary adenomas. Pituitary. 2010;13(3):223–9. https://doi.org/10.1007/s11102-010-0221z.

Estrada J, Boronat M, Mielgo M, Magallón R, Millán I, Díez S, Lucas T, Barceló B. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med. 1997;336:172–7.

Fatemi N, Dusick JR, de Paiva Neto MA, Kelly DF. The endonasal microscopic approach for pituitary adenomas and other parasellar tumors: a 10-year experience. Neurosurgery. 2008;63(4 Suppl 2):244–56.

Griffith HB, Veerapen R. A direct transnasal approach to the sphenoid sinus. Technical note. J Neurosurg. 1987;66:140–2.

Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, Mintz A. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. Laryngoscope. 2006;116:1882–6.

Hardy J. Transsphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg. 1969;16:185–217.

Honegger J, Tatagiba M. Craniopharyngioma surgery. Pituitary. 2008;11:361–73.

Honegger J, Ernemann U, Psaras T, Will B. Objective criteria for successful transsphenoidal removal of suprasellar nonfunctioning pituitary adenomas. A prospective study. Acta Neurochir. 2007;149:21–9.

Jenkins PJ, Bates P, Carson N, Stewart PM, Wass JAH, On behalf of the UK National Acromegaly Register Study Group. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab. 2006;91:1239–45.

Jeswani S, Nuno M, Wu A, Bonert V, Carmichael JD, Black KL, Chu R, King W, Mamelak AN. Comparative analysis of outcomes following craniotomy and expanded endoscopic endonasal transsphenoidal resection of craniopharyngioma and related tumors: a single-institution study. J Neurosurg. 2016;124:627–38.

Jho HD, Carrau RL, Ko Y, Daly MA. Endoscopic pituitary surgery: an early experience. Surg Neurol. 1997;47:213–23.

Juraschka K, Khan OH, Godoy BL, Monsalves E, Kilian A, Krischek B, Ghare A, Vescan A, Gentili F, Zadeh G. Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection. J Neurosurg. 2014;121:75–83.

Kim EH, Ahn JY, Kim SH. Technique and outcome of endoscopy-assisted microscopic extended transsphenoidal surgery for suprasellar craniopharyngiomas. J Neurosurg. 2011;114:1138–349.

Knappe UJ, Moskopp D, Gerlach R, Conrad J, Flitsch J, Honegger JB. Consensus on postoperative recommendations after transsphenoidal surgery. Exp Clin Endocrinol Diabetes 2018 doi: 10.1055/a-0664-7710. [Epub ahead of print].

Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. Eur J Endocrinol. 2008;158:11–8.

Lee CC, Vance ML, Lopes MB, Xu Z, Chen CJ, Sheehan J. Stereotactic radiosurgery for acromegaly: outcomes by adenoma subtype. Pituitary. 2015;18(3):326–34. https://doi.org/10.1007/s11102-014-0578-5.

Marek J, Jezková J, Hána V, Krsek M, Liscák R, Vladyka V, Pecen L. Gamma knife radiosurgery for Cushing's disease and Nelson's syndrome. Pituitary. 2015;18:376–84.

Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Tamburrano G, Cantore G. Evolving criteria for postoperative biochemical remission of acromegaly: can we achieve a definitive cure? An audit of surgical results on a large series and a review of the literature. Endocr Relat Cancer. 2003;10(4):611–9. https://doi.org/10.1677/erc.0.0100611.

Minniti G, Esposito V, Amichetti M, Enrici RM. The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngiomas. Neurosurg Rev. 2009;32:125–32.

Mortini P, Barzaghi LR, Albano L, Panni P, Losa M. Microsurgical therapy of pituitary adenomas. Endocrine. 2018;59(1):72–81. https://doi.org/10.1007/s12020-017-1458-3. Epub 2017 Oct 24.

Pollock BE, Brown PD, Nippoldt TB, Young WF. Pituitary tumor type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas. Neurosurgery. 2008;62:1271–8.

Schloffer H. Erfolgreiche Operation eines Hypophysentumors auf nasalem Wege. Wien Klin Wochenschr. 1907;20:621–4.

Schöfl C, Franz H, Grussendorf M, Honegger J, Jaursch-Hancke C, Mayr B, Schopohl J. Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register. Eur J Endocrinol. 2013;168:39–47.

Sheehan JP, Xu Z, Lobo MJ. External beam radiation therapy and stereotactic radiosurgery for pituitary adenomas. Neurosurg Clin N Am. 2012;23:571–86.
Tanaka S, Link MJ, Brown PD, Stafford SL, Young WF, Pollock BE. Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. World Neurosurg. 2010;74:147–52.

Key Reading

1. Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2013;84:843–9.
2. Chandler WF, Barkan AL, Hollon T, Sakharova A, Sack J, Brahma B, Schteingart DE. Outcome of transsphenoidal surgery for Cushing disease: a single-center experience over 32 years. Neurosurgery. 2016;78:216–23.
3. Honegger J, Tatagiba M. Craniopharyngioma surgery. Pituitary. 2008;11:361–73.
4. Sheehan JP, Xu Z, Lobo MJ. External beam radiation therapy and stereotactic radiosurgery for pituitary adenomas. Neurosurg Clin N Am. 2012;23:571–86.
5. Schöfl C, Franz H, Grussendorf M, Honegger J, Jaursch-Hancke C, Mayr B, Schopohl J. Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register. Eur J Endocrinol. 2013;168:39–47.

Pituitary Surgery: Nursing Implications

23

Sarah Benzo and Christina Hayes

Contents

23.1 **Introduction** 435

23.2 **Review of the Physiology of the Pituitary Gland** 435

23.3 **Postoperative Nursing Care Considerations** 435
23.3.1 Surgical Approach 435

23.4 **Key Endocrinological and Neurosurgical Nursing Considerations** 435
23.4.1 Perioperative Glucocorticoid Replacement 436

23.5 **Monitoring Neurosurgical Complications** 440
23.5.1 Infection 440
23.5.2 CSF Leak 440
23.5.3 Lumbar Drainage 441
23.5.4 Visual Loss 442
23.5.5 Epistaxis 442

23.6 **Summary of Patient Education** 443
23.6.1 Perioperative 443
23.6.2 Discharge 444

References 445

Keywords

Pituitary surgery · Postoperative complications · Diabetes insipidus (DI) · SIADH · Adrenal insufficiency · Patient education

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
AI	Adrenal insufficiency

S. Benzo (✉) · C. Hayes
Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
e-mail: sarah.benzo@nih.gov; christi.hayes@nih.gov

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_23

CD	Cushing's disease
CRH	Corticotropic releasing hormone
CSF	Cerebrospinal fluid
DDAVP	Desmopressin
DI	Diabetes insipidus
HPA axis	Hypothalamic-pituitary-adrenal axis
IV	Intravenous
SIADH	Syndrome of inappropriate antidiuretic hormone

Key Terms

- **Hypothalamic-Pituitary-Adrenal (HPA) Axis:** Complex hormonal interaction between the hypothalamus, pituitary, and adrenal glands that takes place in order to provide hormonal homeostasis.
- **Adrenal Insufficiency:** Inadequate production of cortisol (steroid hormone) from the adrenal glands to support physiologic needs.
- **Antidiuretic Hormone (ADH):** Hormone secreted by the pituitary gland that works at the level of the kidney to regulate fluid and electrolyte balance to maintain appropriate intravascular hydration.
- **Diabetes Insipidus (DI):** Insufficient secretion of ADH results in excessive urinary secretion of dilute urine resulting in intravascular dehydration characterized by elevated serum sodium and decreased urinary specific gravity.
- **Desmopressin (DDAVP):** Medication consisting of a synthetic form of ADH that may be administered to patients with DI.
- **Syndrome of Inappropriate Antidiuretic Hormone (SIADH):** Oversecretion of ADH resulting in excessive retention of free water despite low serum osmolality resulting in intravascular hyponatremia and increased intravascular circulating volume.
- **Cerebrospinal Fluid (CSF):** A clear fluid that circulates in and around the brain and spinal cord.
- **Lumbar Drainage:** Catheter inserted into the lumbar subarachnoid space in order to remove CSF from the body.
- **Transsphenoidal Surgery:** Approach to the pituitary gland for surgery by route of the sphenoid sinus, most commonly through the nose or upper lip.
- **Epistaxis:** Bleeding from the nose, most often originates from the nasal mucosa after transsphenoidal surgery, however may indicate bleeding from more critical structures.

Key Points

- Nursing considerations in the care of the patient undergoing pituitary surgery include knowledge of patient's preoperative hormone levels, surgical approach, and postoperative monitoring needs.
- Diligent monitoring for disturbances of water and electrolyte balance, and HPA axis dysfunction are essential to the care of pituitary surgery patients.
- The nurse caring for the neurosurgical pituitary patient should monitor for the following potential postoperative complications: infection, CSF leak, visual loss, and epistaxis.
- Key neurologic components in the care of pituitary surgery patients include visual field testing, monitoring for visual changes, CSF leak monitoring, and lumbar drain management, when applicable.
- Thorough patient discharge teaching regarding activity restrictions, prescribed hormone replacement, sign and symptoms of HPA axis dysfunction (with emphasis on signs of adrenal insufficiency), and scheduled follow-up with medical and surgical teams is paramount.

23.1 Introduction

Pituitary surgery is performed to address a variety of pathologies. Surgical technique will vary based upon surgeon preference, tumor location, and any involvement of surrounding structures. Nursing care of the patient undergoing pituitary surgery is founded in a comprehensive understanding of pituitary physiology and pathophysiology. Expert knowledge of the pituitary gland, the hypothalamic-pituitary-adrenal (HPA) axis, underlying pathology, and surgical risks allows for early identification and intervention of postoperative complications. It is important to be aware of hospital specific protocols regarding the routine care of patients undergoing pituitary surgery, as they may vary from institution to institution. Comprehensive, broad based knowledge empowers the nurse to provide diligent, comprehensive care and identify potentially life-threatening complications promptly.

23.2 Review of the Physiology of the Pituitary Gland

Review of the role of the pituitary gland in the endocrine system, each hormonal axis function, and the mechanisms of hormonal homeostasis is recommended (Amar and Weiss 2003; Yuan 2013; Greenberg 2016; Ben-Shlomo and Melmed 2011). For details, refer to Chap. 12.

23.3 Postoperative Nursing Care Considerations

23.3.1 Surgical Approach

The surgical risks for patients undergoing removal of a pituitary adenoma may vary depending on the location of the tumor and the surgical approach as described in Chap. 22. The three standard surgical approaches for pituitary adenomas are transsphenoidal, transethmoidal, and transcranial. Transsphenoidal surgery is often the approach of choice for many surgeons, and this procedure may be performed via a sublabial or trans-nare approach depending upon the tumor characteristics and surgeon skill set and preferences. There are specific nursing implications associated with the different surgical approaches.

23.3.1.1 Sublabial Approach

Patients who undergo a transsphenoidal procedure with a sublabial approach will have an incision under their lip, and oral care will be essential in preventing infection. Dietary considerations include soft foods and liquid protein supplements until sutures have dissolved. Oral care should be performed after every meal. The use of a straw is usually discouraged (Yuan 2013).

23.3.1.2 Extended Transsphenoidal Skull Base Approach

In this approach, additional cranial base bone is removed to provide better exposure to the parasellar and clival region compared with the standard transsphenoidal approach (Zhao et al. 2010). Both patients who undergo an "extended" transsphenoidal skull base approach and those found to have a CSF leak at the conclusion of a transsphenoidal surgery may require a lumbar drain placement postoperatively (Yuan 2013). Thus, it is important for nurses to be trained in proper care of lumbar drains. The key principle is the drainage is gravity dependent so the amount of drainage will change with the position of the patient (Overstreet 2003). Refer to individual facility lumbar drainage guidelines and physician orders regarding clamping versus opening lumbar drains. Patients with lumbar drainage systems and their family members require education pertaining to lumbar drainage, specifically in regards to patient position and mobilization.

23.4 Key Endocrinological and Neurosurgical Nursing Considerations

The pituitary gland is essential for normal endocrinologic function (See Chap. 1). It is important to know if your patient experienced endocrine dysfunction prior to surgery, and if so what hormones were impacted to determine their level of perioperative risk (Malenković et al. 2011). If hormonal oversecretion was evident, which

hormone(s) were biochemically overactive and what disease symptoms was the patient experiencing. These symptoms will need to be monitored postoperatively. Likewise, if there is a deficiency in one or more hormonal axis, it is important to know if these deficiencies were replaced and if they are currently stable. These will also necessitate a monitoring plan postoperatively. Evidence suggests a multidisciplinary team approach to the care of transsphenoidal surgery patient is most effective, inclusive of neurosurgery, neuroendocrinology, and a pituitary nurse specialist (Carminucci et al. 2016). Length of stay was significantly reduced without compromising patient safety or outcomes (Fig. 23.1).

23.4.1 Perioperative Glucocorticoid Replacement

Patients undergoing pituitary surgery are frequently given glucocorticoid replacement therapy during the perioperative period to treat potential cortisol deficiency. However, the practice of glucocorticoid administration post pituitary surgery varies between institutions and remains a controversial practice (Kelly and Domajnko 2013; Glowniak and Loriaux 1997; Pimentel-Filho et al. 2005; Inder and Hunt 2002). There are some data favoring treatment only when the patient is symptomatic of adrenal insufficiency versus protocol driven replacement, and depending on the status of the patient's HPA axis function on preoperative testing. In the event of adrenal insufficiency in the latter circumstance, glucocorticoids must be replaced and continued until postoperative testing indicates normal HPA axis function. In other patients who have an intact HPA function preoperatively, and whom selective adenomectomy is possible, perioperative glucocorticoids may not be necessary. However, most patients with a large adenoma are at risk for cortisol deficiency following surgery. Therefore a stress dose 40–100 mg of IV steroids is frequently given to patients immediately before, during and/or immediately after surgery (Kelly and Domajnko 2013). The recommended replacement dose of glucocorticoid by Endocrine Society Clinical Guidelines is 15–30 mg of oral cortisol daily in divided doses (Nieman et al. 2015). It should be reiterated that the use of glucocorticoid replacement will vary based upon institution protocol, patient pathology, and surgical or endocrine team preference.

Postoperative assessment of glucocorticoid requirement is dependent on clinical assessment and diagnosis of the patient. In cases of Cushing's disease, some centers recommended that all patients in postoperative remission with morning plasma cortisol levels less than 5 μg/dL be treated with glucocorticoids until further testing indicates a normal HPA axis function (Inder and Hunt 2002). Thus, it is important that nurses ensure morning cortisol levels and ACTH levels are drawn postoperatively in order for the physicians to assess HPA axis function and determine if oral hormone replacement after discharge is needed (Yuan 2013). See Box 23.1 for a suggested postoperative glucocorticoid regimen.

If the patient is to be discharged on a glucocorticoid regime, it is essential to provide the patient and family with education regarding: symptoms of adrenal insufficiency (AI); symptoms to report urgently to their physician; administration of emergency glucocorticoid injection for symptoms of AI; to report to the nearest hospital emergency room for evaluation of the etiology of AI. Adrenal insufficiency following surgery may be temporary or permanent. Therefore, it is important for the patient to establish ongoing, follow-up care with a local endocrinologist.

23.4.1.1 HPA Axis Function

Adrenal insufficiency or HPA axis dysfunction may be evident immediately after a successful surgery to remove an ACTH producing tumor or in remitted Cushing's disease. However, manipulation or damage to the pituitary during surgery can also impair ACTH secretion, thus disrupting the HPA axis and secretion of cortisol. Lack of cortisol following surgery can result in adrenal insufficiency (AI). AI can be a life-threatening condition if not identified and treated (Yuan 2013; Nieman et al. 2015) (See clinical indication of AI, Box 23.2).

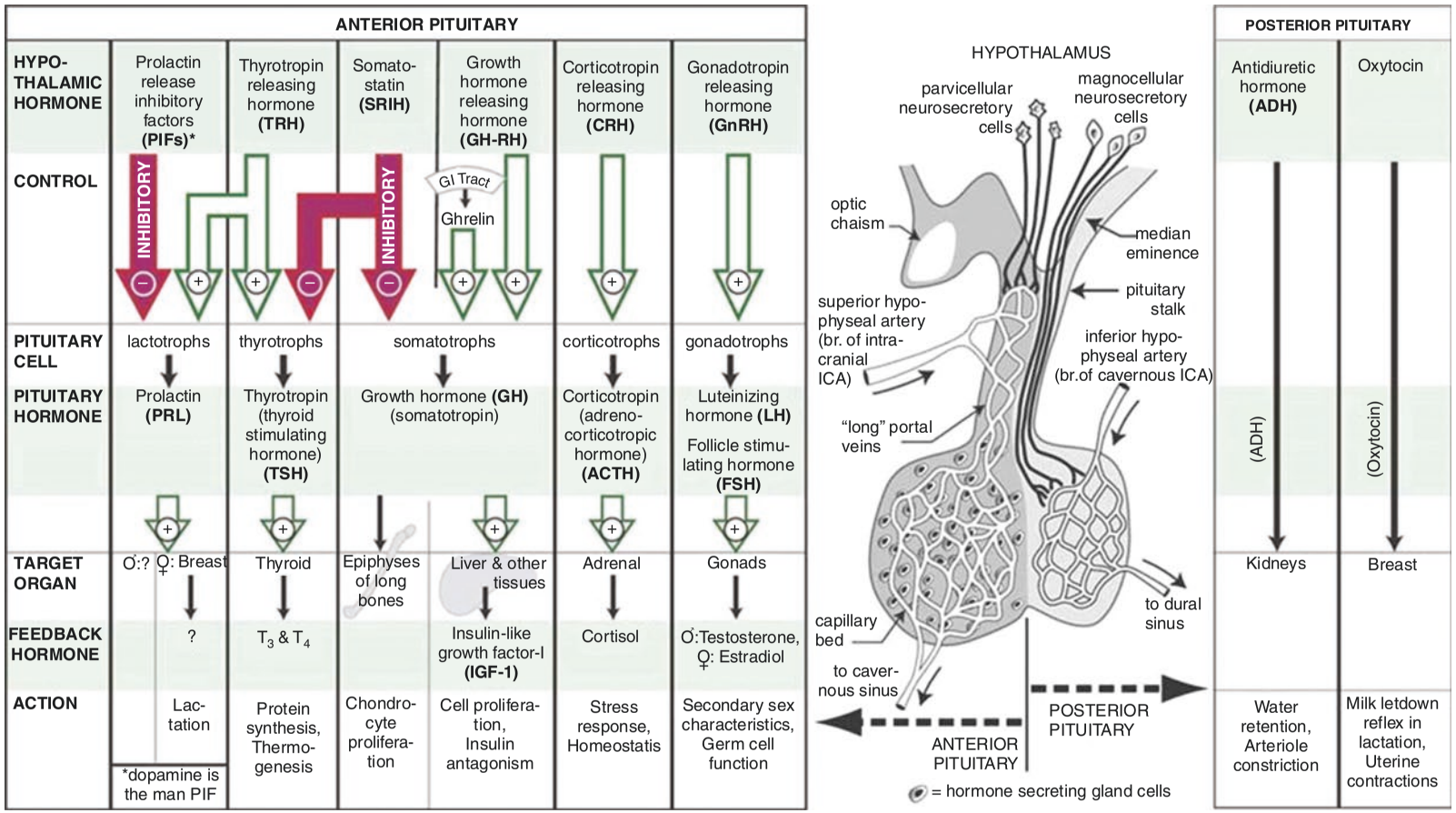


Fig. 23.1 Pituitary neuroendocrinology. Used with permission from Greenberg, M. S. (2016). Handbook of neurosurgery, image 8.1 pg153

Box 23.1 Example of a Postoperative Glucocorticoid Regime

Day 0: *50 mg hydrocortisone (IV or PO) every 8 h*

Day 1: *25 mg hydrocortisone PO every 8 h*

Day 2: *20–25 mg hydrocortisone PO at 8 am daily*

Discharge*: as needed (15–30 mg daily in divided doses)*

(Inder and Hunt (2002))

Box 23.2 Clinical Symptoms of AI

- Headache
- Fatigue
- Weakness
- Dizziness with standing
- Nausea and/or vomiting
- Diarrhea and abdominal discomfort
- Decreased appetite and anorexia

Clinical Signs of AI

- Hypotension
- Tachycardia
- Hyponatremia
- Hypoglycemia

(Yuan (2013))

The patient may initially complain of worsening headache, dizziness, and fatigue before other symptoms become apparent. Depending on the level of deficiency, symptoms may develop slowly over several hours or become quickly apparent with stressful stimuli such as a blood draw, straining with post-op constipation, or with air travel. If an adrenal crisis is evident, parenteral (intravenous or intramuscular) injection of 100 mg (50 mg/m^2 for children) hydrocortisone must be administered immediately (Naziat and Grossman 2000; Bornstein et al. 2016). Measurement of serum electrolytes (particularly serum sodium) followed by fluid resuscitation is recommended. Glucocorticoids should be continued every 6 h for 24–48 h (half-life of hydrocortisone is 90–120 min) and until follow-up testing indicates normal function or the patient is stable on a physiologic dose of hydrocortisone (15–30 mg in divided doses daily (Naziat and Grossman 2000; Bornstein et al. 2016)).

23.4.1.2 Cushing Disease: ACTH Hypersecretion

Patients with Cushing Disease have ACTH secreting pituitary adenomas resulting in hypercortisolemia. Oversecretion of ACTH by the pituitary adenoma causes suppression of the normal circadian production of ACTH from surrounding normal corticotrophs and hypersecretion of cortisol from the adrenal glands (Nieman et al. 2015). There may also be a suppressive effect on hypothalamic CRH production that inhibits normal ACTH production. After the ACTH secreting pituitary adenoma is removed, the normal circadian corticotroph production of ACTH may still be absent or suppressed; therefore, ACTH and cortisol levels may be low in remitted disease. The Endocrine Society Guidelines define remission of Cushing's disease as:

> "a morning serum cortisol level < 5 μg/dL (<138 nmol/L) or UFC < 28–56 nmol/day (<10–20 μg/day) within 7 days of selective tumor resection (Nieman et al. 2015)."

There is some controversy around glucocorticoid replacement in patients with CD post remission unless cortisol levels remain low and the patient becomes symptomatic (Pimentel-Filho et al. 2005; Simmons et al. 2001). However, these patients are at increased risk for hypocortisolemia or adrenal insufficiency and, if postoperative cortisol levels indicate remission, most often require glucocorticoid replacement postoperatively. The dose should be adjusted to avoid symptoms of adrenal insufficiency (see Box 23.2 and Part XII; Adrenal Insufficiency). These patients should be monitored closely and require education regarding glucocorticoid taper and adrenal crisis avoidance and management.

23.4.1.3 Hypopituitarism

Postoperative levels of hormones regulated by the anterior pituitary gland will also need to be evaluated to assess for hypopituitarism and perhaps panhypopituitarism which is more common in cases necessitating removal of significant amounts of the anterior gland. The posterior pituitary gland controls Antidiuretic Hormone (ADH) secretion. Manipulation of the posterior pituitary gland and/or pituitary stalk during surgery increases risk for water and electrolyte imbalance.

Box 23.3 Symptoms of SIADH

- *Headache*
- *Lethargy*
- *Anorexia*
- *Nausea/vomiting*
- *Muscle cramps*
- *Agitation*
- *Delerium/disorientation*
- *Seizure*

23.4.1.4 Disturbance of Water Balance

Disturbance in water balance and electrolytes are the most common complication after pituitary surgery with some reports of postoperative water and electrolyte balance occurring in up to 75% of patients (Kristof et al. 2009). Apart from alterations in vasopressin secretion, other factors such as non-atrial natriuretic peptide excess, inappropriate thirst and fluid intake, and low dietary salt intake may contribute (Olson et al. 1997). Although estimates vary between centers, diabetes insipidus (DI) is estimated to occur in between 0.5 and 25% of patients and syndrome of inappropriate antidiuretic hormone (SIADH) 9–25% of cases (Dumont et al. 2005) (See Part XII).

23.4.1.1 Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Manipulation of the posterior pituitary may trigger excessive release of antidiuretic hormone (ADH), resulting in syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia. In this syndrome, under the influence of increased secretion of ADH, despite low serum osmolality, free water intake is in excess of free water excretion, resulting in hyponatremia, increased circulating volume, and increased sodium excretion. SIADH clinically presents as increased extremely concentrated urine output. This is a common condition following hospital discharge or approximately 5–7 days following surgery (Yuan 2013; Dumont et al. 2005).

Although some patients may be asymptomatic, many experience multiple symptoms described in Box 23.3. Laboratory evaluation of SIADH typically displays high urine specific gravity, urine sodium, and urine osmolality; and low serum sodium osmolality (Yuan 2013). Treatment of SIADH is individualized and aimed at correcting sodium and plasma osmolality. In patients with mild and asymptomatic cases of hyponatremia, fluid restriction (typically 1000 cc per day fluid) and daily serum electrolyte monitoring may be the only treatment necessary. Extremely low levels of sodium place the patient at a higher risk for seizures and even death; therefore, a more aggressive treatment may be indicated (Dumont et al. 2005). Patients with severe and symptomatic hyponatremia may require treatment with intravenous hypertonic solution (3% sodium chloride), frequent electrolyte monitoring, and strict fluid restriction (Yuan 2013). It is important for nurses to perform careful monitoring of fluid intake, and electrolyte status when caring for patients with SIADH. Due to the fact that this condition typically presents following hospital discharge, clear and thorough instructions prior to leaving the hospital are essential. Discharge instructions should include information on fluid restrictions, attention to salt intake, and knowledge on the symptoms of hyponatremia (Dumont et al. 2005) (See Part XII).

23.4.1.2 Diabetes Insipidus (DI)

Disturbing the posterior pituitary gland, pituitary stalk, or hypothalamus during surgery may impair the ADH pathway, causing diabetes insipidus (DI). DI occurs when there is an inadequate release of ADH, resulting in the excretion of large

amounts of dilute urine. DI is reported to occur in 0.5–25% of cases with most cases of being transient, occurring 24–48 h following surgery, and typically subsiding within 72 h (Dumont et al. 2005) See Symptoms, Box 23.4.

Laboratory values show low urine specific gravity, sodium, and osmolality; and high levels of serum sodium and osmolality (Yuan 2013; Dumont et al. 2005). DI can be very dangerous if not addressed quickly, therefore screening is a very important aspect of postoperative care. It is important for nurses to perform daily weights, thorough intake and output, and assess for thirst, dehydration, hypernatremia, and hypokalemia. Screening should also include monitoring daily serum chemistries, serum and urine osmolality (or more frequently if indicated), as well as urine specific gravities every 4 h (Dumont et al. 2005). Treatment of DI is individualized and based on the severity and duration of the condition. Standard treatment for DI at many institutions consists of monitoring serum electrolytes and urine specific gravity every 4 h, until osmotic homeostasis is restored (Yuan 2013). Specific treatment of DI includes administration of Desmopressin (DDAVP), a synthetic form of ADH, which can be administered orally, subcutaneously, intranasally, or intravenously (Dumont et al. 2005). When caring for a patient following pituitary surgery, it is important to be aware that many patients undergo postoperative diuresis due to intravenous fluid administration during surgery. This is a normal response that does not require treatment. Thus, prior to treatment for DI, it is essential to distinguish between mobilization of postoperative fluids and DI. It is important for nurses to ensure the patient has access to oral fluids and to continue monitoring urine output, urine specific gravity, urine osmolality, serum sodium, serum osmolality, and mental status (Yuan 2013).

Box 23.4 Symptoms of DI
Polyuria
Polydipsia
Excessive thirst
Hypotension secondary to hypovolemia
Fever

23.5 Monitoring Neurosurgical Complications

In addition to the endocrinological complications following surgery, there are also direct neurosurgical complications that may occur following pituitary surgery. These include infection, cerebral spinal fluid (CSF) leak, visual loss, epistaxis, intracranial hematoma, and HPA axis dysfunction.

23.5.1 Infection

As with all surgical patients, the pituitary surgery patient should be monitored for signs of infection with routine labs, vital signs, and incision assessment. Signs of meningitis should also be observed for, particularly in the patient with CSF leak and/or lumbar drain. Signs and symptoms of meningitis (Box 23.5) must be reported urgently so that appropriate antibiotic coverage may be initiated promptly (AANN Clinical Practice Guidelines Series 2011). When the sublabial approach for transsphenoidal pituitary surgery is used, diligent oral care is essential for infection prevention.

23.5.2 CSF Leak

Every patient who undergoes transsphenoidal surgery is at risk for CSF leak. This complication is reported in about 4% of cases (Dumont et al. 2005). There is a layer of dura known as the diaphragma sellae that lies above the pituitary gland. If the pituitary tumor invades the diaphragma sellae, or if the diaphragma sellae is violated intraoperatively, CSF leak will occur. When CSF leak

Box 23.5 Signs and Symptoms of Meningitis
- *Fever*
- *Photophobia*
- *Nuchal rigidity*
- *Headache*
- *Vomiting*
- *Change in mental status*

is encountered intraoperatively, CSF diversion with lumbar drainage is generally performed. Nursing care of the patient undergoing lumbar drainage is discussed further below. If CSF leak occurs postoperatively, patients may present with persistent clear, odorless rhinorrhea or complain of a salty, bitter, or metallic taste in their mouth if CSF drains posteriorly (Yuan 2013). Exposure of the meninges to nasopharyngeal flora via CSF leak places the patient at high risk of meningitis. Therefore, signs of CSF leak must be reported to the neurosurgeon immediately and addressed promptly. CSF leak is treated with lumbar drainage, antibiotics, and may require surgery for repair (Yuan 2013). Mucous from rhinorrhea may be sent to the lab to evaluate for presence of beta-2 transferrin, a protein found in CSF but not nasal mucosal secretions; if there is uncertainty, the rhinorrhea is CSF (Naziat and Grossman 2000). It should be noted that availability and turnaround time of this test will vary from institution to institution. Precautions to reduce pressure at the surgical site should be implemented to help reduce the risk of postoperative CSF leak. Precautions should include head of bed elevation per surgeon direction, aggressive postoperative nausea control to avoid vomiting, avoiding use of straws, no sneezing, no nose blowing, no nasal sniffing or bending over such that the head is below the level of the heart (Dumont et al. 2005). Valsalva maneuvers such as in straining with constipation and lifting can cause changes in intracranial pressure and should be avoided (Prabhakar et al. 2007) Patients using CPAP (continuous positive airway pressure for sleep apnea) may require increased oxygen but CPAP should be withheld until no CSF leak is evident.

23.5.3 Lumbar Drainage

American Association of Neuroscience Nurses, AANN, provides guidelines regarding care of the neurosurgical patient undergoing lumbar drainage (AANN Clinical Practice Guidelines Series 2011). The nurse caring for the pituitary surgery patient must also be familiar with lumbar drain care procedures at their practicing institution.

Lumbar drains are inserted under sterile conditions into the lumbar subarachnoid space at the level of L2-L3 or below so as to avoid injury to the spinal cord, which ends at L1-L2. After insertion, great care should be taken to maintain a sterile lumbar drainage system including monitoring integrity of the insertion site and dressing. Diligent hand hygiene is paramount. Transparent dressings allow for easy visualization of the insertion site and may stay in place so long as they are clean, dry, and intact. Dressings with gauze may require routine dressing changes (AANN Clinical Practice Guidelines Series 2011). The nurse should monitor the insertion site for signs of drainage and notify the neurosurgical provider if drainage is noted. Lumbar drainage may be ordered as continuous or intermittent per surgeon preference and/or institution policy (Lynn 2016) (See Fig. 23.2).

Protocol	Description
Draining at a specific level	• Physician order or hospital policy determins vertical level at which drainage collection device is maintained. • Designated level may be at shoulder height or level of catheter insertion • Amount of CSF to be drained varies.
Draining to a specific volume	• Physician order and hospital protocol determine amount of drainage desired durine specific period: average drainage is 10-15ml/hour • Vertical level of drain is repositioned to achieve desired drainage volume. • Attention to drain level is critical to avoid CSF backflow.

Ref: Lynn, S J. Caring for patients with lumbar drains. American Nurse Today. 2016 Vol. 11 No. 3

Fig. 23.2 Lumbar drain management protocols. Ref: Lynn, S J. Caring for patients with lumbar drains. American Nurse Today. 2016 Vol. 11 No. 3 https://www.americannursetoday.com/caring-patients-lumbar-drains/

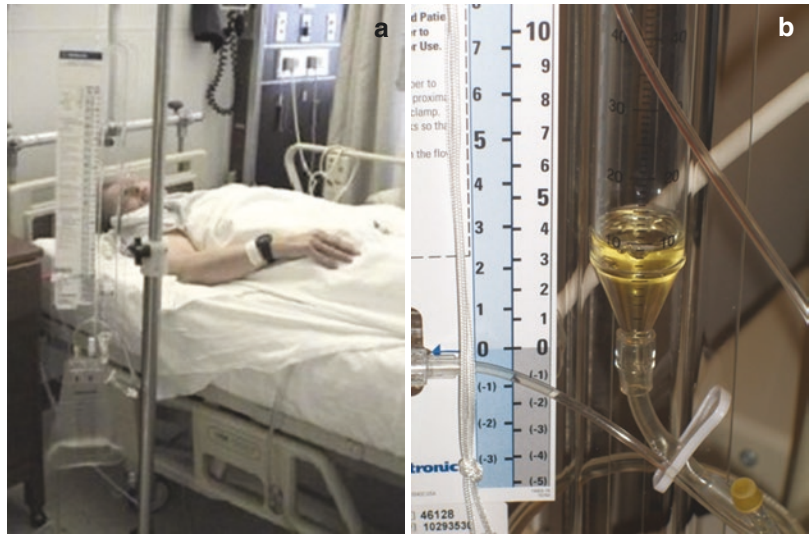


Fig. 23.3 (**a**) Patient with CSF drain for CSF fistula. The Burton report Jan 2018 Edition http://www.burtonreport.com/. (**b**) Lumbar CSF drain

Patients require education regarding their positioning while lumbar drain is in place. Specifically, any changes in bed height, head of bed, or changes in the patient position and mobilization, will require adjustment to the height of the collection chamber and nursing assistance. Any change in patient position while the drainage system is openly draining places the patient at risk for CSF over-drainage (AANN Clinical Practice Guidelines Series 2011; Lynn 2016) (Fig. 23.3a, b).

At the time of insertion, CSF may be collected and sent to the laboratory for analysis. It should be noted that CSF requires prompt delivery to the laboratory for accurate analysis due to rapid decrease in cell counts after collection, 32% decrease after 1 h, and 50% decrease after 2 h. Additionally, bacteria may not survive for long periods of time in the collection tubes (AANN Clinical Practice Guidelines Series 2011).

23.5.4 Visual Loss

The optic chiasm lies directly above the pituitary gland. Therefore, the tumor addressed by pituitary surgery may have caused compression of the optic nerves, causing loss of peripheral vision (Amar and Weiss 2003; Ben-Shlomo and Melmed 2011). Patient will report preoperative visual field deficits or restrictions preoperatively, i.e., when driving. Many surgeons will request formal visual field testing with a neuro-ophthalmologist preoperatively when optic chiasm compression is suspected. Postoperatively the nurse should monitor visual fields and check extraocular movements to evaluate for any changes in vision. Acute postoperative changes in vision should be urgently reported to the surgeon as it may indicate a potential complication such as bleeding at the surgical site.

23.5.5 Epistaxis

Epistaxis may occur in the immediate post-op period or many days delayed postoperatively (Smith et al. 2015). Nasal mucosa is highly vascular and interruption of the nasal mucosa via transsphenoidal approach for resection of pituitary tumors increases risk for epistaxis. Most bleeding originates from the nasal mucosa and resolves quickly by holding pressure and tilting the head forward or nasal packing if bleeding persists. However, proximity of the pituitary gland to the cavernous sinus and internal carotid arteries makes epistaxis a potentially life-threatening symptom that should be taken seri-

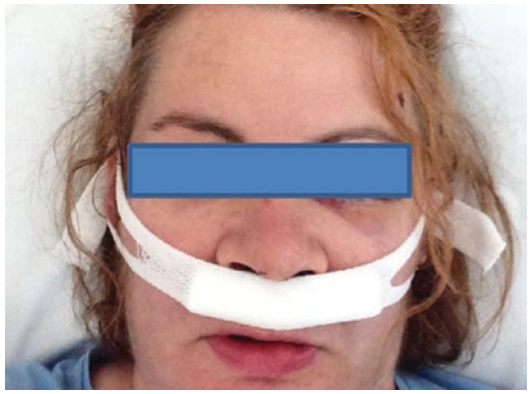


Fig. 23.4 Moustache dressing

ously and reported to the neurosurgeon. Severe epistaxis may require surgical exploration, cautery, or embolization (Smith et al. 2015).

Normal nasal drainage following transsphenoidal surgery is blood tinged mucoid drainage, which is often captured on a nasal drip pad or "moustache" dressing (Fig. 23.4), the first few days following surgery and after the nasal packing is removed. Patients are unable to effectively humidify the air they breathe following transsphenoidal surgery due to disruption of the sinuses and nasal congestion. Humidified air provides comfort to patients recovering from transsphenoidal surgery and should be offered. Additionally, the use of nasal sterile saline spray can help moisturize the nasal mucosa and improve patient comfort after any nasal packing is removed. Use of humidified air and intranasal sterile saline spray should be discussed with the patient's surgeon prior to initiating therapy. It should also be noted that due to the highly vascular nature of the nasal mucosa it is common for patients to ingest blood intraoperatively, which contributes to postoperative nausea.

23.6 Summary of Patient Education

Patient and family education is an important aspect in the management of patients undergoing pituitary surgery. Patient education should be an ongoing process and consideration should be given to education needs during the following phases of surgery.

23.6.1 Perioperative

Patient education should begin as early as possible. Provide the patient with written and verbal information regarding what to expect during the perioperative period (Yuan 2013). This may alleviate anxiety and have a positive impact on patient outcomes.

23.6.1.1 Preoperative

Education should include information pertaining to rationale for surgery, surgical approach, risks of surgery, preoperative medication and food restrictions, and common preoperative routines (i.e., standard preoperative testing and when and where to arrive at the hospital). Prepare the patient for common postoperative complications and treatments. Inform the patient of what to expect through the course of hospitalization and the treatment teams they will encounter in addition to the neurosurgeons such as Ear Nose and Throat (ENT) surgeon(s), anesthesiologists, and endocrinologists.

23.6.1.2 Intraoperative

Education may include information regarding general anesthesia, surgical techniques (possible need for fat graft or lumbar drain), and recovery location immediately following surgery (ICU or PACU).

23.6.1.3 Postoperative

Education should focus on activity. Key aspects may include: elevated head of bed, early ambulation, required assistance when ambulating in the event of a lumbar drain, nasal packing, urinary catheter, monitoring intake and output, monitoring for CSF leak, incision care, and oral care. Oral care is especially important for patients undergoing transsphenoidal surgery. Patients should only brush their teeth using a special ultra-soft toothbrush (for approximately 2 weeks), and special mouthwash and

swabs should be utilized to rinse their mouth throughout the day (especially after eating and drinking).

23.6.2 Discharge

Discharge instructions should be provided to the patient in written and verbal format, and be reviewed with the patient prior to leaving the hospital. Clear discharge instructions facilitate a smooth recovery process (Yuan 2013). Specific instructions will vary across hospitals. All discharge instructions should include information on the following:

23.6.2.1 Postoperative Follow-Up Appointment and Testing Needs

Following surgery, patients are typically seen by their neurosurgeon a few weeks after surgery to assess wound healing and by their endocrinologist at approximately 1–6 weeks after surgery to check hormone replacement (Yuan 2013). Patients then typically undergo a magnetic resonance imaging (MRI) and evaluation 3 months following surgery, and then at yearly intervals (or at the discretion of the physician) to follow-up on residual tumor recurrence. Some patients with persistent or recurrent disease may be referred for radiation therapy or radiosurgery (Dumont et al. 2005; Prather et al. 2003).

23.6.2.2 Symptom Management

Upon discharge, patients should be instructed to monitor and report any signs and symptoms of AI, SIADH, DI, and any other neurosurgical complications previously discussed.

23.6.2.3 Activity

It is important for patients to be careful performing certain types of activities following surgery. Specific restrictions may vary depending on the surgical procedure. It is also important to avoid heavy lifting (over 20 lb) for the first 4 weeks following surgery (Yuan 2013). For patients undergoing transsphenoidal surgery, it is important to avoid coughing, blowing or aggressively cleaning or picking the nares, sneezing, bending below the knee level, or straining for 1 month following surgery. Patients are instructed to refrain from using CPAP devices for sleep apnea until cleared by ENT clinicians. Patients are typically able to return to work 3–6 weeks following surgery. However, return to work should be discussed with the neurosurgery team.

Case Study

Ms. S is a 38-year-old woman with a 2 year history of excessive weight gain, despite dietary modification and exercise, development of hypertension and diabetes mellitus, thinning skin with easy bruising, and irregular menstruation. Her primary care provider performed blood testing including cortisol and ACTH levels, which were found to be abnormally elevated. She was therefore referred for pituitary imaging which demonstrated a lesion measuring under 10 mm on the left side of her pituitary gland. She was referred to an endocrinologist who identified pituitary source of excess ACTH production therefore confirming Cushing's Disease. Her endocrinologist referred her to neurosurgery for resection of her pituitary microadenoma. She is currently post-op day 1 status post transsphenoidal surgery via sublabial approach and has been assigned to your care today. During your shift you notice an increase in urine output and Ms. S is complaining of excessive thirst. Her serum sodium 8 h ago was 138 mEq/L and now is 146 mEq/L. Her urine specific gravity upon last void is 1.002. She is urinating hourly 300–500 mL/h over the past 3 h.

1. What hormone imbalance do you suspect?

   The increased serum sodium in the setting of decreased urine specific gravity and excessive urine output is characteristic of diabetes insipidus. Diabetes insipidus results when the pituitary gland does not excrete adequate amounts of antidiuretic hormone (ADH).

2. What should you do next?

   Ms. S's medical/surgical providers should be notified of the changes in her fluid balance. Notification to her providers should include most recent intake/output, specifically urine output; laboratory results, specifically serum

sodium, serum osmolality, urine specific gravity; daily weight and updated set of vital signs.

3. What are the nursing considerations of the patient with diabetes insipidus?

   Maintaining diligent intake and output in addition to monitoring daily weights to monitor patient's hydration status is paramount. Understanding that the patient with diabetes insipidus is at risk for dehydration should guide the nurse to monitor vital signs for tachycardia/bradycardia and be cautious during mobilization due to risk for orthostatic hypotension from inadequate intravascular volume. Increased frequency of laboratory testing may be indicated. The nurse should discuss potential need for fluid replacement with the medical/surgical providers.

4. What medication may be ordered for treatment of diabetes insipidus?

   Desmopressin (DDAVP).

5. Ms. S is prescribed hydrocortisone postoperatively for steroid replacement. She will discharge on this medication. What nursing education must occur prior to her discharge?

   Ms. S must receive detailed patient education regarding adrenal insufficiency and the importance of continuing hydrocortisone therapy as prescribed by her providers. She should be taught signs of adrenal insufficiency, what to do and who to contact if she notices any of these signs. The body's steroid needs increase in times of sickness therefore patients require additional steroid medication when they are ill, instructions should be provided to the patient regarding what to do when they are ill. She will require instructions to taper her dose of hydrocortisone if discharged on supraphysiologic doses. Follow-up with endocrinology within approximately 6 weeks postoperatively is important. She will require testing to evaluate HPA axis function to determine her ongoing need for glucocorticoids.

6. What other discharge education should be provided?

Given this patient underwent transsphenoidal surgery via *a sublabial approach, she should be taught about oral care needs and activity restrictions. Specific activity restrictions may vary slightly from institution to institution; however, they are all generally aimed at avoidance of placing pressure on the sphenoid sinus surgical site. General limitations include avoiding nose blowing, sneezing (sneeze with open mouth to diffuse pressure if the patient must sneeze), heavy lifting over 20 lb, or straining. The patient's follow-up plans should be outlined prior to discharge. Follow-up for further endocrinological monitoring is essential.*

References

AANN Clinical Practice Guidelines Series. Care of the patient undergoing intracranial pressure monitoring/external ventricular drainage or lumbar drainage. Chicago: AANN; 2011.

Amar P, Weiss MH. Pituitary anatomy and physiology. Neurosurg Clin N Am. 2003;14(1):11–2.

Ben-Shlomo A, Melmed S. Pituitary development. In: Melmed S, editor. The pituitary. 3rd ed. San Diego: Elsevier; 2011. p. 21–41.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89. https://doi.org/10.1210/jc.2015-1710.

Carminucci AS, Ausiello JC, Page-Wilson G, Lee M, Good L, Bruce JN, Freda PU. Outcome of implementation of a multidisciplinary team approach to the care of patients after transsphenoidal surgery. Endocr Pract. 2016;22(1):36–44. https://doi.org/10.4158/EP15894.OR. Epub 2015 Oct 5.

Dumont AS, Nemergut EC II, Jane J Jr, Laws ER Jr. Postoperative care following pituitary surgery. J Intensive Care Med. 2005;20:127Y140. https://doi.org/10.1177/0885066605275247.

Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery. 1997;121(2):123–9.

Greenberg MS. Handbook of neurosurgery. 8th ed. New York: Thieme Medical Publishers, Inc; 2016.

Inder WJ, Hunt PJ. Glucocorticoid replacement in pituitary surgery: guidelines for perioperative assessment and management. J Clin Endocrinol Metab. 2002;87(6):2745–50. https://doi.org/10.1210/jc.87.6.2745.

Kelly KN, Domajnko B. Perioperative stress-dose steroids. Clin Colon Rectal Surg. 2013;26(3):163–7. https://doi.org/10.1055/s-0033-1351132.

Kristof RA, Rother M, Neuloh G, Klingmüller D. Incidence, clinical manifestations, and course of

water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. J Neurosurg. 2009;111(3):555–62. https://doi.org/10.3171/2008.9.JNS08191. PubMed PMID: 19199508.

Lynn SJ. Caring for patients with lumbar drains. American Nurse Today 2016;11(3). https://www.americannursetoday.com/caring-patients-lumbar-drains/

Malenković V, Gvozdenović L, Milaković B, Sabljak V, Ladjević N, Zivaljević V. Preoperative preparation of patients with pituitary gland disorders. Acta Chir Iugosl. 2011;58(2):91–6.

Naziat A, Grossman A. Adrenal insufficiency. [Updated 2015 Apr 12]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth: MDText.com, Inc; 2000. https://www-ncbi-nlm-nih-gov.liboff.ohsu.edu/books/NBK279122/.

Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818.

Olson BR, Gumowski J, Rubino D, Oldfield EH. Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. J Neurosurg. 1997;87(4):499–507.

Overstreet M. Clinical Queries: how do I manage a lumbar drain? Nursing. 2003;33(3):74–5.

Pimentel-Filho FR, Silva MER, Nogueira KC, Berger K, Cukiert A, Liberman B. Pituitary-adrenal dynamics after ACTH-secreting pituitary tumor resection in patients receiving no steroids post-operatively. J Endocrinol Invest. 2005;28:502.

Prabhakar H, Bithal PK, Suri A, Rath GP, Dash HH. Intracranial pressure changes during valsalva manoeuvre in patients undergoing a neuroendoscopic procedure. Minim Invasive Neurosurg. 2007;50(2):98–101. https://doi.org/10.1055/s-2007-982505.

Prather SH, Forsyth LW, Russell KD, Wagner VL. Caring for the patient undergoing transsphenoidal surgery in the acute care setting: an alternative to critical care. J Neurosci Nurs. 2003;35(5):270–5. PubMed PMID: 14593938.

Simmons NE, Alden TD, Thorner MO, Laws ER Jr. Serum cortisol response to transsphenoidal surgery for Cushing disease. J Neurosurg. 2001;95(1):1–8.

Smith TR, Hulou M, Huang KT, Nery B, Miranda de Moura S, Cote DJ, Laws ER. Complications after transsphenoidal surgery for patients with Cushing's disease and silent corticotroph adenomas. Neurosurg Focus. 2015;38(2):E12.

Yuan W. Managing the patient with transsphenoidal pituitary tumor resection. J Neurosci Nurs. 2013;45(2):101–7. https://doi.org/10.1097/JNN.0b013e3182828e28. Review. PubMed PMID: 23422696.

Zhao B, Wei Y-K, Li G-L, Li Y-N, Yao Y, Kang J, Ma W-B, Yang Y, Wang R-Z. Extended transsphenoidal approach for pituitary adenomas invading the anterior cranial base, cavernous sinus, and clivus: a single-center experience with 126 consecutive cases. J Neurosurg. 2010;112(1):108–17. https://doi.org/10.3171/2009.3.JNS0929.

Key Reading

1. Ben-Shlomo A, Melmed S. Pituitary development. In: Melmed S, editor. The pituitary. 3rd ed. San Diego: Elsevier; 2011. p. 21–41.
2. Liyanarachchi K, Ross R, Debono M. Human studies on hypothalamo-pituitaryadrenal (HPA) axis. Best Pract Res Clin Endocrinol Metab. 2017;31:459e473.
3. Rollin GAF, Ferreira NP, Junges M, et al. Dynamics of Serum Cortisol Levels after transsphenoidal surgery in a cohort of patients with Cushing's disease. J Clin Endocrinol Metab. 2004;89:1131–9.
4. Barkan AL, Blank H, Chandler WF. Pituitary surgery: peri-operative management. In: Swearingen B, Biller BMK, editors. Diagnosis and management of pituitary disorders. Totowa: Humana Press; 2008. p. 303–19.
5. Eisenberg AA, Redick EL. Transsphenoidal resection of pituitary adenoma: using a critical pathway. Dimens Crit Care Nurs. 1998;17(6):306–12.

Radiotherapy

24

Ahmed Al Sajwani and Mark Sherlock

Contents

24.1 **Introduction** 449

24.2 **Pituitary Tumors** 450

24.3 **Action of Radiotherapy** 450

24.4 **Histological Changes in the Pituitary Gland and Pituitary Adenomas Following Radiotherapy** 451

24.5 **Methods of Delivery of Radiotherapy** 452
24.5.1 Radiotherapy Techniques 452
24.5.2 Forms of Radiotherapy 454

24.6 **Use of Radiotherapy in Patients with Pituitary Adenoma** 456

24.7 **Effect of Radiotherapy on Secretory Tumors** 456
24.7.1 Use of Radiotherapy in Patients with Acromegaly 456
24.7.2 Use of Radiotherapy in Patients with Cushing's Disease 458
24.7.3 Use of Radiotherapy in Patients with Prolactinoma 459
24.7.4 Radiotherapy for Non-functioning Pituitary Adenoma (NFPA) 459

24.8 **Complications of Pituitary Radiotherapy** 460
24.8.1 Short-Term Complications 460
24.8.2 Long-Term Complications 460

24.9 **The Impact of Radiotherapy on Specific Anterior Pituitary Hormones** 462
24.9.1 Growth Hormone 462
24.9.2 FSH/LH 463
24.9.3 Adrenocorticotropic Hormone 463
24.9.4 TSH 463
24.9.5 Prolactin 464
24.9.6 The Long-Term Implications of Pituitary Dysfunction 464

A. Al Sajwani
Department of Endocrinology, Tallaght Hospital,
Dublin and Trinity College, Dublin, Ireland

M. Sherlock (✉)
Department of Endocrinology, Beaumont Hospital and
Royal College of Surgeons in Ireland, Dublin, Ireland
e-mail: marksherlock@beaumont.ie

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_24

24.10 **The Endocrine Nurse Specialist Role** 464
24.10.1 Patient Preparation 464
24.10.2 Short-Term Side Effects of Radiation Therapy 465
24.10.3 Long-Term Side Effects of Radiation Therapy 465
24.11 **Conclusions** 465
References 466

Abstract

Ionizing radiation, discovered in the late nineteenth century, is used to treat pituitary tumors as an adjunctive therapy. Radiotherapy works at a cellular level via a number of mechanisms to cause cell death. This occurs slowly, often taking years to normalize hormone levels. Therefore, adjunctive medical therapies may be required in the interim.

External beam radiation is most commonly used to treat pituitary adenomas with conventional radiotherapy (CRT), the most frequently used method. In CRT, radiation doses are administered in small, fractionated doses, usually for a total of 45–50 Gy. Targeted treatment planning uses CT/MRI and a customized mask is used for head stabilization and precise tumor targeting with each subsequent treatment. Stereotactic radiosurgery (SRS) includes Gamma Knife, and proton beam therapy. These require neuroimaging techniques such as CT/MRI or PET scan mapping for precise targeting of the lesion.

Radiation is delivered using a Linear Accelerator (LINAC), Gamma Knife, Cyberknife, proton beam and, rarely, brachytherapy with the implantation of radioactive seeds. Post treatment progressive hypopituitarism may become apparent in up to 50% of patients, necessitating ongoing monitoring and replacement therapies.

Radiation therapies are used to control tumor growth in persistent or recurrent pituitary tumors or to control excess hormonal production. Radiation has been shown to be effective in a significant proportion of patients to arrest tumor growth and normalize hormonal levels in acromegaly, Cushing's disease, and in large prolactinomas when primary surgical and/or medical therapies fail or when the patient is intolerant or resistant to second line medical therapies. Risk benefit must be considered as in all therapies.

Keywords

Pituitary · Radiation · Hypopituitarism · Adenoma

Abbreviations

ACTH	Adrenocorticotropic hormone
BED	Biological effective dose
CRT	Conventional radiotherapy
CT	Computerized tomography
CVA	Cardiovascular accident
DNA	Deoxyribonucleic acid
FSH	Follicle stimulating hormone
GH	Growth hormone
GHD	Growth hormone deficiency
GK	Gamma Knife radiation therapy
Gy	Gray
HP	Hypothalamic-pituitary axis
HPA	Hypothalamic-pituitary-adrenal axis
IGF-1	Insulin growth factor 1
ITT	Insulin tolerance test
LH	Luteinizing hormone
LINAC	Linear accelerator
MRI	Magnetic resonance imaging
NFA	Non-functioning adenoma
NFPA	Non-functioning pituitary adenoma

PET	Positron emission tomography
RT	Radiotherapy
SRS	Stereotactic radiosurgery
SST	Standard Synacthen Test
TSH	Thyroid stimulating hormone

Key Terms

- **The Gray (Gy)** is the unit used to describe the patient absorbed dose of any form of ionizing radiation (1 Gy = 1 J/kg).
- **Biological effective dose (BED)** is a calculation that aims to quantify the biological effect of any radiotherapy treatment, taking into account changes in dose-per-fraction or dose rate and total dose, over time.
- **Pre-treatment tumor mapping** uses sophisticated coordinated computerized CT/MRI/PET imaging system to construct the shape of the tumor and plan for targeted delivery of radiation.
- **Fractionated conventional radiotherapy** is delivered in the form of small doses of 25–30 fractions over 5–6 weeks.
- **A linear accelerator** is a machine that uses electricity to generate high-energy photons or X-rays.

Key Points

- Radiation therapy is most commonly used as an adjunctive therapy when both surgery and available medical therapies have failed to control the growth or the excess hormonal production from a pituitary adenoma.
- Radiotherapy damages cellular viability by generating highly reactive free radicals and hydrogen reducing species, disrupting plasma membranes, DNA damage and DNA double-strand breakage. Radiation damaged cells die either immediately or more slowly following cell division.
- External beam radiation in the form of fractionated conventional radiotherapy (CRT) is the most commonly used radiation to treat pituitary tumors.
- Stereotactic radiosurgery (SRS) can be divided into Gamma Knife radiation therapy, linear accelerator based and proton beam therapy.
- The efficacy of radiotherapy for different types of pituitary adenomas varies related to factors such as type and dose of radiotherapy; type, size, and position of the pituitary tumor; surgical intervention, prior to irradiation and concurrent use of medical therapy.
- Efficacy for control of hormonal excess may be delayed by many years requiring a patient to continue adjunctive treatment and long-term endocrine monitoring.
- Hormonal deficiencies develop in almost 50% of patients after radiation necessitating close endocrine monitoring and dynamic testing particularly for HPA axis function.
- Other rare complications post radiation therapy include: neural dysfunction; cerebrovascular effects; secondary neoplasms; infertility; memory, cognitive executive function changes.
- Many aspects of planning, patient and family preparation need to be addressed prior to therapy by all members of the care team.

24.1 Introduction

Ionizing radiation, that has sufficient energy to pass through a medium, has been utilized in medicine since the late nineteenth century, soon after the discovery of X-rays by Roentgen in 1895

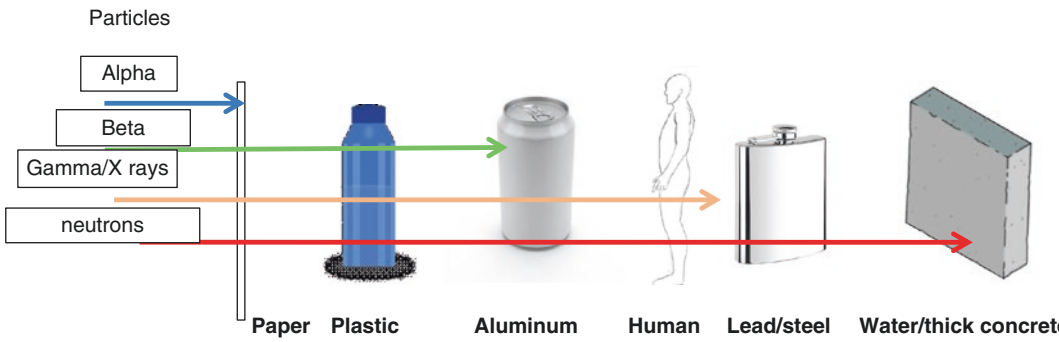


Fig. 24.1 Radiation particles and penetration. Ref: https://www.nrc.gov/about-nrc/radiation/health-effects/radiation-basics.html

and Radium by Marie and Pierre Curie in 1897 (Fig. 24.1). Intracranial tumors are commonly treated with irradiation and approximately 10% of these tumors originate in the pituitary gland. The most common pituitary tumors are adenomas which are benign tumors arising from the adenohypophysis, the anterior part of the pituitary gland. There are a number of other tumors that may arise in the sellar region including: craniopharyngioma, meningioma, optic nerve glioma, osteomas, chordomas, and other rare lesions.

24.2 Pituitary Tumors

Pituitary adenoma are generally classified into functional (secretory) and non-functional (non-secretory). Functional pituitary adenomas may secrete one (or more) of the following hormones: prolactin, growth hormone, adrenocorticotropic hormone (ACTH), less frequently thyroid stimulating hormone, and gonadotropin secreting adenoma (luteinizing hormone and follicle stimulating hormone).

The first-line management of pituitary tumors, when required, is surgical with the exception of prolactin-secreting tumors, which are primarily treated by medical therapy. Microsurgery in the form of transsphenoidal tumor resection is regarded as one of the most reliable surgical modalities. Open craniotomy is reserved for cases when tumors are not accessible by the endonasal approach (See Chap. 22).

The majority of patients who receive pituitary irradiation do so as an adjuvant therapy following surgery but have a residual tumor (or persistent hormonal hypersecretion) or tumor recurrence. Radiotherapy can be used as the sole therapy in patients not amenable to surgery, when there is little or no medical management to offer, or when tumor has close proximity to sensitive areas particularly in the cavernous sinuses where surgery carries significant morbidity risk. The response to radiotherapy for secretary adenomas is often slow compared to surgery and medical management, the time to endocrine control can be up to 10 years, this is felt to be due to slow rate of division of irradiated cells, which die only after a few divisions. Therefore, patients with functional pituitary adenoma may require medical therapy in the intervening years while waiting for sufficient radiation-induced damage to allow endocrinological control.

24.3 Action of Radiotherapy

At the cellular level, radiotherapy works via a number of mechanisms including the generation of highly reactive free radicals and hydrogen reducing species, plasma membrane disturbance, DNA damage, and DNA double-strand breakage. Radiation damaged cells die either immediately or more slowly following cell division. In general, non-tumorous, normal cells have a better capacity to repair their DNA than abnormal cells (Fig. 24.2).

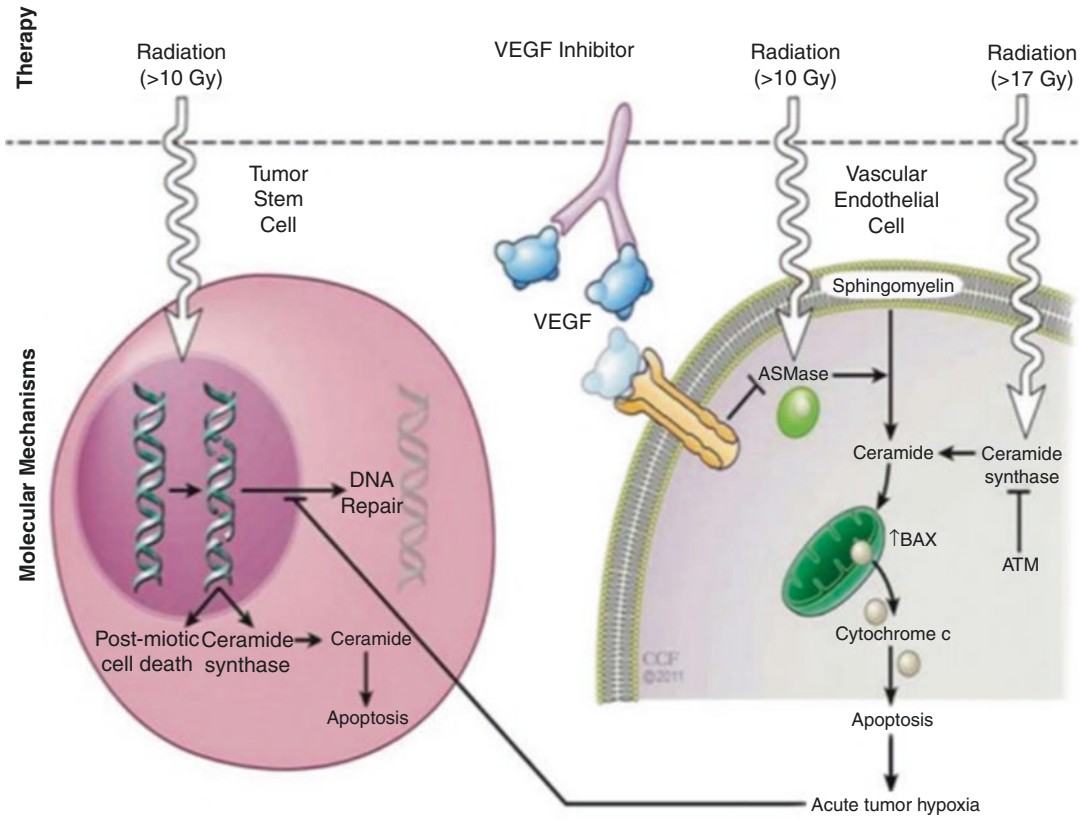


Fig. 24.2 Cell changes with radiation exposure. Used with permission from LAKSHMI DEEPTHI GEDELA, Junior Resident in Radiation Oncology, Postgraduate Institute of Medical Education and Research

Dosing schedules for various conditions can vary between radiotherapy centers with respect to the total radiation dose administered or the number of treatment fractions used. The Gray (Gy) is the unit used for the patient absorbed dose of any form of ionizing radiation (1 Gy = 1 J/kg). It is recognized that the same radiation dose delivered in larger fractions will have a greater biological impact. Another important factor that determines the impact of radiation is the sensitivity of the tissue being exposed: for example, the very rapid cell turnover of intestinal cells make them more sensitive than nervous tissue, which has a much slower turnover rate.

Taking these factors into account, the biological effective dose (BED) can be calculated when considering the impact of different protocols on a tissue. This was pioneered by Barendsen (1982) and Fowler (1989), and makes it possible to standardize the biological effects of a given total radiation dose for any tissue within the body taking into account the fractionation schedule. A key concept in the cell survival theory is that different tissues have different fractionation sensitivities, these tissues have been labelled early and late responding tissues (Schmiegelow et al. 2000).

24.4 Histological Changes in the Pituitary Gland and Pituitary Adenomas Following Radiotherapy

Ionizing radiation is known to affect cell nuclei, the plasma membrane and disturb extracellular as

well as intracellular signalling systems (Vincent 1995; Dainiak 1997). Acutely, following radiotherapy, one can visualize pyknosis (irreversible nuclear chromatin changes) or other nuclear changes that indicate imminent cell necrosis or apoptosis. However, long term no apoptotic cells are found as these are quickly cleared by phagocytosis (Vincent 1995).

Two histologic studies comparing tissue samples from patients who underwent anterior pituitary gland irradiation found differences between normal and tumor cells (Nishioka et al. 2001, 2002). Fibrotic changes with thickened connective tissue between glandular structures were found in normal pituitary tissues. This effect was more pronounced the farther the patient was from the original treatment. Fibrosis was found to be absent or mild in pituitary tumor/adenomas cells following conventional fractionated radiotherapy and stereotactic fractionated radiotherapy (Nishioka et al. 2001, 2002). However, diffuse hyaline deposits were found in pituitary adenoma tissue following Gamma Knife radiosurgery (Nishioka et al. 2002). The underlying cellular mechanism of radiation-induced fibrosis has been studied in detail by Rodemann and Bamberg (Rodemann and Bamberg 1995) who have described an altered cytokine and growth factor profile leading to a disturbance in the well-balanced cell type ratio of the interstitial fibroblast/fibrocyte cell system. On immunohistochemical staining of irradiated pituitary tissue, there are stellate-shaped (star shaped) S100 protein positive cells. These stellate-shaped cells are known to synthesize cytokines including interleukin-6 and fibroblast growth factor (Vankelecom et al. 1993) and have been implicated in radiation-induced fibrosis (Nishioka et al. 2001).

Adenohypophyseal (anterior pituitary) necrosis is rare with conventional doses of radiotherapy and it has been reported that doses of greater than 185 Gy are necessary to induce necrosis in the normal adenohypophysis. As one would suspect from the low incidence of cranial diabetes insipidus following cranial irradiation, the neurohypophysis does not show any histological changes (Nishioka et al. 2001, 2002).

24.5 Methods of Delivery of Radiotherapy

Radiotherapy can be administered externally (external beam radiation—teletherapy) or internally (pellets, seeds, etc.—brachytherapy). External beam radiation is the most commonly used to treat pituitary tumors. Radiation can be delivered in the form of photons like X-rays or Gamma rays or in the form of charged particles or protons.

24.5.1 Radiotherapy Techniques

24.5.1.1 Conventional Radiotherapy (CRT)

Conventional radiotherapy (CRT) is the most frequently used method of radiation therapy for pituitary tumors. It is most frequently used in patients who have a tumor remnant with evidence of progression following surgery or if surgery does not lead to normalization of hormone excess. The techniques used for CRT include high-energy CRT with opposed lateral fields, 360° rotational fields, moving arcs, and three field techniques (two lateral fields and a vertex field) (Fig. 24.3a, b) (Suh and Saxton 2000). The lesion anatomy is defined with MRI/CT and 3-D treatment planning with field conformation (Becker et al. 2002). During planning, a custom mask (Fig. 24.4) is made using a thermoplastic mesh, which attaches directly to the radiotherapy treatment machine. This mask limits mobility and minimizes head rotation and chin tilt variation. To account for the larger variation in positioning in 3D-CRT than is seen in stereotactic radiosurgery (SRS), a set up error margin is included in the planned treatment volume that results in a larger radiation target area compared to SRS (Shi et al. 2008).

Radiation doses range from 45 to 50 Gy at 180–200 cGy fractions (Colin et al. 2002; Tran et al. 1991; Tsang et al. 1996). Fractionated conventional radiotherapy is delivered in the form of small doses of 25–30 fractions over 5–6 weeks (Shi et al. 2008). Because stereotactic radiosurgery (SRS) is only a relatively new therapy, the majority of data regarding efficacy and potential adverse effects of radiotherapy is derived from studies assessing the use of CRT. However, there

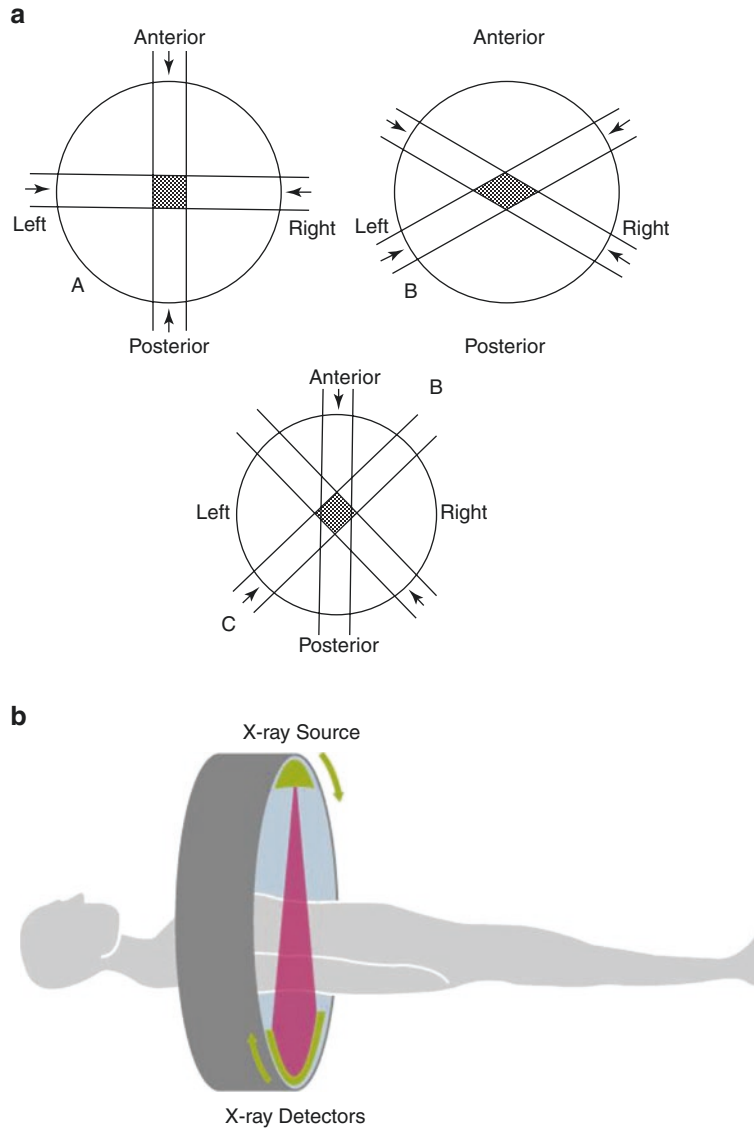


Fig. 24.3 Conventional radiation techniques. (**a**) Conventional radiation—two opposed lateral fields. (**b**) Conventional radiation 360° rotational fields

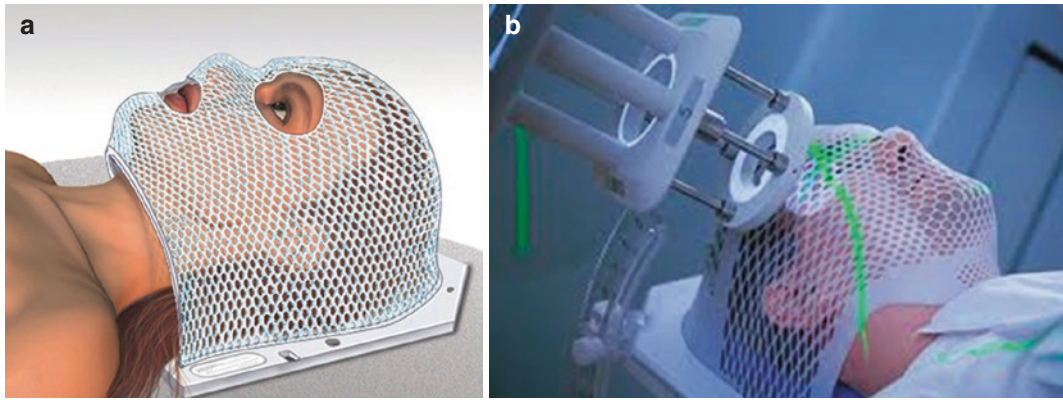


Fig. 24.4 Treatment masks. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet; http://oncocare.co.zw/blog/service/radiation-therapy/

is an increase in the amount of data regarding SRS in recent years.

24.5.1.2 Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery (SRS) can be divided into Gamma Knife radiation therapy, linear accelerator based and proton beam therapy. Gamma Knife radiation therapy (GK, Elekta, Stockholm, Sweden) uses multiple cobalt-60 gamma radiation emitting sources. Linear accelerator based SRS (LINAC) in which energy is accelerated, shaped and delivered in the form of electrons, or photons. Proton beam therapy uses heavy charged protons and has the added advantage of leading to less excess radiation exposure to surrounding tissue (Shih and Loeffler 2008). SRS is delivered most frequently as a single treatment with the patient immobilized after careful stereotactic imaging planning.

SRS requires accurate mapping of the target tissue (Fig. 24.5) through modern neuroimaging techniques such as CT scan, MRI, and PET/CT. Immobilization of the patient is crucial, allowing radiation to be delivered to a precise location, providing a steep dose gradient that falls off rapidly leading to limited impact on nearby normal tissues. The SRS delivered via a single dose is biologically more active than the same dose delivered in fractions. It also results in faster response to radiation when compared to fractionated radiotherapy. The dose employed to control tumor growth is usually lower than that required to achieve biochemical remission in secretory pituitary adenoma.

SRS is more convenient for patients but its use depends on patient eligibility, i.e., provided that, the pituitary lesion is not in close proximity to critical brain structures like the optic apparatus and the cranial nerves. Hypothalamic-pituitary dysfunction has been reported to occur less frequently following more focused cranial irradiation delivered via stereotactic radiotherapy.

24.5.2 Forms of Radiotherapy

24.5.2.1 Linear Accelerator (LINAC)

LINAC delivered radiotherapy is the most commonly used form of radiotherapy, and it uses electricity to generate high-energy photons or X-rays. The delivery of radiation is shaped to tumor size

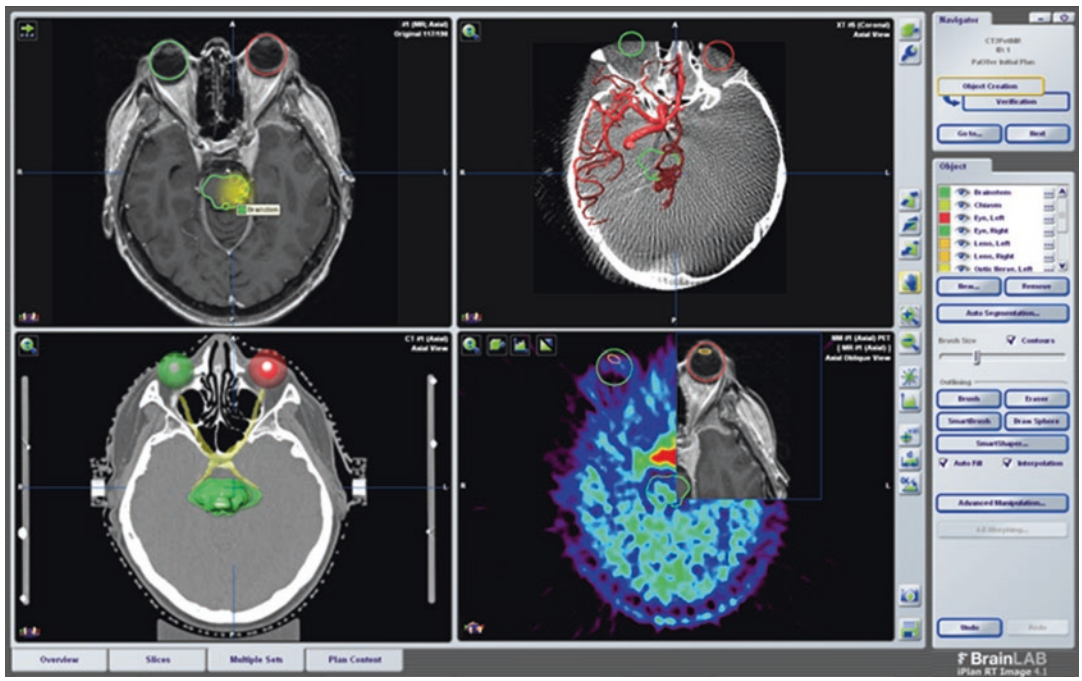


Fig. 24.5 Mapping for stereotactic radiosurgery (SRS) (permission granted). From Epworth Stereotactic radiosurgery and radiotherapy (Australia) Dr. Media enquiries, Contact Colleen Coghlan, Media Manager, Phone: 03 9426 8816, Fax: 03 9426 8997, Mobile: 0423 777 452, colleen.coghlan@epworth.org.au

and location. New devices offer multiple rotating beams and moving arcs, to target desired fields more accurately. The multileaf collimator confers radiation beams shaped automatically to focus on desired locations based on computerized input. The 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) are examples of targeted radiotherapy delivery in linear accelerators to confront the shape of the tumor by a coordinated system, aided by sophisticated calculations and computerized imaging techniques (Fig. 24.6).

24.5.2.2 Gamma Knife

Gamma Knife was the first stereotactic radiosurgery (SRS) developed and is widely used to treat pituitary adenomas. Gamma Knife uses radioactive cobalt-60 to deliver photons via numerous sources around the head, which are held by a minimally invasive metal head frame. This results in the emission of low energy beams from numerous sources directed at the center of the tumor, which ultimately receives the maximum dose with great dose heterogeneity between the center and margins of the tumor. This minimizes the radiation exposure to the adjacent tissues. Treatment is usually completed in one session, however; multisession treatment can be extended to deliver a smaller amount of radiation over 2–5 therapeutic sessions, which causes less toxicity to adjacent normal tissues (Fig. 24.7).

Fig. 24.6 Linear accelerator 3D-CRT. Linear accelerator used for external beam radiation therapy. A LINAC uses electricity to form a stream of fast-moving subatomic particles. This creates high-energy radiation that may be used to treat tumors. www.cancer.gov

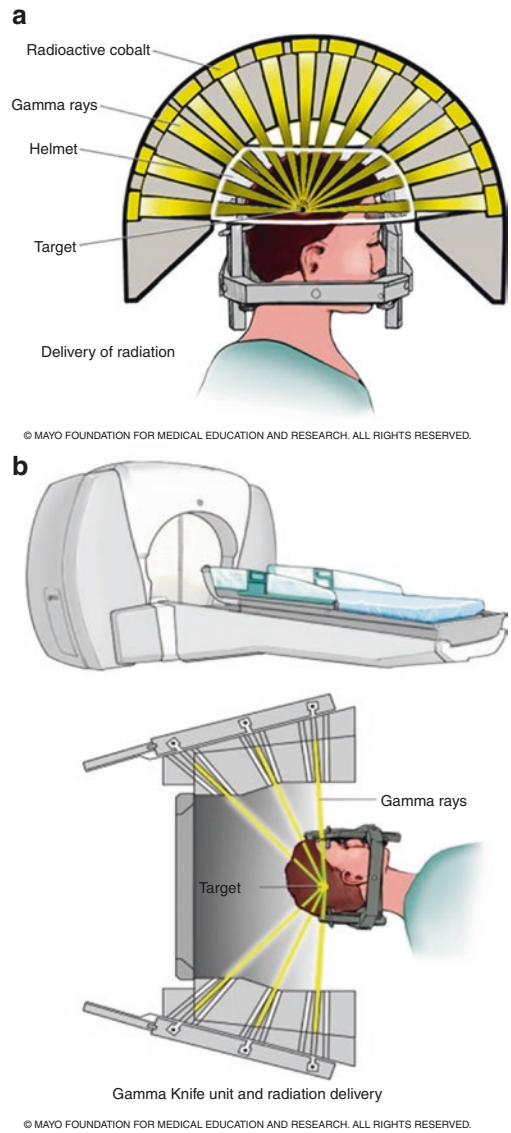


Fig. 24.7 Gamma Knife. Mayo foundation for medical education and research

24.5.2.3 CyberKnife

CyberKnife can deliver radiation therapy in a single or multiple sessions, using a robotic arm with mounted radiotherapy source (Linear Accelerator). CyberKnife has an enhanced targeting system for tumors resulting in better accuracy than other radiotherapy modalities. It is also non-invasive allowing for more movement flexibility without the need for head clamps, molds, or frames as the source can adjust itself with patient movement. The length of treatment with CyberKnife, however, is typically longer.

24.5.2.4 Proton Radiation

Proton therapy is available in few centers worldwide and therefore is not widely used at present because of the cost and complexity (Fig. 24.8). The novelty of this method is due to the physical properties and heavy weight of the charged particles used, which result in significantly less damage to the normal tissues and reduce the late side effects of radiation exposure compared with previous methods. The beam is aimed precisely at the tumor and tends not to widen as it reaches the target lesion. Because of dose-distribution characteristics and localized radiation delivery with absent exit dose, increasing radiation dose results in a greater impact on tumor cells and maximizes their damage without increasing risks to the surrounding normal tissues (Fig. 24.9).

24.5.2.5 Brachytherapy

Brachytherapy is rarely practiced now and involves implanting yttrium-90 (Y-90) or gold-198 (AU-198) radioactive seeds into the pituitary gland through a transsphenoidal approach.

Fig. 24.8 Cyberknife. http://indiamedcare.com/wp-content/uploads/2016/12/Cyberknife-radiosurgery-inindia.jpg

24.6 Use of Radiotherapy in Patients with Pituitary Adenoma

In general, radiotherapy is effective in arresting tumor growth or even decreasing tumor size especially if the target lesion is clear and discrete. Hormonal remission is less likely achieved solely by radiotherapy and may take a number of years.

The efficacy of radiotherapy reported in the literature for different types of pituitary adenomas are variable. This may be due to variations in the:

- Type and dose of radiotherapy used
- Type and size of the pituitary tumor
- Rates of surgical intervention prior to irradiation and concurrent use of medical therapy
- Differences in biochemical assays and criteria to define biochemical remission in secretory tumors
- Definition of efficacy used for tumor growth or biochemical control
- Length of follow-up in the study (as these tumors are frequently slow growing and impact on endocrine outcomes may take many years. A long period of follow-up is required for accurate assessment of efficacy)

24.7 Effect of Radiotherapy on Secretory Tumors

24.7.1 Use of Radiotherapy in Patients with Acromegaly

Acromegaly is an excess of growth hormone caused, in the majority of cases, by a pituitary tumor producing excess GH and a subsequently excess IGF-1 from the liver. Acromegaly is associated with increased cardiovascular, respiratory

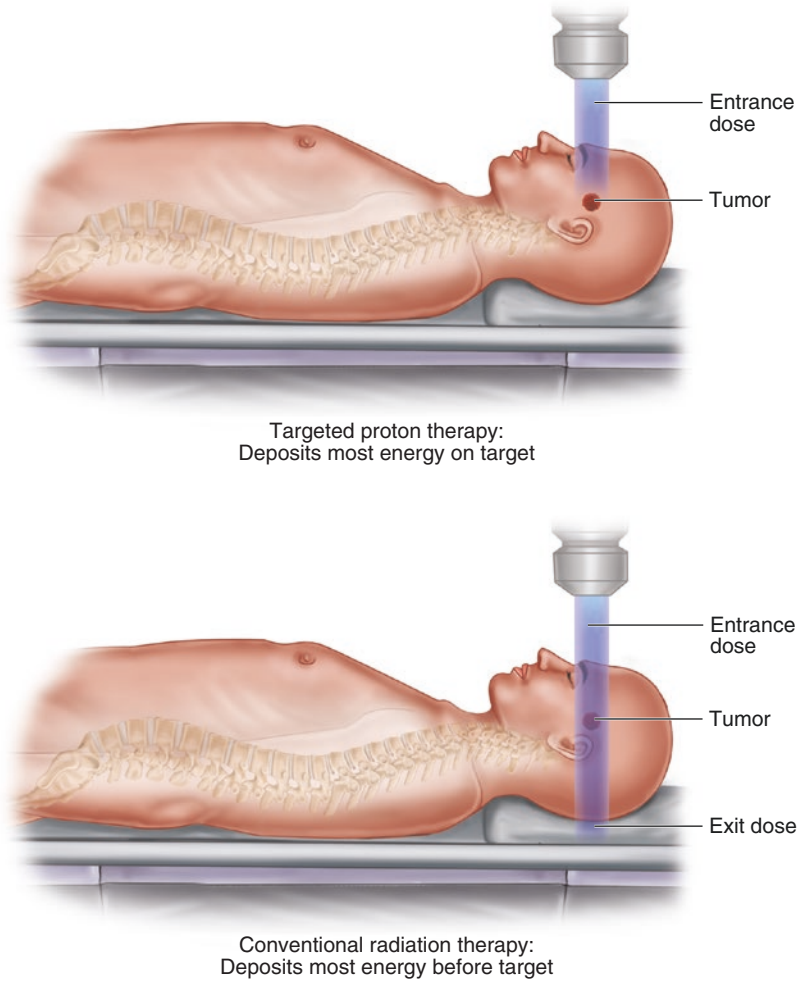


Fig. 24.9 Proton beam and no exit dose

and cancer morbidity and increased mortality (Katznelson et al. 2014). Normal life expectancy can be restored by lowering random GH levels to <1.0 μg/L and normalizing IGF-1 concentrations (Katznelson et al. 2014). Surgery remains the first choice therapy for acromegaly; however, adjuvant therapy is often required as surgery renders GH/IGF-1 to safe levels in only 40–80% of patients depending on the tumor size and surgical expertise (Ahmed et al. 1999; Sheaves et al. 1996; Clayton et al. 1999). Medical therapy with long acting somatostatin analogue therapy will lower GH and IGF-1 levels in approximately 90% of patients; however, only ~50% will achieve GH levels <2.5 μg/L and IGF-1 concentrations in the age-related reference range (Jenkins 2000; Lancranjan and Atkinson 1999; Turner et al. 1999). Other medical therapies include dopamine agonists and GH receptor antagonists.

Conventional radiotherapy has been used in acromegaly for over 30 years and has been shown to be effective in lowering GH levels (Jenkins et al. 2006). GH/IGF-1 physiology is known to be altered following radiotherapy (Peacey et al. 2001). These studies may have been prone to selection bias as patients who followed up regularly and for long duration of time may have also been patients with more active disease. In a study of 884 patients who had received radiotherapy from the UK acromegaly database, a mean

GH level decrease from 13.5 to 5.3 ng/mL was achieved by 2 years, 2.0 ng/mL by 10 years, and 1.1 ng/mL by 20 years after radiotherapy. A GH of <2.5 ng/mL was achieved by 22% of patients at 2 years, 60% by 10 years, and 77% by 20 years after radiotherapy. The IGF-1 levels fell in parallel with GH with 63% of patients having a normal level by 10 years (Jenkins et al. 2006). This is in keeping with other reports (Biermasz et al. 2000a, b; Powell et al. 2000). The single most important factor in eventual success of radiotherapy appears to be the pre-radiotherapy GH/IGF-1 concentration (Jenkins et al. 2006). The higher the baseline lGH/IGF-1 levels the longer to normalization after radiotherapy (Jenkins et al. 2006).

Both fractionated radiotherapy or SRS can be used as an adjunctive modality to surgical and medical therapy in acromegaly, they can be effective in controlling local tumor growth in 95–100% of the cases, but biochemical remission is often more difficult to achieve. The mean time for hormonal normalization is faster with single fraction radiotherapy compared to fractionated therapy. In a recent prospective study of SRS, Hiromitsu et al. (Iwata et al. 2016) reported results using CyberKnife in 52 patients with acromegaly over 5 years duration with 60% of all cases achieving a GH <2.5 ng/mL and normal IGF-1 (age and gender matched) by the end of the study. However, only 17% achieved remission by Cortina consensus criteria (Box 24.1).

Box 24.1 Cortina Consensus Criteria

Random GH >1 μg/L

Nadir GH after OGTT ≥0.4 μg/L

Age and gender adjusted normal IGF-1

Ref: A. Giustina, P. Chanson, M. D. Bronstein, A. Klibanski, S. Lamberts, F. F. Casanueva, P. Trainer, E. Ghigo, K. Ho, S. Melmed; A Consensus on Criteria for Cure of Acromegaly, The Journal of Clinical Endocrinology & Metabolism, Volume 95, Issue 7, 1 July 2010, Pages 3141–3148, https://doi.org/10.1210/jc.2009-2670

24.7.2 Use of Radiotherapy in Patients with Cushing's Disease

Cushing's disease results from oversecretion of ACTH from a pituitary adenoma which in turn leads to hypercortisolism. Chronic hypercortisolemia can result in significant morbidity such as cardiometabolic conditions, thromboembolic events, muscle weakness, bone loss, skin manifestations, gonadal dysfunction, ophthalmic disorders, neuropsychological changes, infections, and increased mortality. Most of these tumors are microadenomas with only 10% of patients having a macroadenoma. The diagnosis and localization of the lesion in Cushing's disease can be challenging. Transsphenoidal excision remains the cornerstone for management of Cushing's disease.

Radiotherapy in patients with Cushing's disease may be considered after non-curative surgery, recurrence of the tumor or disease invading the cavernous sinuses. Adjuvant medical therapy with agents such as metyrapone or ketoconazole (or newer agents see Chap. 21) is often required to treat hypercortisolemia following non-curative surgery and while awaiting the therapeutic effects of radiotherapy. Conventional radiotherapy is administered in fractions to achieve a cumulative dose between 40 and 50 Gy. SRS has been shown in studies to lead to better tumor control and more efficient hormonal control than conventional fractionated radiotherapy. Because these tumors are often small and well circumscribed, they can be effectively treated with SRS provided that disease is 3–5 mm away from optic chiasm. Sheehan et al. (Sheehan et al. 2013a) followed up in a retrospective trial 96 patients with Cushing's disease receiving a mean dose of 16 Gy through SRS Gamma Knife. During 48 months follow-up, tumor control was achieved in 98% of patients and 70% had biochemical remission. In this study, 5% developed new or worsening optic neuropathy and 36% new or progressive pituitary deficiencies. Wan et al. (Wan et al. 2009) and his colleagues demonstrated biochemical remission in 27.9% of 68 patients who received Gamma Knife for ACTH-producing adenoma, while

tumor growth arrested in 89.7% of the patients, only one patient developed hypopituitarism during the period of follow-up.

Nelson's syndrome results from pituitary ACTH-secreting tumor growth following bilateral adrenalectomy for the management of refractory Cushing's disease. Lifelong follow-up is required for patients with Nelson's syndrome that can occur decades after adrenalectomy. Surgery should be the first-line treatment if possible as these tumors are more radioresistant than corticotroph adenomas. Interestingly, there is data suggesting that administration of radiotherapy post adrenalectomy may protect against the development of Nelson syndrome (Gil-Cardenas et al. 2007). In a study with 39 patients assessing the effect of radiotherapy when administered as a neoadjunctive therapy, none of the patients who received radiotherapy developed Nelson's syndrome up to 15 years following surgery compared to 50% in those patients who did not receive prophylactic radiation.

24.7.3 Use of Radiotherapy in Patients with Prolactinoma

Prolactinomas are the most common secretory pituitary adenomas, and they are divided into microprolactinoma and macroprolactinomas. Macroprolactinomas are rarer and can present with tumor mass effects such as headache, visual defects, and neurological manifestations; or symptoms due to prolactin hypersecretion, such as galactorrhea, amenorrhea, infertility, and erectile dysfunction.

Currently, medical therapy with a dopamine agonist is considered first-line treatment. Cabergoline is considered more efficacious than bromocriptine and is better tolerated. In the vast majority of patients dopamine agonist therapy effectively decreases tumor size and leads to normalization of prolactin concentrations (Gillam et al. 2006). Resistance to dopamine agonists can occur (defined as failure to normalize the prolactin or shrink tumor size by less than 50%).

Radiotherapy is reserved for non-responders to medical or surgical treatment. Pan et al. (Pan et al. 2000) have reported results from 128 patients treated with Gamma Knife for prolactinoma with a median follow-up of 33 months at a median dose of 31 Gy. In this study, 99% of patients achieved tumor control and 41% achieved biochemical remission. Wan et al. (2009) reported that 23.3% of 176 patients receiving Gamma Knife for macroprolactinoma achieved biochemical remission without medical therapy after radiosurgery, and tumor volume control was achieved in 90.3%. Repeat Gamma Knife was required in a majority of large tumors. The risk of hypopituitarism over time was estimated at close to 50%, which includes a recognized risk to fertility.

24.7.4 Radiotherapy for Non-functioning Pituitary Adenoma (NFPA)

NFPAs are the most common type of pituitary tumor and may be asymptomatic or present with symptoms secondary to compression of key structures or hypopituitarism. They can compress the optic chiasm and encroach on other vital structures within the cavernous sinuses. These tumors are often managed conservatively but if treatment is required, surgery is the first-line therapy. Radiotherapy may be considered if surgery is not successful or feasible or there is a tumor recurrence which is inoperable.

In the past conventional fractionated radiotherapy was commonly practiced, but due to the high risk of hypopituitarism and other adverse effects this is less frequently used currently. SRS is now gaining popularity and proven to be effective for these adenomas, in a dose range between 14 and 16 Gy. Normally these tumors require less radiation to halt their growth compared to secretory adenomas, as both tumor size and biochemical control are desired in the latter. Sheehan et al. (2013b) reported tumor control following stereotactic radiosurgery with overall tumor control of 93.4%; the actuarial tumor control post radiotherapy were achieved as 98%, 95%, 91%, and 85% in 3 years, 5 years, 8 years, and 10 years, respectively. Better out-

comes were observed in patients with smaller size adenoma and tumors without suprasellar extension. New or worsening hypopituitarism was noted in 21% of the patients.

24.8 Complications of Pituitary Radiotherapy

Despite the established effectiveness of radiotherapy for the treatment of both functional and nonfunctional pituitary adenoma, it is rarely regarded as a first-line management for such conditions. In addition to the delay of therapeutic effect following irradiation, the potential irreversible side effects of radiotherapy makes this option less appealing as a first-line therapy. The risk of complications, especially hypothalamic-pituitary axis dysfunction, does not decline with time but rather increases slowly with time and may take years to develop. It is imperative to understand these potential complications and weigh them in relation to any therapeutic benefit.

24.8.1 Short-Term Complications

Nausea, headache, tiredness, hair loss, and skin changes are often reported following radiotherapy. They can be managed symptomatically and are usually self-limiting.

24.8.2 Long-Term Complications

24.8.2.1 Neural Damage

The optic pathway is radiosensitive and more prone to damage compared to other cranial nerves. With increasing understanding of radiation doses and tolerance, this potential risk can be minimized by using fractionated radiotherapy if the optic nerve apparatus is close to the field of radiation. Doses larger than 55 Gy or fractions more than 2 Gy in conventional radiotherapy and single dose exceeding 8 Gy with stereotactic radiosurgery are associated with potential optic nerve injury. If vision deteriorates following radiotherapy, other causes should be considered and excluded such as tumor compression and/or edema.

Cranial nerve palsies can be avoided by careful planning and limiting higher doses of radiation to these nerves, particularly CNIII, IV, V, and VI. These nerves reside in the parasellar (cavernous sinus) and suprasellar regions and can easily be affected by the field of radiation. Brain parenchymal necrosis can manifest with focal neurological deficits, neurocognitive decline, and/or seizures due to changes in vascular permeability, brain edema or even demyelination disorder. Such complications arise within the radiation fields although current modern techniques have reduced these sequelae.

24.8.2.2 Secondary Brain Neoplasms

Secondary oncogenesis following pituitary radiotherapy is controversial. It is impossible to calculate the true incidence of tumors arising following pituitary radiotherapy as patients with pituitary disease in many studies have historically received disproportionate radiation exposure in the form of frequent CT imaging. In recent years, MRI has become the most common form of surveillance imaging for pituitary tumors. In some studies, the incidence of secondary neoplasm is as high as 1–2% occurring with a latency of 8–15 years (Bliss et al. 1994; Brada et al. 1992; Tsang et al. 1993). One study has estimated an incidence of extracranial tumors in NFA patients to be 3.9 fold that of the general population irrespective of whether the patient had radiotherapy or not (Popovic et al. 1998), therefore having a pituitary adenoma may be associated with and underlying increased susceptibility to tumorigenesis. Secondary intracranial tumors (most commonly gliomas or meningioma) due to pituitary irradiation are now relatively rare due to newer techniques which expose a smaller volume of cranial tissue to radiation (Shih and Loeffler 2008). Future studies focusing on patients treated with surgery alone and followed with surveillance MRIs as control subjects rather than using a normal population sample as controls may find different outcomes with respect to secondary neoplasms after radiotherapy (Gittoes 2003).

24.8.2.3 Cerebrovascular Morbidity and Mortality

Increased cerebrovascular disease and death have been reported in a number of studies following conventional pituitary irradiation. In a series of 156 patients with non-functioning pituitary adenoma (NFPA), increased cerebral infarction rates were found in patients administered higher doses of radiotherapy (Flickinger et al. 1989). A relative risk of CVA of 4.1 (Cl3.6–4.7) was found in a study of 331 patients who received pituitary radiotherapy for a number of underlying diagnoses compared with the general population (Brada et al. 1999). On multivariate analysis the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared to biopsy or no operation, higher doses of radiotherapy, and an underlying diagnosis of acromegaly (Brada et al. 1999). Brada et al. assessed cerebrovascular mortality in 344 patients who had received radiotherapy (79% also had transcranial or transsphenoidal surgery). Cerebrovascular disease accounted for 26% of all deaths [33 deaths compared to 8 deaths expected (RR 4.11, (CI 2.84–5.75))], with an even further increased risk in female patients [RR 6.9, (CI 4.29–10.6)] compared to males [RR 2.4, (CI 1.24–4.2), $p = 0.002$] (Brada et al. 2002). Surgery also plays a role in the increased cerebrovascular mortality. Patients with prior surgery had an increase RR compared to those with no surgery or biopsy alone [RR 5.19, (CI 3.5–7.42)] vs. [RR 1.33, (CI 0.27–3.88), $p = 0.02$], but there may be several confounders which may have led to this increase such as hypopituitarism (Brada et al. 2002). Data collection was also hampered by variability in reports of cause of death.

24.8.2.4 Hypopituitarism

Over 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiency within the following decade (Barrande et al. 2000; Littley et al. 1989a; Tsang et al. 1994). The classic pattern of pituitary hormone deficiency to radiotherapy of GH (100% at 5 years), gonadotrophin (91% at 5 years), ACTH (77% at 5 years) then TSH deficiency (42% at 5 years) (Littley et al. 1989a) is not always seen and deficiencies may occur in any order. As deficiencies can occur at any time point even up to 20 years later, long-term testing is required (Tsang et al. 1994; al-Mefty et al. 1990; Brada et al. 1993). With conventional RT, the speed of onset of hypopituitarism is related to the total and fractional doses of radiotherapy (Tsang et al. 1994). The rate of hypopituitarism increases with time from irradiation.

24.8.2.4.1 Factors Which Influence the Development of Hypopituitarism Include

- Sensitivity of the hypothalamus compared to the pituitary to irradiation
- Radiation dose
- Length of time since cranial irradiation
- Age of patient at time of cranial irradiation
- The type of radiotherapy administered
- The different radiosensitivities of pituitary hormones

24.8.2.4.2 Sensitivity of the Hypothalamus Compared to the Pituitary to Irradiation

The hypothalamus is more radiosensitive than the pituitary gland (Sklar and Constine 1995) and is therefore more easily damaged by lower doses of radiation (<40 Gy). However, at higher doses of radiation (>50 Gy) there is evidence for both hypothalamic and anterior pituitary damage (Constine et al. 1993; Shalet et al. 1988; Sklar 1991).

The preponderance of early hypothalamic dysfunction following cranial irradiation has been elicited from a number of studies, which have assessed the response of pituitary hormones in subjects using exogenous hypothalamic releasing factors (Chrousos et al. 1982; Samaan et al. 1975; Blacklay et al. 1986; Lam et al. 1986; Darzy et al. 2003) (See Chap. 5).

24.8.2.4.3 Radiation Dose

The dose of radiation delivered to the HP axis is the most important factor in the future development of HP axis dysfunction (Littley et al. 1989b). Low doses of radiation (18–24 Gy) used as prophylactic cranial irradiation for childhood

hematological malignancies usually result in only isolated GH deficiency (Brennan et al. 1998; Adan et al. 2001). Patients who receive high dose (60 Gy) cranial irradiation for the treatment of nasopharyngeal carcinoma or non-pituitary intracranial neoplasms are at greater risk of developing multiple hormone deficiencies (Agha et al. 2005), with a small percentage developing panhypopituitarism (Lam et al. 1991).

24.8.2.4.4 Length of Time Since Cranial Irradiation

Hypothalamic-pituitary axis dysfunction may take several years to develop following cranial irradiation. However, in some patients the onset of HP axis dysfunction may be rapid (Duffner et al. 1985) and as such, radiation-induced HP axis dysfunction should be clinically suspected in all patients who develop symptoms early following cranial irradiation. Therefore, the timing of dynamic pituitary testing following cranial irradiation is paramount in the interpretation of a patient's test results and likewise in interpreting the effect of radiation on the HP axis in clinical studies (Littley et al. 1989a). Using stepwise multiple linear regression analysis, Clayton and Shalet (1991) demonstrated that both radiation dose, and time from irradiation, have a significant influence on peak GH response to dynamic testing in children. The late incidence of GH deficiency was similar over the whole dose range, but the speed of onset was dependent on dose. Agha et al. (2005) have shown that in a cohort of patients treated with radiotherapy for non-pituitary brain tumors the development of any degree of hypopituitarism (using multivariate regression models) depended on both the BED and time since irradiation. GH deficiency and ACTH deficiency were associated with the duration since radiotherapy.

It is important to recognize that hypopituitarism develops over a period of years following irradiation and that patients must undergo regular endocrine follow-up with dynamic testing as appropriate. It is for this reason that any patient who has received cranial irradiation is recommended to have up to yearly dynamic pituitary function assessment in order not to miss evolving HPA axis dysfunction or with the development of any symptoms.

24.8.2.4.5 Age of Patient at Time of Cranial Irradiation

Patients who receive cranial irradiation during childhood are more likely to develop HP axis dysfunction than patients receiving cranial irradiation during adult life. Littley et al. (1991) studied 21 adult patients (16–49 years) treated with total body irradiation (10 Gy in 5 fractions or 12–13.2 Gy in 6 fractions) for hematological malignancies. After a mean follow-up of 2.4 years, no patient showed evidence of HPA axis dysfunction. Endocrine abnormalities in these patients were limited to direct radiation-induced damage to either the thyroid gland or gonadal tissue. In contrast, Ogilvy-Stuart et al. (1992) showed that almost 50% of children who received the same total body irradiation protocol developed GH deficiency over a similar time frame.

24.9 The Impact of Radiotherapy on Specific Anterior Pituitary Hormones

24.9.1 Growth Hormone

Growth hormone deficiency is the most common manifestation of HP axis dysfunction following cranial irradiation and often occurs in isolation, with reported incidence between 50 and 100% after radiotherapy for sellar masses. Somatotrophs are reported to be more radiosensitive in children as compared with adults. GHD occurs after low dose radiation with reported cases occurring with doses as low as 18 Gy to the HP axis (Rappaport and Brauner 1989). The development of HP axis dysfunction with single doses of radiation of 9–10 Gy can be explained when the single fraction dose is factored into the equation for the BED. Littley et al. (1989a) reported that GHD occurred in all patients treated for pituitary adenomas 5 years after administration of 37.5–42.5 Gy in 15–16 fractions (Fig. 24.10).

Interestingly, a number of studies using sensitive GH assays have shown that in patients with GHD, GH concentrations never fall to an undetectable level. Darzy et al. (2005) studied

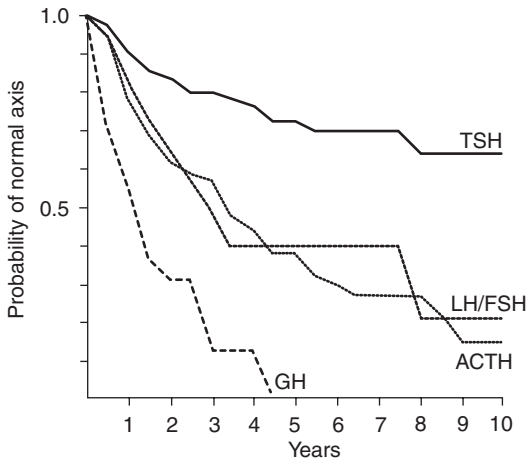


Fig. 24.10 The probability of the anterior pituitary hormone axes remaining normal following radiotherapy for pituitary adenoma. All patients had normal axes before radiotherapy. The presence of underlying pituitary disease increases the speed with which hypopituitarism develops. From Littley et al. Q. J. Med. 70 (1989) 145–160

the dynamics of GH secretion (using a sensitive chemiluminescence GH assay) in GHD adults who received cranial irradiation during childhood for the treatment of non-pituitary brain tumors. GH samples were assessed every 20 min over 24 h. The GH profiles in these patients were compared to GH profiles in 30 gender, age, and BMI matched normal healthy volunteers. This study showed that there was a significant decrease in all amplitude-related measurements of GH secretion (mean GH levels, area under the curve for GH, absolute GH peak height, mean peak GH height, and mean pulse area) for adults post childhood cranial radiation. There was not, however, any difference in frequency-related measurements (GH pulse frequency, GH pulse duration, and interpulse interval) compared with control subjects. The authors conclude that the integrity of the HP axis and GH neuroregulation is fundamentally preserved in irradiated GHD patients with a GH secretory pattern similar to that observed in normal subjects and those with GHD secondary to other causes; however, they are rendered GHD due to the decrease in amplitude of GH secretory bursts (Darzy et al. 2005).

24.9.2 FSH/LH

Gonadotropin deficiency is the second commonest pituitary hormone deficiency following cranial irradiation, and it results in estrogen or testosterone deficiency which in turn affects the development of secondary sexual characteristics, fertility, and bone mineralization. In contrast, low dose radiation can induce central precocious puberty in children younger than 7 years old by altering cortical puberty inhibition. Adult patients with pituitary disease develop gonadotropin deficiency more readily after radiation than children with 33% of adults developing gonadotropin deficiency after 20 Gy and 66% after 35–40 Gy (Toogood 2004).

24.9.3 Adrenocorticotropic Hormone

ACTH deficiency is less likely than GH and gonadotropin deficiency following low dose radiation therapy. However, HPA axis dysfunction still occurs and assessment needs to be included in monitoring programs. Lam et al. (1991) have shown that ACTH deficiency is present in 27% of patients 5 years after receiving high-dose radiotherapy (hypothalamus and pituitary were 39.79 +/− .78 (+/− SD) and 61.67 +/− 12.2 Gy, respectively) for nasopharyngeal carcinoma. Agha et al. (2005) have shown that ACTH deficiency occurs in 21% of patients who received cranial irradiation (median BED 54 Gy) for non-pituitary intracranial neoplasms. In this study, development of ACTH deficiency was dependent on time since irradiation and not radiation dose. Schmiegelow et al. (2003) studied the hypothalamic-pituitary-adrenal axis in 73 patients treated with radiotherapy (median dose 73 Gy) for childhood brain tumors. HPA axis insufficiency was noted in 19% using dynamic testing with either the ITT or the SST.

24.9.4 TSH

Central (secondary) hypothyroidism due to pituitary or hypothalamic damage is characterized by a reduced free thyroxine (fT4) level with a

normal or reduced TSH level. As with the development of other pituitary hormone deficiencies, the incidence of central hypothyroidism is directly related to the total cranial radiation dose. Primary hypothyroidism as a consequence of direct radiotherapy-induced thyroid gland dysfunction is characterized by a low fT4 and elevated TSH; however, many patients may have elements of both primary and secondary hypothyroidisms due to radiation exposure to both areas (particularly following total body irradiation and craniospinal irradiation). Constine et al. (1993) have shown that at doses <40 Gy to the HP axis in patients with non-pituitary brain tumors central hypothyroidism is rare, but the incidence increases considerably when the dose exceeds 50 Gy. In one study assessing patients with pituitary adenoma who received 40–50 Gy in 25–30 fractions, the incidence of central hypothyroidism after 19 years follow-up was 72% (Brada et al. 1993).

24.9.5 Prolactin

Hyperprolactinemia has been reported to be common following cranial irradiation. Hyperprolactinemia can lead to alterations in the hypothalamic-pituitary gonadal axis by causing alterations in gonadotrophins secretion, which may aggravate the hypogonadotropic hypogonadism that often develops following cranial irradiation. Hyperprolactinemia develops following cranial irradiation due to radiation-induced hypothalamic damage with damage to dopaminergic neurons. As a result, lactotrophs escape from the inhibitory effect of dopamine and prolactin levels subsequently rise.

Following the initial increase in prolactin post cranial irradiation, there is a progressive decline in prolactin levels. This phenomenon is due to a delayed direct radiation effect on the pituitary and was more pronounced in females (Littley et al. 1989a). Mukherjee et al. (2003) have shown that acquired prolactin deficiency following radiotherapy is an indicator of severe pituitary damage with co-existing multiple anterior pituitary hormone deficiencies.

24.9.6 The Long-Term Implications of Pituitary Dysfunction

Hypopituitarism is associated with increased morbidity and mortality. The clinical consequences of GHD, gonadotrophin deficiency, ACTH deficiency, and TSH deficiency have been well described (Vance 1994). A number of studies have described an increased mortality in patients with hypopituitarism compared to age and sex matched controls (Bates et al. 1996; Bulow et al. 1997; Rosen and Bengtsson 1990; Tomlinson et al. 2001). In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. There are conflicting data regarding the impact of radiotherapy on mortality in pituitary patients but it would appear from historic studies that patients with hypopituitarism who have received prior radiotherapy have an increased mortality (Bates et al. 1996; Bulow et al. 1997; Rosen and Bengtsson 1990; Tomlinson et al. 2001; Erfurth et al. 2002).

24.10 The Endocrine Nurse Specialist Role

The endocrine nurse specialist, in conjunction with the radiotherapy team, plays a vital role in counseling and patient education regarding preparation, side effects of radiation, and the importance of hormone monitoring following irradiation. The endocrine nurse specialist is a key member of the multidisciplinary team who performs and interprets the results of dynamic pituitary tests and performs ongoing assessment of pituitary status following cranial irradiation.

24.10.1 Patient Preparation

Patients referred for radiotherapy will usually first consult with the radiation oncologist. Therapy planning and tumor mapping requires CT/MRI to determine the requirements for therapy. The plan will be discussed with the patient in terms of the fractions and length of treatment, risks and benefits as described above.

Patients need to be aware that a thermoplastic mask can be custom made to precisely fit their face. This takes about 15 min. The patient will lie on his/her back on the simulation table while the technician places a warm wet plastic mesh film over their face and neck to create the mask shape. Openings are created for the mouth, eyes, and nose to allow for normal breathing. The patient is asked to bite on a plastic bite block until the mask has hardened and again during each treatment to limit motion. The mask is designed to be secured to a treatment table and gently hold the patients' head in the correct position to ensure accurate and consistent delivery of radiation treatments.

Educating the patient in relaxation breathing and techniques, the use of music or other psychological techniques for distraction that can be employed can help the patient cope with both mask formation and during successive treatments. Extremely anxious patients may require mild sedation.

24.10.2 Short-Term Side Effects of Radiation Therapy

These are usually minimal and include fatigue, lethargy, or a lack of energy, which may persist for some time after radiation is completed.

Local irritation to the skin is rare but may cause some redness, swelling, or a sunburned or tanned appearance. Some hair loss is possible but usually not excessive. Nausea and vomiting is also rare. Many patients return to work or regular activities after each radiation treatment.

24.10.3 Long-Term Side Effects of Radiation Therapy

Some delayed wound healing is possible with a fresh craniotomy scar and a spidery red or purple appearance (similar to telangiectasias) caused by dilated capillary blood vessels on the skin surface. Hormonal deficiencies may develop shortly after radiation as previously discussed or may develop over a number of years and require ongoing testing and monitoring with the patients endocrinology team.

Some patients may require planning for potential changes. Infertility may occur post radiation and should be discussed with the patient prior to starting treatment. A fertility consult with egg or sperm or embryo preservation should be offered when appropriate. Patients complain of difficulty with short-term memory and alterations to cognitive function such as attention and executive function. Improved tumor targeting techniques limit this effect but it may also be progressive with time. Involvement of occupational therapists and psychologist for psychometric assessment may be helpful in dealing with such changes.

Secondary cancer risks after radiation exposure have been reported, as discussed above, but remain relatively rare. The patient needs to be aware that accurate records are kept of the amount of radiation administered and the area exposure. During treatments health professionals, who deliver radiation, will wear protective equipment to minimize their own exposure.

A patient must determine their own personal risks and benefits in their decision to follow the care team's recommendation for radiation therapy. The nurse can provide guidance in this decision by ensuring all information is available to both the patient and their family members using clear and understandable methods and that all their questions are satisfactorily answered.

24.11 Conclusions

Provider and patient awareness regarding the area of radiation-induced HP axis dysfunction has increased considerably in recent years. The development of "late effects" clinics for adult survivors of childhood cancers has led to an improved multidisciplinary approach to the management of such patients. The number of patients at risk of radiation-induced hypopituitarism will continue to rise as treatment strategies are refined and the number of patients surviving increases. The presence of HP axis dysfunction

in this cohort of patients may in itself lead to increased mortality and morbidity, in a group of patients already heavily burdened by significant symptomatology. A multidisciplinary approach in which the endocrine nurse specialist is a key member leads to optimal management of these patients.

References

Adan L, Trivin C, Sainte-Rose C, Zucker JM, Hartmann O, Brauner R. GH deficiency caused by cranial irradiation during childhood: factors and markers in young adults. J Clin Endocrinol Metab. 2001;86:5245–51.

Agha A, Sherlock M, Brennan S, O'Connor SA, O'Sullivan E, Rogers B, Faul C, Rawluk D, Tormey W, Thompson CJ. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab. 2005;90:6355–60.

Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf). 1999;50:561–7.

al-Mefty O, Kersh JE, Routh A, Smith RR. The long-term side effects of radiation therapy for benign brain tumors in adults. J Neurosurg. 1990;73:502–12.

Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys. 1982;8:1981–97.

Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP, Bertherat J. Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab. 2000;85:3779–85.

Bates AS, Van't HW, Jones PJ, Clayton RN. The effect of hypopituitarism on life expectancy. J Clin Endocrinol Metab. 1996;81:1169–72.

Becker G, Kocher M, Kortmann RD, Paulsen F, Jeremic B, Muller RP, Bamberg M. Radiation therapy in the multimodal treatment approach of pituitary adenoma. Strahlenther Onkol. 2002;178:173–86.

Biermasz NR, Dulken HV, Roelfsema F. Postoperative radiotherapy in acromegaly is effective in reducing GH concentration to safe levels. Clin Endocrinol (Oxf). 2000a;53:321–7.

Biermasz NR, van DH, Roelfsema F. Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. J Clin Endocrinol Metab. 2000b;85:2476–82.

Blacklay A, Grossman A, Ross RJ, Savage MO, Davies PS, Plowman PN, Coy DH, Besser GM. Cranial irradiation for cerebral and nasopharyngeal tumours in children: evidence for the production of a hypothalamic defect in growth hormone release. J Endocrinol. 1986;108:25–9.

Bliss P, Kerr GR, Gregor A. Incidence of second brain tumours after pituitary irradiation in Edinburgh 1962-1990. Clin Oncol (R Coll Radiol). 1994;6:361–3.

Brada M, Ford D, Ashley S, Bliss JM, Crowley S, Mason M, Rajan B, Traish D. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. BMJ. 1992;304:1343–6.

Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, Uttley D. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf). 1993;38:571–8.

Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. Int J Radiat Oncol Biol Phys. 1999;45:693–8.

Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B. Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol (Oxf). 2002;57:713–7.

Brennan BM, Rahim A, Mackie EM, Eden OB, Shalet SM. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. Clin Endocrinol (Oxf). 1998;48:777–83.

Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf). 1997;46:75–81.

Chrousos GP, Poplack D, Brown T, O'Neill D, Schwade J, Bercu BB. Effects of cranial radiation on hypothalamic-adenohypophyseal function: abnormal growth hormone secretory dynamics. J Clin Endocrinol Metab. 1982;54:1135–9.

Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr. 1991;118:226–8.

Clayton RN, Stewart PM, Shalet SM, Wass JA. Pituitary surgery for acromegaly. Should be done by specialists. BMJ. 1999;319:588–9.

Colin P, Delemer B, Nakib I, Caron J, Bazin A, Bernard MH, Peruzzi P, Scavarda D, Scherpereel B, Longuebray A, Redon C, Petel F, and Rousseaux P. [Unsuccessful surgery of Cushing's disease. Role and efficacy of fractionated stereotactic radiotherapy]. Neurochirurgie. 2002;48:285–93.

Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, Rubin P. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med. 1993;328:87–94.

Dainiak N. Mechanisms of radiation injury: impact of molecular medicine. Stem Cells. 1997;15(Suppl 2):1–5.

Darzy KH, Aimaretti G, Wieringa G, Gattamaneni HR, Ghigo E, Shalet SM. The usefulness of the combined growth hormone (GH)-releasing hormone and arginine stimulation test in the diagnosis of radiation-induced GH deficiency is dependent on the post-irradiation time interval. J Clin Endocrinol Metab. 2003;88:95–102.

Darzy KH, Pezzoli SS, Thorner MO, Shalet SM. The dynamics of growth hormone (GH) secretion in adult cancer survivors with severe GH deficiency acquired

after brain irradiation in childhood for nonpituitary brain tumors: evidence for preserved pulsatility and diurnal variation with increased secretory disorderliness. J Clin Endocrinol Metab. 2005;90:2794–803.
Duffner PK, Cohen ME, Voorhess ML, MacGillivray MH, Brecher ML, Panahon A, Gilani BB. Long-term effects of cranial irradiation on endocrine function in children with brain tumors. A prospective study. Cancer. 1985;56:2189–93.
Erfurth EM, Bulow B, Svahn-Tapper G, Norrving B, Odh K, Mikoczy Z, Bjork J, Hagmar L. Risk factors for cerebrovascular deaths in patients operated and irradiated for pituitary tumors. J Clin Endocrinol Metab. 2002;87:4892–9.
Flickinger JC, Nelson PB, Taylor FH, Robinson A. Incidence of cerebral infarction after radiotherapy for pituitary adenoma. Cancer. 1989;63:2404–8.
Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989;62:679–94.
Gil-Cardenas A, Herrera MF, Diaz-Polanco A, Rios JM, Pantoja JP. Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. Surgery. 2007;141:147–51; discussion 151–42
Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27:485–534.
Gittoes NJ. Radiotherapy for non-functioning pituitary tumors—when and under what circumstances? Pituitary. 2003;6:103–8.
Iwata H, Sato K, Nomura R, Tabei Y, Suzuki I, Yokota N, Inoue M, Ohta S, Yamada S, Shibamoto Y. Long-term results of hypofractionated stereotactic radiotherapy with CyberKnife for growth hormone-secreting pituitary adenoma: evaluation by the Cortina consensus. J Neurooncol. 2016;128:267–75.
Jenkins PJ. The use of long-acting somatostatin analogues in acromegaly. Growth Horm IGF Res. 2000;10(Suppl B):S111–4.
Jenkins PJ, Bates P, Carson MN, Stewart PM, Wass JA. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab. 2006;91:1239–45.
Katznelson L, Laws RE, Melmed S, Molitch ME, Murad MH, Utz A, Wass JAH. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51. https://doi.org/10.1210/jc.2014-2700S.
Lam KS, Wang C, Yeung RT, Ma JT, Ho JH, Tse VK, Ling N. Hypothalamic hypopituitarism following cranial irradiation for nasopharyngeal carcinoma. Clin Endocrinol (Oxf). 1986;24:643–51.
Lam KS, Tse VK, Wang C, Yeung RT, Ho JH. Effects of cranial irradiation on hypothalamic-pituitary function—a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med. 1991;78:165–76.
Lancranjan I, Atkinson AB. Results of a European multicentre study with Sandostatin LAR in acromegalic patients. Sandostatin LAR Group. Pituitary. 1999;1:105–14.
Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med. 1989a;70:145–60.
Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML. Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf). 1989b;31:363–73.
Littley MD, Shalet SM, Morgenstern GR, Deakin DP. Endocrine and reproductive dysfunction following fractionated total body irradiation in adults. Q J Med. 1991;78:265–74.
Mukherjee A, Murray RD, Columb B, Gleeson HK, Shalet SM. Acquired prolactin deficiency indicates severe hypopituitarism in patients with disease of the hypothalamic-pituitary axis. Clin Endocrinol (Oxf). 2003;59:743–8.
Nishioka H, Ito H, Haraoka J, Hirano A. Histological changes in the hypofunctional pituitary gland following conventional radiotherapy for adenoma. Histopathology. 2001;38:561–6.
Nishioka H, Hirano A, Haraoka J, Nakajima N. Histological changes in the pituitary gland and adenomas following radiotherapy. Neuropathology. 2002;22:19–25.
Ogilvy-Stuart AL, Clark DJ, Wallace WH, Gibson BE, Stevens RF, Shalet SM, Donaldson MD. Endocrine deficit after fractionated total body irradiation. Arch Dis Child. 1992;67:1107–10.
Pan L, Zhang N, Wang EM, Wang BJ, Dai JZ, Cai PW. Gamma knife radiosurgery as a primary treatment for prolactinomas. J Neurosurg. 2000;93(Suppl 3):10–3.
Peacey SR, Toogood AA, Veldhuis JD, Thorner MO, Shalet SM. The relationship between 24-hour growth hormone secretion and insulin-like growth factor I in patients with successfully treated acromegaly: impact of surgery or radiotherapy. J Clin Endocrinol Metab. 2001;86:259–66.
Popovic V, Damjanovic S, Micic D, Nesovic M, Djurovic M, Petakov M, Obradovic S, Zoric S, Simic M, Penezic Z, Marinkovic J. Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. Clin Endocrinol (Oxf). 1998;49:441–5.
Powell JS, Wardlaw SL, Post KD, Freda PU. Outcome of radiotherapy for acromegaly using normalization of insulin-like growth factor I to define cure. J Clin Endocrinol Metab. 2000;85:2068–71.
Rappaport R, Brauner R. Growth and endocrine disorders secondary to cranial irradiation. Pediatr Res. 1989;25:561–7.
Rodemann HP, Bamberg M. Cellular basis of radiation-induced fibrosis. Radiother Oncol. 1995;35:83–90.
Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 1990;336:285–8.
Samaan NA, Bakdash MM, Caderao JB, Cangir A, Jesse RH Jr, Ballantyne AJ. Hypopituitarism after external

irradiation. Evidence for both hypothalamic and pituitary origin. Ann Intern Med. 1975;83:771–7.

Schmiegelow M, Lassen S, Poulsen HS, Feldt-Rasmussen U, Schmiegelow K, Hertz H, Muller J. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. Clin Endocrinol (Oxf). 2000;53:191–7.

Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Lange M, Poulsen HS, Muller J. Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. J Clin Endocrinol Metab. 2003;88:3149–54.

Shalet SM, Clayton PE, Price DA. Growth and pituitary function in children treated for brain tumours or acute lymphoblastic leukaemia. Horm Res. 1988;30:53–61.

Sheaves R, Jenkins P, Blackburn P, Huneidi AH, Afshar F, Medbak S, Grossman AB, Besser GM, Wass JA. Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol (Oxf). 1996;45:407–13.

Sheehan JP, Xu Z, Salvetti DJ, Schmitt PJ, Vance ML. Results of gamma knife surgery for Cushing's disease. J Neurosurg. 2013a;119:1486–92.

Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, Lee JY, Kano H, Park KJ, Niranjan A, Kondziolka D, Barnett GH, Rush S, Golfinos JG, Lunsford LD. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg. 2013b;119:446–56.

Shi XE, Wu B, Fan T, Zhou ZQ, Zhang YL. Craniopharyngioma: surgical experience of 309 cases in China. Clin Neurol Neurosurg. 2008;110:151–9.

Shih HA, Loeffler JS. Radiation therapy in acromegaly. Rev Endocr Metab Disord. 2008;9:59–65.

Sklar CA. Growth and pubertal development in survivors of childhood cancer. Pediatrician. 1991;18:53–60.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys. 1995;31:1113–21.

Suh JH, Saxton JP. Conventional radiation therapy for skull base tumors: an overview. Neurosurg Clin N Am. 2000;11:575–86.

Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. 2001;357:425–31.

Toogood AA. Endocrine consequences of brain irradiation. Growth Horm IGF Res. 2004;14(Suppl A):S118–24.

Tran LM, Blount L, Horton D, Sadeghi A, Parker RG. Radiation therapy of pituitary tumors: results in 95 cases. Am J Clin Oncol. 1991;14:25–9.

Tsang RW, Laperriere NJ, Simpson WJ, Brierley J, Panzarella T, Smyth HS. Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. Cancer. 1993;72:2227–33.

Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. Int J Radiat Oncol Biol Phys. 1994;30:557–65.

Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Role of radiation therapy in clinical hormonally-active pituitary adenomas. Radiother Oncol. 1996;41:45–53.

Turner HE, Vadivale A, Keenan J, Wass JA. A comparison of lanreotide and octreotide LAR for treatment of acromegaly. Clin Endocrinol (Oxf). 1999;51:275–80.

Vance ML. Hypopituitarism. N Engl J Med. 1994;330:1651–62.

Vankelecom H, Matthys P, Van Damme J, Heremans H, Billiau A, Denef C. Immunocytochemical evidence that S-100-positive cells of the mouse anterior pituitary contain interleukin-6 immunoreactivity. J Histochem Cytochem. 1993;41:151–6.

Vincent PC. Apoptosis and the assessment of radiation injury. Stem Cells. 1995;13(Suppl 1):153–64.

Wan H, Chihiro O, Yuan S. MASEP gamma knife radiosurgery for secretory pituitary adenomas: experience in 347 consecutive cases. J Exp Clin Cancer Res. 2009;28:36.

Hypopituitarism and Growth Hormone Deficiency in Adults

25

Sofia Llahana, Anne Marland, Mila Pantovic, and Vera Popovic

Contents

25.1 **Introduction** 471
25.2 **Part A: Hypopituitarism** 471
25.3 **Prevalence, Mortality, and Morbidity of Hypopituitarism** 473
25.4 **Causes of Hypopituitarism** 473
25.5 **Clinical Presentation and Diagnosis of Hypopituitarism** 473
25.6 **Hormone Replacement Therapy in Hypopituitarism** 475
25.7 **Importance of Patient Education and Adherence to Medication in Hypopituitarism** 476
25.7.1 The Role of Patient Advocacy Groups 477

S. Llahana (✉)
School of Health Sciences, City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

A. Marland
Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
e-mail: Anne.Marland@ouh.nhs.uk

M. Pantovic
Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center Serbia, Belgrade, Serbia
e-mail: millapantovic@gmail.com

V. Popovic
Medical Faculty, University of Belgrade, Belgrade, Serbia
e-mail: popver@Eunet.rs

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_25

25.8 **Part B: Growth Hormone Deficiency in Adults** 478
25.8.1 Clinical Features and Abnormalities of GHD in Adults 478
25.8.2 Isolated GH deficiency and Evolving Hypopituitarism 479
25.9 **Diagnosis of Adult GH Deficiency and Provocative Tests** 480
25.9.1 When Is Provocative Testing Not Needed? 481
25.10 **Transition from Child to Adult and GH Treatment** 481
25.11 **GH Treatment Initiation and Monitoring in Adults** 484
25.11.1 Safety, Adverse Effects, and Contraindications of GH in Adults 485
25.11.2 GH Treatment and Safety in Childhood Cancer Survivors 489
25.11.3 Interactions with Other Hormones and Medications 489
25.12 **New Developments in GH Treatment (Long-Acting GH)** 489
25.12.1 Unmodified GH Superimposed on Inert Prolongation Technology 490
25.12.2 Active GH Analogues: Modified GH Molecule 490
25.13 **Conclusions** 491
References 491

Abstract

Pituitary conditions are associated with several physical, psychological, and social symptoms. Treatment involves surgery, medical treatment, and/or radiotherapy. Most patients with pituitary conditions have permanent hypopituitarism (congenital or acquired) and require lifelong hormone replacement therapy. Polypharmacy with multiple daily dosing and complex treatment regimens are common and patients may often require more than five different medications daily.

The treatment goal is to achieve normal physiological hormone levels with minimal side effects and to avoid adverse effects associated with deficiency or over-replacement. Growth hormone (GH) deficiency is very common in adults with hypopituitarism and requires replacement with daily subcutaneous injections. A provocative stimulation test is required to establish the diagnosis of GH deficiency in adults with the insulin tolerance test being regarded as the "gold standard". Individualised selection of a suitable injecting device is important in improving adherence to medication and optimal replacement. Treatment with GH in adults improves quality of life, body composition, and bone density. Long-acting GH formulations are in development and aim to improve adherence and convenience with treatment via weekly or monthly injections.

Keywords

Hypopituitarism · Pituitary disorders · Growth hormone deficiency · Hormone replacement therapy · Daily injections · Quality of life

Abbreviations

ACTH	Adreno-corticotropic hormone
ADH	Antidiuretic hormone
DI	Diabetes insipidus
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHRH	GH-releasing hormone
GST	Glucagon stimulation test
IGF-1	Insulin-like growth factor-1
ITT	Insulin tolerance test
LAGH	Long-acting growth hormone
LH	Luteinising hormone
PRL	Prolactin
QoL	Quality of life
rhGH	Recombinant human growth hormone
TSH	Thyroid-stimulating hormone

Key Terms

- **Anterior pituitary**: The front lobes of the pituitary gland, responsible for secreting TSH, LH, FSH, PRL, GH, and ACTH.
- **Posterior pituitary**: The rear lobes of the pituitary, responsible for producing ADH and oxytocin.
- **Hypopituitarism**: The loss of one or more anterior pituitary hormones leading to deficient hormone production in the corresponding target gland.
- **Panhypopituitarism**: The insufficiency or deficiency of all the pituitary hormones from the anterior and posterior pituitary lobes.
- **Hormone replacement therapy**: Chronic replacement of the hormone produced by the target gland to restore physiological body function and well-being.
- **Growth hormone (GH)**: Produced by the anterior pituitary gland. It has a role throughout lifespan in the regulation of protein, lipid, and carbohydrate metabolism and other important metabolic effects on a variety of target tissues, in addition to linear growth in children.
- **Provocative/dynamic/stimulation testing**: The exposure of patients to a substance or drug to evaluate their bodies' response. This response is compared to average responses from unaffected individuals.
- **Cut-off values** differentiate normal responses from abnormal or dysfunctional responses.

Key Points

- Hypopituitarism refers to the deficiency of one or more hormones secreted by the pituitary gland
- Patients with hypopituitarism have increased mortality and impaired quality of life. They require lifelong hormone replacement therapy with multiple medications and different treatment modalities daily
- Growth hormone deficiency in adults can cause reduced metabolic rate, muscle mass and bone density, and impaired quality of life
- Growth hormone treatment involves daily subcutaneous injections

25.1 Introduction

A tormentor traced *by Simon Neil*
A function is planned for family and friends,
Been absent so many, "I hope he attends",
Sit anxious and quiet, unwilling wall-flower,
Please open up floor, for me to devour,
Embarrassed and saddened with such awkwardness,
My tongue tightly tied, void of loquaciousness.
Impatiently, angrily although they Placate,
Utter intolerance of when they are late,
Anxious, depressed, in total despair,
Will nobody listen, does nobody care,
Apathy of mood, thinning of skin,
Central obesity, "please look further in".
No libido, no interest, no passion, no lust,
"Please join up the pieces, my enthusiasm is trussed",
No strength, no stamina, no staying power,
No concentration, my mind turning sour,
Aches and pains so hard to describe,
Drilling in my head of which I often writhe.
Unexplained tears, no equilibrium of mood,
Cholesterol sky high but it's not down to food,
Weakness of limbs, I feel so unwell,
No end in sight of my enduring hell,
Dull aching pain, disarrayment of sight,
What will it take to discover my blight?
Decrease of muscle, flushing of face,
"Your hormones Sir are all over the place",
No smiling, no banter, no sense of humour,
All above symptoms of my 'Pituitary tumour',
A matter of years for my tormentor to trace,
My Endocrine team, 'My saving grace'….

25.2 Part A: Hypopituitarism

The term *hypopituitarism* refers to the deficiency of one or more hormones of the pituitary gland which is formed of the anterior and posterior lobes (Fig. 25.1). The posterior lobe secretes two hormones: vasopressin (or antidiuretic hormone - ADH) the deficiency of which is called diabetes

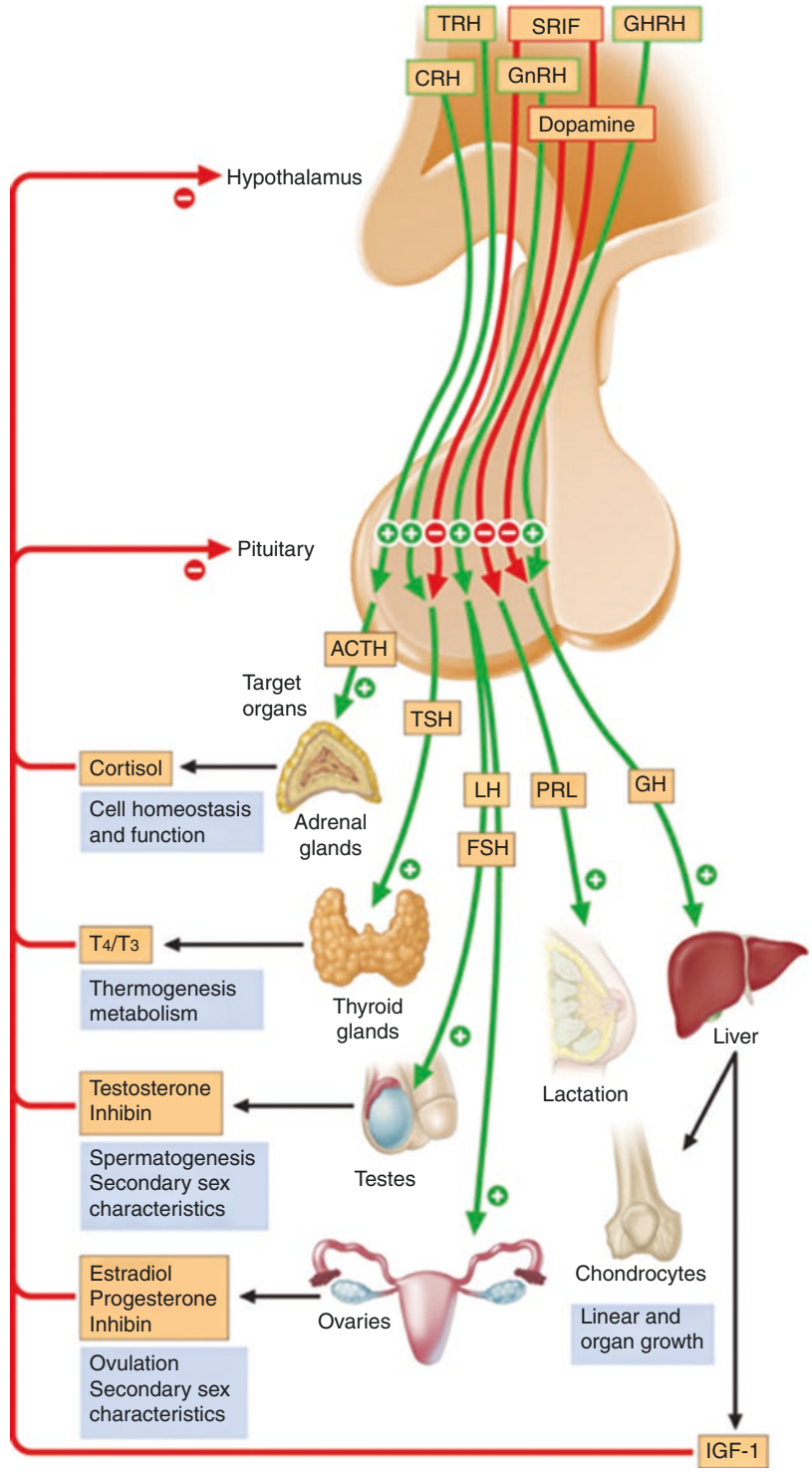


Fig. 25.1 Diagram of anterior pituitary axes and target gland secretion. Used with permission from Melmed, S. & Jameson, J. L. 2017. Anterior pituitary: physiology of pituitary hormones, chapter 3, pages 18–24. In: Jameson, J. L. (ed.) *Harrison's Endocrinology, 4th Edition.* New York: McGraw Hill Education

insipidus (DI), and oxytocin. The term *panhypopituitarism,* is used to describe the insufficiency or deficiency of all the pituitary hormones (Toogood and Stewart 2008; Burt and Ho 2016). The pituitary gland is found in the pituitary fossa of the sphenoid bone close to the optic nerves at the base of the skull. It is not part of the brain, but communicates with the hypothalamus via the pituitary stalk which consists of neurones and portal blood vessels. Within the anterior lobe of the pituitary, six hormones are produced: growth hormone (GH), the gonadotropins follicle-stimulating hormone (FSH) and luteinising hormone (LH), adreno-corticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and prolactin (PRL). Hypothalamic hormones regulate anterior pituitary trophic hormones that in turn determine target gland secretion (Fig. 25.1).

25.3 Prevalence, Mortality, and Morbidity of Hypopituitarism

Hypopituitarism is a rare endocrine condition. Prevalence ranges from 375 to 455 patients per million of the population (Regal et al. 2001; Fernandez-Rodriguez et al. 2013). This, for example, indicates that there are approximately 30,000 patients with hypopituitarism in the UK, although this number is estimated to be significantly higher as these epidemiologic studies only included patients with pituitary adenomas and not the many other causes of hypopituitarism, such as childhood cancer survivors or brain tumours affecting the hypothalamic-pituitary function (Toogood and Stewart 2008).

The standard mortality rate (SMR) for patients with hypopituitarism ranges from 1.10 to 3.6 (95% CI) times higher than the average population (Pappachan et al. 2015; Ntali et al. 2015; Olsson et al. 2015; Burman et al. 2013). Patients also report impaired quality of life (QoL) (Andela et al. 2015) and more than twice health care costs, disability pensions, and sick leave compared to the average population (Ehrnborg et al. 2000; Jonsson and Nilsson 2000; Hahner et al. 2007). Prevalence of hospitalisations and deaths is high in patients with ACTH-induced adrenal insufficiency; 1 in 12 patients experience at least one hospital admission annually and 0.5 adrenal crisis-related deaths per 100 patient-years occur due to potentially preventable adrenal crisis (Hahner et al. 2015) (please see Chaps. 37 and 62 for more details).

25.4 Causes of Hypopituitarism

Hypopituitarism is the consequence of diseases or treatments that reduce or destroy the secretory function of the pituitary gland leading to stimulating and target gland hormone deficiencies. Hypopituitarism can be congenital (genetic and developmental/structural) or acquired such as tumours involving the hypothalamic-pituitary axis. Causes of hypopituitarism are summarised in Table 25.1 (Burt and Ho 2016; Fleseriu et al. 2016; Melmed and Jameson 2017).

25.5 Clinical Presentation and Diagnosis of Hypopituitarism

Hypopituitarism results from complete or partial deficiency of one or more hormones of the pituitary gland and includes adrenal insufficiency, hypothyroidism, hypogonadism, GH deficiency, and more rarely, diabetes insipidus (Toogood and Stewart 2008; Burt and Ho 2016; Fleseriu et al. 2016; Melmed and Jameson 2017). It is challenging to ascribe specific symptoms to a single hormone deficiency as hypopituitarism presents with similar clinical features such as: weight loss or gain, fatigue, depression, cognitive decline, sexual impairment and infertility, and muscle weakness (except for diabetes insipidus which presents with polyuria, increased thirst). Due to the non-specific symptoms of hypopituitarism, it may often be many years before patients receive the correct diagnosis, as Simon describes in his patient story (Box 25.1) and expressed in his poem earlier.

Table 25.1 Common causes of hypopituitarism

Congenital and developmental/structural
Transcription factor defect
Pituitary dysplasia aplasia
Empty sella syndrome
Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Kallmann syndrome)
Midline cerebral and cranial malformations
Genetic: isolated or combined pituitary hormone deficiencies
Idiopathic hypopituitarism
Acquired
Neoplastic
Pituitary adenoma (functioning or non-functioning), craniopharyngioma, meningioma, cysts (e.g. Rathke's cleft), germinoma, glioma, astrocytoma, paraganglioma, teratoma, chordoma, pituitary carcinoma, neoplastic metastases
Surgery for hypothalamic and pituitary tumours
Radiotherapy treatment affecting hypothalamic-pituitary (HP) axis
HP axis tumours, brain tumours, head and neck cancer, acute lymphoblastic leukaemia
Infiltrative/inflammatory disease
Autoimmune (lymphocytic hypophysitis), hemochromatosis, granulomatous hypophysitis, sarcoidosis, Langerhans cell histiocytosis,
Infectious diseases
Bacterial, fungal (histoplasmosis), parasitic (toxoplasmosis), tuberculosis, syphilis
Vascular
Pituitary apoplexy, postpartum Sheehan's syndrome, sickle cell disease, intrasellar carotid artery aneurysm, subarachnoid haemorrhage
Traumatic (head injury)
Medications suppressing pituitary function
E.g. opiates (primarily gonadotropin ACTH, GH), glucocorticoids (ACTH only), Somatostatin analogs (GH, ACTH, TSH)

Note: This table is not inclusive of all causes of hypopituitarism; summarised from Fleseriu et al. (2016), Melmed and Jameson (2017) and Burt and Ho (2016)

Box 25.1 A Patient's Story on Delayed Diagnosis on Hypopituitarism

I have struggled with illness for many years. I struggled to tell people face-to-face how I felt and what the exact symptoms were, and after more than 15 years, I finally got a correct diagnosis last year. I have hypopituitarism including adult-onset growth hormone deficiency due to a small pituitary adenoma. The social isolation of the disease has hit me the hardest; I haven't been able to attend any family or social functions for many years, but until recently didn't know the reason for this. Over the course of the past few months, listening to articles published by your organisation [*The Pituitary Foundation, a UK Patient Advocacy Group, https://www.pituitary.org.uk*], I have come to realise that I am not alone in my disease and that in fact, some of the things I have struggled to describe to doctors are shared by other patients.

This poem [*at the start of the chapter*] is what I have been trying to say about my illness for years but couldn't…

Used with patient consent, contacted by the Pituitary Foundation

The symptoms and treatment of hypopituitarism in adults are summarised in Table 25.2 (Toogood and Stewart 2008; Burt and Ho 2016; Fleseriu et al. 2016; Melmed and Jameson 2017; van Aken and Lamberts 2005).

Table 25.2 Hormone deficiencies, symptoms, and replacement in hypopituitarism (summarised from Bart and Ho 2016; van Aken and Lamberts 2005; Melmed and Jameson 2017; Fleseriu et al. 2016)

Pituitary hormone	Target gland: hormone	Symptoms of hormone deficiency in adults	Treatment (hormone replacement)
ACTH	Adrenals: Cortisol	Hypoadrenalism: weakness, fatigue, dizziness on standing, pallor, hypoglycaemia, hypothermia, shock/coma from adrenal crisis	Tablets 1–3 times daily
			IM injections when nil by mouth
TSH	Thyroid: Free T4 (thyroxine)	Hypothyroidism: fatigue, constipation, dry skin, hair loss, cold intolerance, weight gain	Tablets once daily
LH & FSH (females)	Ovaries: Oestrogen & Progesterone	Hypogonadism: hot flushes, amenorrhoea, infertility, breast atrophy, osteoporosis, weight gain, fatigue, dyspareunia	Tablets once daily
			Transdermal patches twice weekly
LH & FSH (males)	Testes: Testosterone	Hypogonadism: impaired libido and sexual function, infertility, osteoporosis, weight gain, fatigue, reduced muscle mass, small soft testes, and reduced body/facial hair	Intramuscular injections monthly or 3-monthly
			Transdermal gel once daily
			Subcutaneous implant 6-monthly
Growth Hormone (GH)	All cells and organs in the body	GH deficiency: fatigue, impaired quality of life, depression, weight gain, reduced muscle mass & strength	Daily subcutaneous injections (self-administered)
ADH	Kidneys	Diabetes Insipidus: polydipsia, polyuria, weight loss, dehydration, hypernatremia, renal impairment	Nasal spray 1–3 times daily
			Tablets 1–4 times daily

ACTH adrenocorticotrophic hormone, *TSH* thyroid-stimulating hormone, *LH* luteinising hormone, *FSH* follicle-stimulating hormone, *GH* growth hormone, *ADH* antidiuretic hormone

The clinical presentation and the cause of hypopituitarism will guide the selection of the diagnostic biochemistry and/or dynamic investigations. Initial investigations with basal hormone measurements will either confirm the diagnosis of hypopituitarism or prompt for further investigations and dynamic tests. The blood tests should be drawn early morning, preferable before 9 am, to reflect diurnal cortisol secretion; testosterone is also higher in the morning. Evaluation of baseline hormones should include the pituitary hormone and target hormone concentrations to assess the appropriateness of both values. In hypopituitarism, the pituitary hormones are generally low which also results in low target gland hormones. This differentiates hypopituitarism (secondary deficiency) from primary gland failure such as Addison's disease or primary adrenal insufficiency, primary hypothyroidism, primary hypogonadism, and primary ovarian insufficiency (please refer to relevant chapters in the textbook for further details). Dynamic testing is required to diagnose ACTH, ADH, and GH deficiencies for most patients.

It is, however, important to remember that a pituitary mass can lead to the secretion of biologically inactive pituitary hormones, which can present with normal pituitary concentrations but decreased target hormone concentrations (Fleseriu et al. 2016; van Aken and Lamberts 2005). A comprehensive overview of dynamic tests and investigations used to diagnose hypopituitarism is presented in Chap. 15.

25.6 Hormone Replacement Therapy in Hypopituitarism

Polypharmacy is common in hypopituitarism and patients may be taking up to five different medications for replacement therapy in different treatment modalities and multiple daily dosing (Toogood and Stewart 2008; Lee and Ho 2010; Prabhakar and Shalet 2006). Treatment in hypopituitarism includes chronic replacement of the hor-

mone produced by the target gland (Table 25.2) for relevant deficiencies with:

- Cortisol (glucocorticoids);
- Free T4 (thyroxine);
- testosterone for men;
- oestrogen/progesterone for women;
- growth hormone (somatropin)
- desmopressin (DDAVP).

Growth hormone treatment is discussed in details in the next section of this chapter. The reader is also encouraged to refer to relevant chapters in the textbook regarding treatment of other hormone deficiencies: hypothyroidism in Chap. 30; ACTH and cortisol deficiency in Chap. 37; oestrogen deficiency in Chap. 41, and testosterone deficiency in Chap. 46.

The goals of treatment in hypopituitarism are to achieve normal levels of all missing hormones with minimal side effects and to avoid the symptoms and adverse effects associated with deficiency or over-replacement (Toogood and Stewart 2008; Burt and Ho 2016; Filipsson and Johannsson 2009). Full treatment benefit is not achieved unless all missing hormones are optimised.

25.7 Importance of Patient Education and Adherence to Medication in Hypopituitarism

Achieving optimal replacement in hypopituitarism, given the complexity of the treatment regimens, requires the patient to understand and engage with their treatment planning and perceive it as necessary for their condition. Patient education, self-management, and adherence to medication are crucial to achieve optimised well-being and normalise QoL. However, empirical evidence has so far failed to provide a holistic focus on the patients' needs taking into consideration all the hormone replacement therapies found in hypopituitarism. Previous cross-sectional studies looked at patients' adherence to one specific single treatment [cortisol (van Eck et al. 2014; Flemming and Kristensen 1999; Peacey et al. 1993; Forss et al. 2012; Tiemensma et al. 2014; Chapman et al. 2016), GH (Rosenfeld and Bakker 2008; Abdi et al. 2014) and testosterone (Dwyer et al. 2014; Schoenfeld et al. 2013)], even though many patients were on multiple hormone treatments.

This is a significant limitation as treatment benefit is not achieved unless all hormones are assessed as a single treatment. Interactions between replacement hormones means that untreated deficiencies and changes in dose, initiation, discontinuation, or nonadherence to any of the hormones can lead to adverse effects such as impaired well-being and QoL, precipitation of adrenal crisis and hypothyroidism, and medicational side effects (Losa et al. 2008; Cook et al. 1999; Janssen et al. 2000; Wolthers et al. 2001; Omori et al. 2003; Ragnarsson et al. 2014), but also higher cost of the drug. For example, we found that changing the modality for oestrogen treatment to transdermal patches led to significant savings on the cost of GH as patients' daily dose of GH reduced almost by half compared to previous daily dose (Phelan et al. 2012).

Low persistence and high discontinuation rates of 25–65% were reported by patients on GH and testosterone treatment (Abdi et al. 2014; Dwyer et al. 2014; Schoenfeld et al. 2013). GH and testosterone deficiency are associated with risk of osteoporosis, impaired QoL and sexual function (Burt and Ho 2016; Fleseriu et al. 2016). Abdi et al. found that high adherence to GH was closely associated with improvement in QoL (Abdi et al. 2014). Our recent study of 308 patients on GH replacement found that the reported side effects correlated with nonadherence, concerns and dissatisfaction with treatment, impaired QoL, and high or at upper end of reference range for age levels of insulin-like growth factor-1 (IGF-1) (Llahana et al. 2018).

Over-replacement in GC therapy was reported by 25% of patients in a study by Chapman et al. 2016; there is evidence which shows direct association of excessive cortisol treatment with osteoporosis (Schulz et al. 2016) and impaired QoL (Bleicken et al. 2010). Similarly, side effects and long-term complications can result from over- or under-replacement of all hormones in hypopituitarism.

Patients who are adequately informed and engaged in treatment planning are more likely to adhere to their medication and manage possible side effects (Atkinson et al. 2004; Cooper et al. 2015). Similarly, patients' satisfaction with care services and effective clinician-patient communication have been shown to predict adherence and follow-through with treatment plans and appropriate use of care services (Cooper et al. 2015; Ruiz et al. 2008; George et al. 2005; Zolnierek and Dimatteo 2009; Linn et al. 2016).

Evidence from studies in pituitary conditions shows that the patient's engagement with their treatment planning, their satisfaction with the information they receive, and the knowledge of their treatment and condition influence care outcomes (Martinez-Momblan et al. 2016; Llahana and Conway 2006; Repping-Wuts et al. 2013; van der Meij et al. 2016; Gurel et al. 2014; Adelman et al. 2013; Kepicoglu et al. 2014). Assessment of patients' satisfaction with the care and information they receive and their knowledge and understanding of their condition and treatment is, therefore, crucial in identifying and addressing unmet needs. The endocrine nurse should adopt holistic care approach to meet the complex and multiple needs of patients with hypopituitarism and advanced practice skills and competencies are necessary to perform this role adequately.

25.7.1 The Role of Patient Advocacy Groups

Patient advocacy groups (PAGs) play an essential role in raising awareness of the pituitary conditions and providing patients with reassurance that they are not alone. PAGs work closely with health care professionals to develop evidence-based information leaflets and educational resources. The Pituitary Foundation in the UK, as described below, is a great example of a PAG with a vital contribution in the support and self-management of patients with hypopituitarism.

25.7.1.1 The Pituitary Foundation UK

The Pituitary Foundation was launched in 1994 with the support of one of our founders, Professor Stafford Lightman.

We are the UK's leading charity providing support to people affected by conditions such as acromegaly, Cushing's, prolactinoma, diabetes insipidus, and hypopituitarism. Our objectives are:

- To promote the relief and treatment of persons suffering from pituitary conditions, their families, friends, and carers, and to provide information and support.
- To promote and support research and to disseminate for the public benefit the results of any such research.

Our contactable support includes a Patient Support Helpline, a Patient Support email and text service, and an Endocrine Nurse Helpline. We also have trained Telephone Buddies (patients who support other patients via phone or email). We have an extensive library of booklets and fact sheets, plus our magazine, *Pituitary Life,* is produced three times a year for members. Our website is easy to read and access information. We hold National Pituitary Conferences every 18 months. We collaborate with health care professionals through providing clinical resources about pituitary conditions and co-authoring patient information leaflets and booklets. Our members, as described in the patient story below, find the support from the Foundation invaluable:

A patient's story:

I am 42… recently had surgery on a Rathke's Cleft Cyst. The admission to hospital was nerve-wrecking, having never gone under the knife before, to my first operation being brain surgery! … Just prior to discharge, the endocrine nurse specialist discussed hydrocortisone treatment with me and how important it is to take… The nurse discussed sick-day rules and about doubling my dose. If I am truly honest, it went in one ear and straight out the other without even registering. My head and my thoughts were everywhere.

Even as a nurse myself, I was paranoid of everything. Every time I did not feel like myself,

I thought: *"Is this a crisis? Do I need to double my dose? Do I need to give myself an injection?"* I could look at the list of signs and symptoms and say I have every one of those, but did I? The more I sat back and thought, I would start to get palpitations, the nervous feeling right to the pit of your stomach, thinking: "*what is going on with me? What do I need to do?"* One day, I contacted the Foundation using the Helpline email service, saying I didn't feel well, just not myself and really feeling weak. I didn't want to contact the GP *again* in case they thought I was being a pain.

Pat [Head of Patient and Family Services] responded and what can I say, what an inspirational lady! Pat not only responded to my email but also rang me. She provided me with the information I needed. I also then spent some time looking at The Pituitary Foundation website and found it to be an amazing source of simple information which was easily understood. I watched one of the videos which Alison [the Pituitary Foundation Endocrine Nurse] made, and found comfort now knowing, when to give myself a hydrocortisone injection to prevent adrenal crisis…

To contact the Pituitary Foundation, UK:

Website: www.pituitary.org.uk; Email: helpline@pituitary.org.uk

25.8 Part B: Growth Hormone Deficiency in Adults

25.8.1 Clinical Features and Abnormalities of GHD in Adults

Growth hormone (GH) is produced by the anterior pituitary gland. It has a role throughout lifespan in the regulation of protein, lipid and carbohydrate metabolism, and other important metabolic effects on a variety of target tissues, in addition to linear growth in children (Ahmid et al. 2016a) (Fig. 25.2). Its secretion is intermittent and occurs predominantly during deep sleep. Secretion reaches maximal levels during adolescence and then declines with age by approximately 14% per decade (Burt and Ho 2016; Melmed and Jameson 2017).

GH deficiency is adult-onset or childhood-onset and can occur as isolated GH deficiency or as part of multiple pituitary hormone deficiency. Causes of GH deficiency are the same as those of hypopituitarism (Table 25.1). In adult-onset, GH deficiency is commonly due to pituitary or brain tumours and their treatment with surgery or radiotherapy. Childhood-onset GH deficiency is mainly isolated idiopathic which resolves for many children at the end of growth, but it can also be genetic, associated with brain structural defects or with midline facial defect, which are irreversible and GH deficiency continues into adulthood (Molitch et al. 2011). Acquired GH deficiency can also occur in childhood or adulthood in survivors of childhood cancer, because of previous cranial irradiation and/or chemotherapy (Sklar et al. 2018).

Epidemiological studies in hypopituitarism showed that 60 % of patients were GH-deficient (Regal et al. 2001; Fernandez-Rodriguez et al. 2013), giving a prevalence of GH deficiency between 114 and 270 cases per million population and an incidence of approximately 24 patients with GH deficiency per million per year (Burt and Ho 2016).

Adults with GH deficiency have a range of metabolic, body compositional and functional abnormalities and the degree of severity depends on length of diagnosis, childhood- or adult-onset, and the time of GH replacement. GH deficiency is associated with the following adverse symptoms and signs (Burt and Ho 2016):

- Increased body fat, overweight, increased adiposity especially abdominal
- Reduced muscle bulk and poor muscular development
- Reduced muscle strength and physical performance
- Thin dry skin, reduced sweating
- Impaired psychological well-being and QoL
  - Depressed mood
  - Reduced physical stamina
  - Reduced vitality and energy
  - Increased social isolation
  - Reduced focus and concentration
- Hyperlipidaemia: high LDL cholesterol and low HDL cholesterol

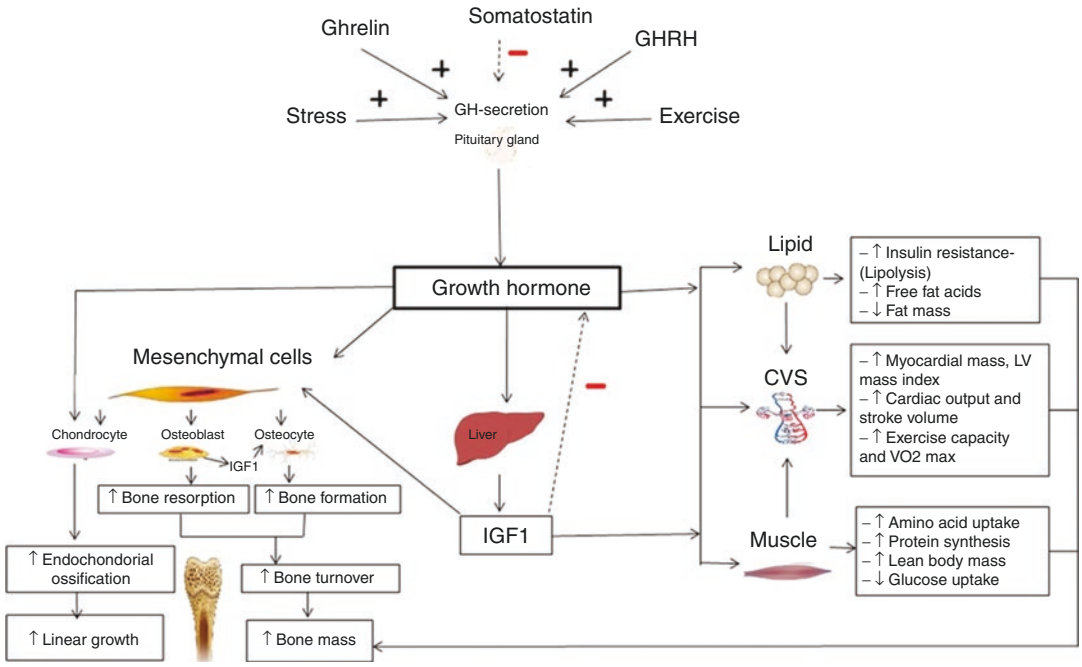


Fig. 25.2 Production of GH and GH-IGF1 actions in bone, muscle, and body metabolism. Key: *GH* growth hormone, *IGF1* insulin-like growth factor-1. GH secretion is regulated by three peptides: GH-releasing hormone (GHRH), ghrelin-stimulating GH release, and somatostatin (SS)-inhibiting GH release. In circulation, GH stimulates the liver and other peripheral tissues to produce IGF1. GH/IGF1 stimulates longitudinal growth, enhances bone mass, and regulates bone metabolism. GH promotes the positive protein balance in skeletal muscle and has lipolytic effects which may play a role in maintaining glucose homeostasis with decreased insulin sensitivity which all promote cardiovascular system (CVS) functional capacity and maximal oxygen consumption (VO_2 max). Used with permission from Ahmid, M., Perry, C. G., Ahmed, S. F. & Shaikh, M. G. 2016b. Growth hormone deficiency during young adulthood and the benefits of growth hormone replacement. *Endocr Connect,* 5, R1-r11

- Insulin resistance and elevated fasting insulin
- Osteopenia or osteoporosis (reduced bone mineral density).

25.8.2 Isolated GH deficiency and Evolving Hypopituitarism

Isolated GH deficiency is the most common pituitary hormone deficiency and can result from congenital or acquired causes; the majority of cases during childhood are idiopathic with no identifiable aetiology and resolve at the end of growth (please refer to Chaps. 1 and 2 on growth and development in childhood). Idiopathic GH deficiency presenting in adulthood is very rare and stringent criteria are necessary with two provocative tests to make the diagnosis. A low insulin-like growth factor-1 (IGF-1) also increases the likelihood of a GH deficiency diagnosis (Molitch et al. 2011; Melmed 2013). Radiotherapy treatment for tumours lying in the hypothalamic and pituitary axis is also a common cause of hypopituitarism which often starts with isolated GH deficiency. The radiological impact resulting in pituitary deficiencies depends on the dose of radiotherapy, number of fractions, patient age, and duration of follow-up. Somatotropes are the most sensitive and the only pituitary cell types affected by radiation dose below 20 Gy. Radiation dose between 20 and 50 Gy causes more rapid onset of GH deficiency and additional progressive onset of other hormone deficiencies over a period of 10–15 years (Burt and Ho 2016). One of the earlier studies looked at 165 patients who underwent external radiotherapy affecting the hypothalamic-pituitary axis; before radiotherapy, 18% of patients had normal GH secretion, 21% had normal gonadotrophin secretion, 57% had normal corticotrophin reserve, and 80% had normal

thyrotrophin secretion. Increasing incidences of progressive hypopituitarism was seen with time; by 8 years post-radiotherapy, all patients were GH-deficient, 96% were gonadotrophin-deficient, 84% were corticotrophin-deficient and 49% were thyrotrophin-deficient (Littley et al. 1989). It is, therefore, important that endocrine testing is performed yearly for the first 10 years and again at 15 years (Burt and Ho 2016). The endocrine nurse should take a detailed history of possible symptoms of hypopituitarism at every consultation and should advise patients and their families to contact the endocrine team should they experience any of these symptoms at any point.

25.9 Diagnosis of Adult GH Deficiency and Provocative Tests

Diagnostic investigations for GH deficiency in adults should be undertaken only in the context of a "probable cause", either a childhood history of GH deficiency or a clinical history making GH deficiency likely (Molitch et al. 2011). The group of adult patients who should be under clinical supervision for developing GH deficiency includes:

- Patients with known or suspected hypothalamic or pituitary disease
- Patients who have received cranial irradiation
- Patients with a deficiency of one or more of the other pituitary hormones
- Patients who have undergone hypophysectomy
- Patients with isolated GH deficiency during childhood

A normal IGF-1 does not exclude the diagnosis of GH deficiency but a low IGF-1, in the absence of poorly controlled diabetes, liver disease, and oral oestrogen therapy, is useful in identifying patients who may potentially be GH-deficient and require further diagnostic investigations (Molitch et al. 2011).

Patients with suspected GH deficiency should undergo pituitary provocative (dynamic) testing to diagnose adult GH deficiency. Several tests are available, with the insulin tolerance test (ITT) being regarded as the 'gold standard' test for adults. The diagnostic criterion for adult GH deficiency (AGHD) is a GH cutoff level between 3 and 5 μg/L in response to insulin-induced hypoglycaemia (glucose <2.2 mmol/L), although this may differ from country to country depending on national guidelines or local assays used for biochemistry analysis (Burt and Ho 2016; Molitch et al. 2011; NICE 2003; Ho 2007).

When the ITT is contraindicated in patients with history of seizure disorders or cardiovascular disease, other tests can be used with equivalent specificity and sensitivity, such as GH-releasing hormone (GHRH)-arginine test or glucagon stimulation test (GST) (Molitch et al. 2011). Please refer to pituitary dynamic testing in Chap. 15.

The endocrine nurse should be vigilant of patients who may develop GH deficiency or require GH replacement for symptom treatment. The following aspects should be included during a patient's routine consultation:

- Ask questions regarding patient's well-being and QoL. Are they feeling more fatigued for no apparent reason? Is the rest of their pituitary profile optimal or adequately replaced?
- If yes to above questions, ask the patient to complete a validated QoL questionnaire such as QoL-AGHDA (Quality of Life Assessment of Growth Hormone Deficiency in Adults) questionnaire (McKenna et al. 1999). An AGHDA-QoL score above 11 indicates impaired QoL and the patient should be investigated for GH deficiency with a provocative test, unless this is not required as discussed earlier. An IGF-1 level should also be checked at every visit.
- Explain to the patient the reason for these tests and what GH treatment involves if the patient is found to be deficient. A number of patients may object to daily injections and it is important to explain the rationale and objectives for treatment and also the simplicity of the GH replacement therapy. If, however, the patient will still object to starting GH replacement, there is no reason to undertake a provocative

testing for GH deficiency (unless indicated for the ACTH-cortisol axis).

For patients younger than 25 years old, continuation or restarting GH is recommended until peak bone mass has been achieved (as indicated by a DEXA bone density scan). If patients report fatigue or impaired well-being after stopping GH, asking them to complete a QoL-AGHDA questionnaire or equivalent is very useful in assessing response to GH treatment with regard to QoL. This also gives an indication that the patient may require GH replacement in the long-term to maintain their well-being.

Criteria for GH treatment in adults may vary from country to country. In the United Kingdom, for example, GH is indicated in adults over the age of 25 years with GH deficiency who report impaired QoL (see Box 25.2) (NICE 2003).

Box 25.2 Criteria for GH Treatment in Adults Set by the National Institute for Clinical Excellence (NICE) in the United Kingdom

The criteria set by NICE in 2003 recommend that an adult older than 25 years of age is treated with GH when:

- Peak GH on an Insulin Tolerance Test or equivalent Dynamic Test such as Glucagon Stimulation Test is less than 9 mU/L (or 3 μg/L);
- Patient has impaired quality of life as measured by an AGHDA_QoL score of 11/25 points or above;
- Patient should be receiving other pituitary replacement and this therapy should be optimised before considering GH start, or in the case of isolated GH deficiency, the pituitary profile should be optimal.
- Assessment of quality of life should be undertaken at 9 months after GH start and continuation of GH replacement long term is determined by an improvement of 7 points on the pretreatment AGHDA_QoL.

Adult patients younger than 25 years of age should continue on GH replacement until this age for achievement of peak bone mass as measured by a DEXA bone mineral density scan. Continuation of treatment past this age will depend on assessment of their quality of life based on above criteria.

AGHDA_QoL: Assessment of Growth Hormone Deficiency in Adults Quality of Life questionnaire

25.9.1 When Is Provocative Testing Not Needed?

Patients in the following two groups do not require a provocative test to establish GH deficiency in adults (Burt and Ho 2016; Molitch et al. 2011), although this may vary between countries or medical insurers:

- Children with GH deficiency following irreversible damage to the hypothalamic-pituitary axis due to structural lesions or proven genetic causes, and a low IGF-1 level at least 1 month off GH therapy at the end of growth;
- Adult patients who have three or more pituitary hormone deficiencies and a low serum IGF-1 level. All pituitary deficiencies must be optimally replaced before GH therapy initiation.

25.10 Transition from Child to Adult and GH Treatment

The transition from paediatric to adult care is an important time to re-evaluate GH status. Once final height is achieved, GH secretion should be retested as a significant percentage of patients with isolated GH deficiency or idiopathic hypopituitarism in childhood recover and have normal GH secretion in adulthood. Patients with confirmed structural damage of the hypothalamic-pituitary axis and low IGF1 do not need to be tested and should continue GH treatment throughout transition. In patients with confirmed GH

deficiency, continuation of GH treatment through the late adolescent years into early adulthood (transition phase) is recommenced in order to complete somatic development, structural skeletal maturity, and peak bone mass which is achieved in the mid-twenties (Burt and Ho 2016).

An algorithm for management of patients during transition after treatment with GH during childhood was proposed in a consensus statement from the European Society of Paediatric Endocrinology (ESPE) (Clayton et al. 2005) (Fig. 25.3). When height velocity has decreased to <1.5/2.0 cm/year, GH should be discontinued for 1–3 months. Patients should then be grouped as either high likelihood of continuing to be GH-deficient, with severe deficiency due to genetic or organic causes and particularly with multiple pituitary hormone deficiencies, or low likelihood, including patients with idiopathic GH deficiency that is either isolated or with additional pituitary hormone deficiencies. Patients with a high likelihood of GH deficiency and an IGF-1 SDS ≤−2 should restart GH without a provocative test. If IGF-1 is >−2 SDS, then a provocative test should be performed, and GH treatment should only be restarted if the stimulated peak GH is below the recommended cutoff value. Patients with low likelihood should have both IGF-1 assessment and a GH provocative test, with GH restarted if both are low indicating continued GH deficiency; if both are normal, then GH deficiency is excluded at that time, and if the results are discordant, then the patient should be followed up in the longterm (Clayton et al. 2005).

The recommended cutoff levels of 3–5 μg/L for peak GH on provocative testing are for measurements in adults, but have not been established for patients in the transition period (Clayton et al. 2005; Aimaretti et al. 2015; Ahmid et al. 2016b).

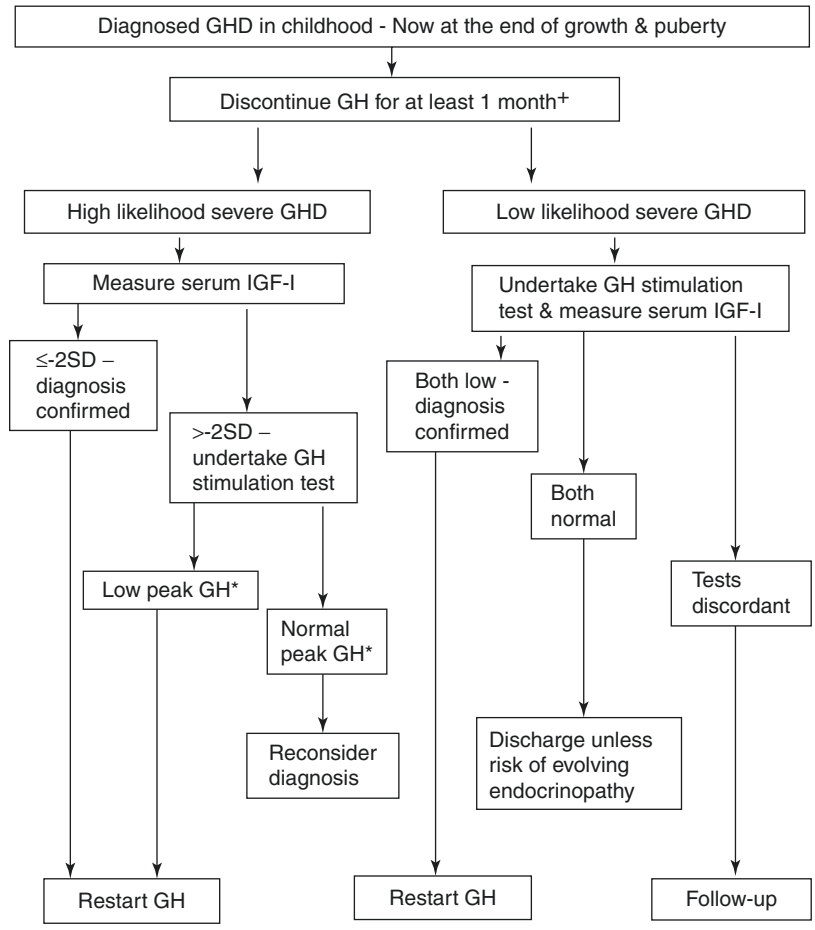


Fig. 25.3 Algorithm for GH treatment during transition and end of growth. Key: *GH* growth hormone, *IGF-1* insulin like growth factor 1, *SD* standard deviation, *asterisk* value of peak GH level may vary depending on assay—confirm local reference range. Used with permission from Clayton, P. E., Cuneo, R. C., Juul, A., Monson, J. P., Shalet, S. M. & Tauber, M. 2005. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. *Eur J Endocrinol,* 152, 165–70

GH dose for patients in the transition period should be adjusted based on IGF-1 levels aiming for upper end of reference range for age. An adequate dose through the transition period is required to attain peak bone mass (Clayton et al. 2005). It is important to remember that young females on oral oestrogen therapy require higher doses of GH, which may be almost a double dose of GH with concomitant ethinylestradiol therapy versus no oestrogen therapy (Wolthers et al. 2001; Phelan et al. 2012). Patients should be advised to inform the endocrine team of any changes to their treatment (e.g. stopping the oral contraceptive pill) as this may lead to potential side effects from over-replacement with GH (see patient case study in Box 25.3).

Box 25.3 Patient Case Study—GH Treatment and Oral Contraceptive Pill

Mary is 24 years old and has a history of isolated idiopathic GH deficiency. She received GH replacement as a child and, following a peak GH level of 1.3 μg/L on insulin tolerance test and low IGF-1 at the end of growth assessment at the age of 18 years, she restarted GH and her daily dose is 1.2 mg. She also takes the oral contraceptive pill (containing ethinylestradiol) for contraception. She reports good adherence to her GH therapy, no side effects, good QoL and her IGF-1 level is stable at the upper end of reference range for age.

She calls the endocrine nurse 4 months after her routine clinic consultation to report joint aches, muscle stiffness, and "aching all over". She stopped running due to severe joint aches. She reports that her relationship with her boyfriend ended recently and she initially attributed these symptoms to her psychological distress. On further questioning, she also reports that she stopped taking the oral contraceptive pill. The endocrine nurse explains that symptoms are most likely due to GH over-replacement and a blood test confirms elevated IGF-1 level. The dose of GH was halved; a repeat blood test 6 weeks later shows normalised IGF-1 level and Mary's symptoms improve and resolve within 2 months.

The endocrine nurse plays a key role in the seamless and successful transition of children to the adult setting. The patient and their families should be supported and provided with the right information and rationale on the importance of continuation of GH treatment when necessary. Many adolescents and young adults will be reluctant to continue GH injections, especially as they become more independent from their parents, and nonadherence to GH is very prevalent at this age (Rosenfeld and Bakker 2008; Abdi et al. 2014). Patients should be provided with information on the continued effects of GH on lipid metabolism, body composition, achievement of peak bone mass, and maintaining QoL. Peer support and meeting with other young patients who have been through the transition process can be very helpful and the endocrine nurse can organise open events or focus groups to facilitate this.

Transition should not be seen as a simple move from one site to another, but as a multistep process during which the patient's and their families' medical, psychological, social, and educational needs must all be considered. The patient gets to know a new physician and group of health care specialists and, therefore, may experience increased anxiety. Multidisciplinary working between the paediatric and the adult teams is crucial to ensure a smooth transition to the adult clinic. Joint clinics and a "patient passport" that includes all relevant health and treatment information to facilitate the smooth transfer from paediatric to adult service can be useful resources. Many evidence-based health care pathways with specific milestones are available for patients in transition and various models can be adopted depending on organisational and patient needs (please read Chap. 6 for more details on the transition process).

25.11 GH Treatment Initiation and Monitoring in Adults

Each patient should be provided with a comprehensive consultation prior to GH treatment to explain patient with details regarding GH treatment, possible side effects, benefits, dose titration, and long-term monitoring. The checklist in Table 25.3 provides a proposed outline for the consultation which can be used by the endocrine nurse as a guide to ensure that patients receive all the relevant information prior to GH replacement therapy initiation. GH should be initiated only after all other pituitary deficiencies have been fully optimised or after adequate pituitary function is confirmed.

GH replacement is administered by daily subcutaneous injections recommended in the evening to mimic physiological secretion of GH at night. Patients can self-administer and the recommended starting dose of GH in young men is 0.2 mg, in young women 0.3 mg daily and in older individuals 0.1 mg daily. IGF-1 is used as a marker for GH treatment optimisation and the goal for adults with GH deficiency, after peak bone mass has been achieved, is to achieve IGF-1 levels in the middle of the normal reference range appropriate for age and sex. Dose titration by increments of 0.1–0.2 mg should be done every 1–2 months based on IGF-1 and taking into consideration the patient's clinical picture and presence of side effects, but also concomitant use of oestrogen therapy in women. The dose should not be increased while the patient experiences side effects. Once optimal level of IGF-1 is achieved, patients should be monitored every 6–12 months, with a clinical assessment for evaluation of IGF-1, adverse and side effects, adherence to treatment, and other parameters for GH response such as body composition and metabolic parameters, cardiovascular risk factors, and QoL (Burt and Ho 2016; Molitch et al. 2011; Gasco et al. 2013). GH replacement requirements decrease with age, mirroring the physiological production of GH.

The endocrine nurse should explain to the patients that any improvement in QoL post GH start may take up to nine months to notice, as patient's expectations for immediate improvement may have a negative impact on their adherence to GH injections. NICE guidelines in the United Kingdom recommend assessment of QoL at 9 months post-GH initiation, aiming for an improvement of 7 points in the QoL-AGHDA score in order to continue GH treatment in the longterm (NICE 2003). Practical aspects such as injection technique and adherence to medication are also important considerations in the optimisation and monitoring of GH replacement in adults (Box 25.4).

Table 25.3 A checklist to facilitate consultation for GH replacement start

1	Explain results of the provocative test	9	What to do if missing an injection
2	Symptoms of GHD and expected benefits	10	Changes in medication, e.g. starting OCP
3	Possible side effects and what to do	11	When to stop GH, e.g. pregnancy, malignancy
4	Starting dose and further titration	12	Travelling with GH: travel letter, cool bag
5	What is IGF-1 and dose adjustment	13	Cool bag or non-refrigerated GH
6	How to ensure accuracy of IGF-1	14	Choosing a suitable injecting device
7	Long-term monitoring	15	Prescriptions, training for GH injections
8	When to take injections, storage	16	Who to contact for what: telephone numbers

GHD growth hormone deficiency, *IGF-1* insulin like growth factor-1; *OCP* oral contraceptive pill

Box 25.4 Practical Aspects in the Assessment of IGF-1 and GH Treatment in Adults

If an abnormal IGF-1 is found in a routine clinic follow-up, it should be repeated in 4–6 weeks. It is important to ask the following questions when interpreting an IGF-1:

- Have you taken all your injections in the last 2 weeks or so? Assessment of adherence to medication should be recorded.
- Is the injection technique correct (ask the patient to demonstrate this in clinic)? Is the injecting device working properly? Is the GH stored properly and used within its time limit?

- Check the patient's injection sites for evidence of nonabsorption.

If YES to any of the above questions, correct as necessary and repeat IGF-1 in 4–6 weeks; NO dose adjustment should be done at this stage.

NOTE: IGF-1 can be inaccurate in malnutrition, liver disease, poorly controlled diabetes, and hypothyroidism

Table 25.4 presents a summary of regular clinical and biochemistry assessment. This, however, depends on each individual patient and the clinical setting/country.

A wide range of GH-injecting devices is available making it possible to select an appropriate device based on individual patient needs, such as needle-phobia, need for non-refrigerated GH, etc. Table 25.5 presents a detailed list of available GH detailed list of available GH treatment options and devices and their characteristics. In addition, Fig. 25.4 presents an algorithm which can help the endocrine nurse and the patient to select the most suitable injecting device for the patient's needs without overwhelming them by demonstrating all the available devices.

25.11.1 Safety, Adverse Effects, and Contraindications of GH in Adults

The patient should be advised of the potential side effects and how these can be managed before they start GH treatment. The most common acute side effects arise from the antinatriuretic action of GH, which causes fluid retention (Burt and Ho 2016). Mild ankle oedema following GH start is a normal response for most patients. Similarly, arthralgia (joint pain), myalgia (muscle pain), carpal tunnel syndrome, and paraesthesia can occur. These effects, if they occur, are usually mild and self-limiting and should generally clear within 2–3 weeks post GH start or following GH dose reduction. Hyperglycaemia and hypoglycaemia have also been reported. GH therapy reduces insulin sensitivity in these patients by antagonising the action of insulin—this could increase the risk of diabetes. Caution should be exercised when treating a patient with Diabetes Mellitus with GH; adjustments in the diabetes treatment may be required (Burt and Ho 2016).

Headaches are also common at the start of treatment. Persistent headaches, visual problems, or nausea and vomiting require investigation with fundoscopy for papilledema, which if confirmed benign intracranial hypertension (rare cases reported) should be considered. This is usually recognised shortly after commencement of GH treatment (Burt and Ho 2016). The endocrine nurse should advise patients to stop treatment and report severe and persistent headaches immediately. Other side effects may include mild hypertension, visual problems, and nausea and vomiting.

There is evidence to support no effect of GH replacement on tumour regrowth or recurrence of pituitary tumours, craniopharyngiomas, or other benign brain tumours and published data provide reassurance on the long-term safety profile of GH treatment (Stochholm and Kiess 2018; Pekic and Popovic 2013). GH treatment is contraindicated in active malignancy, proliferative diabetic retinopathy, benign intracranial hypertension, and in

Table 25.4 GH treatment monitoring: what to check and when?

Parameters to check	Pre-GH start	4 weeks	3 M	6 M	9 M	6-monthly	Yearly
IGF-1, TFTs	**X**	X	**X**	**X**	**X**	**X**	
Glucose, Lipid, BMI/weight, BP	**X**			**X**			**X**
AGHDA-QoL and well-being	**X**				**X**		**X**
Waist circumference	**X**				**X**		**X**
Response to GH and side effects		**X**	**X**	**X**	**X**	**X**	**X**
BMD—DEXA	**X**	2–3 yearly thereafter if abnormal depending on T-scores					
MRI pituitary (where needed)	**X**				**X**		
IGF-1 & TFTs	**Check 6 weeks after any dose adjustments or regime change**						

IGF-1 insulin-like growth factor-1, *TFTs* thyroid function test, *BMI* body mass index, *BP* blood pressure, *GH* growth hormone, *BMD-DEXA* bone mineral density-dual energy X-ray absorptiometry, *MRI* magnetic resonance imaging

Table 25.5 Available GH injecting devices and their characteristics

GH brand and manufacturer	Device	Device photo	Vial strength/dose increments	Liquid vial	Dose preset	Storage	Stable at room temp (<25 °C)	Auto injector
Omnitrope® Sandoz	SurePal™ Pen 5, 10 & 15 (for use with Omnitrope vials)		5 mg/0.05 mg 10 mg/0.1 mg 15 mg/0.1 mg	✓	 ✓	2–8 °C, use within 28 days once in pen	X	X
Genotropin® Pfizer	Genotropin® Pen 5.3 & 12 (for use with Genotropin® vials, needs reconstitution)		5.3 mg/0.1 mg 12 mg/0.2 mg	X	 X	2–8 °C, use within 28 days once in pen	Up to a month before reconstitution	X
	GoQuick® Pen 5.3 & 12 (prefilled multi-dose disposable pen, needs reconstitution)		5.3 mg/0.05 mg 12 mg/0.15 mg	X	 ✓	2–8 °C, use within 28 days once started	Up to a month before reconstitution	X
	MiniQuick® disposable single-use syringe with liquid-powder, needs reconstitution		Set dose 0.2–2.0 mg/ 0.2 mg increments	X	✓	2–8 °C, use within 24 h post-reconstitution	YES - up to 6 months	X
Norditropin® NovoNordisk	NordiPen® 5, 10 & 15 (for use with Norditropin SimpleXx vials)		5 mg/0.05 mg 10 mg/0.1 mg 15 mg/0.1 mg	✓	 X	2–8 °C, use within 28 days once in pen	Up to 21 days, can be used for another 7 days if refrigerated	✓ With PenMate
	NordiFlex® 5, 10 & 15 [Norditropin FlexPro® in USA] (prefilled m-dose disposable pen)		5 mg/0.025 mg 10 mg/0.05 mg 15 mg/0.075 mg	✓	 X	2–8 °C, use within 28 days once in pen	Up to 21 days, can be used for another 7 days if refrigerated	✓ With PenMate

Saizen® MerckSerono	EasyPod® digital autoinjector, injects only at skin contact (for use with Saizen Liquid— *specific dose preset for each vial range with min wastage)		Vial/dose range* 6 mg/0.15–0.45 mg 12 mg/0.5–0.7 mg 20 mg/0.75–6.4 mg	✓	 ✓ 	2–8 °C, use within 28 days once in device	X	✓
	One.click® autoinjector (for use with ClickEasy 8mg, needs reconstitution)		8 mg/0.12 mg (one click increments)	X	X	2–8 °C, use within 28 days once in pen	X	✓
NutropinAq® Ipsen	NutropinAq® 10 Pen (for use with NutropinAq® vials)		10 mg/0.1 mg	✓	X	2–8 °C, use within 28 days once in pen	X	X
Humatrope® Lilly	HumatroPen® 6, 12 & 24 (for use with Humatrope cartridge and prefilled syringe with diluent for reconstitution)		6 mg/0.025 mg 12 mg/0.05 mg 24 mg/0.1 mg	X	 X	2–8 °C, use within 14 days post-reconstitution	X	X
Zomacton® Ferring	ZomaJet VisionX® 4 & 10 NEEDLE FREE pen (for use with Zomacton, needs reconstitution)		4 mg/0.1 mg 10 mg/0.1 mg	X	 X	2–8 °C, use within 14 days post-reconstitution	X	✓
TevTropin® USA only Ferring	Tjet® 5 NEEDLE FREE pen (for use with TevTropin, needs reconstitution)		5 mg/0.1 mg	X		2–8 °C, use within 14 days post-reconstitution	X	✓

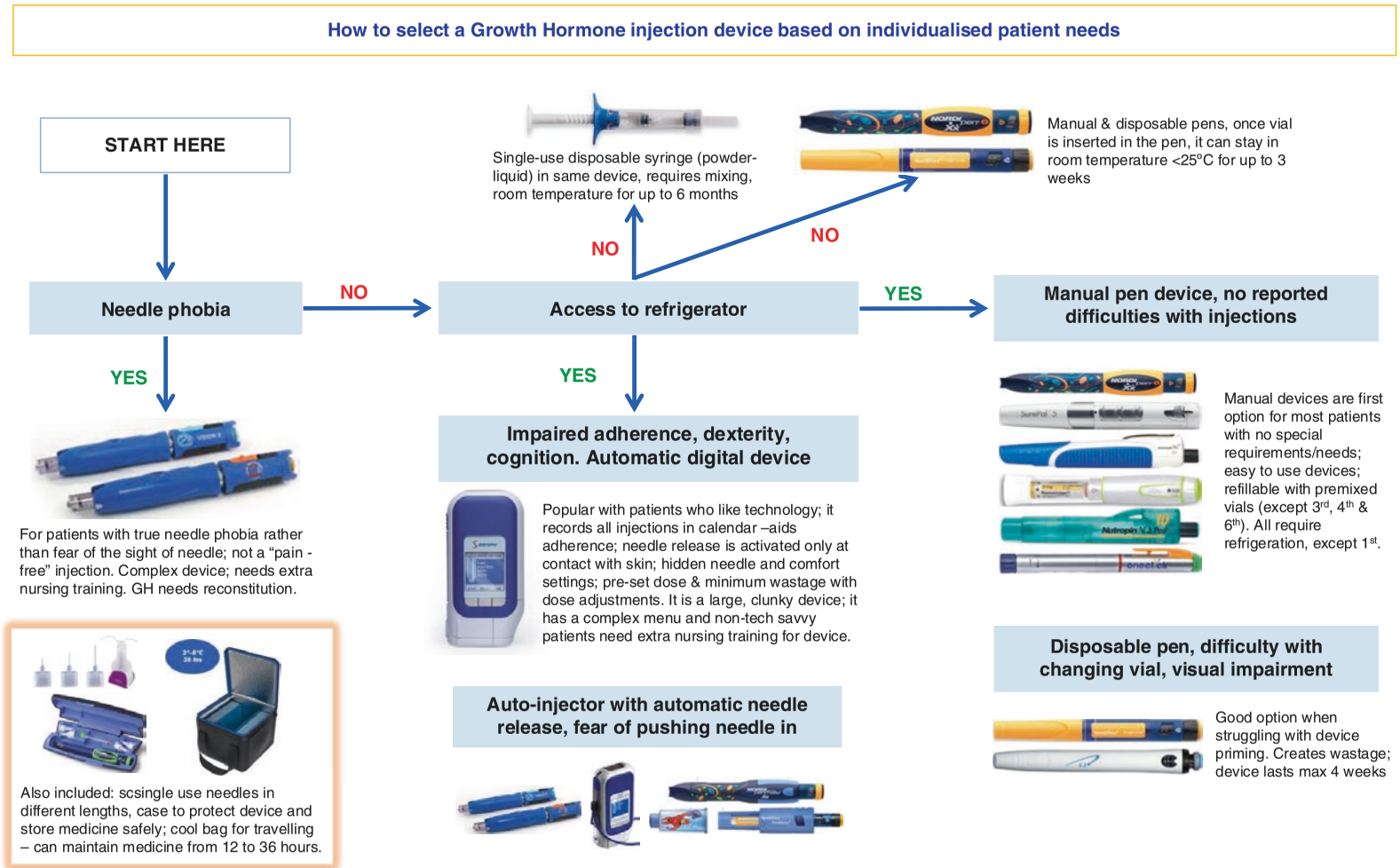


Fig. 25.4 Algorithm for selecting a suitable GH device for each patient's needs

patients with known hypersensitivity to GH or to any of the excipients. Pregnancy is not a contraindication, but GH becomes unnecessary in the second trimester due to sufficient placental GH production and should be discontinued. Moreover, there is no safety data in the use of GH in pregnancy (Burt and Ho 2016; Molitch et al. 2011).

25.11.2 GH Treatment and Safety in Childhood Cancer Survivors

Concerns have been raised regarding the long-term safety of GH treatment in childhood cancer survivors. Previous data on GH-treated childhood cancer survivors suggest that GH might potentially induce a small increase in the relative risk of developing second neoplasms, particularly meningiomas, compared to survivors not receiving GH treatment (Sklar et al. 2002; Woodmansee et al. 2013). However, recent studies have shown no significant association between GH treatment and the development of a second neoplasm of the central nervous system (CNS) in childhood cancer survivors (Mackenzie et al. 2011; Patterson et al. 2014; Brignardello et al. 2014). The recent guidelines from the Endocrine Society recommend offering GH treatment to childhood cancer survivors with confirmed GH deficiency (Sklar et al. 2018).

25.11.3 Interactions with Other Hormones and Medications

GH affects the action and metabolism of other pituitary hormones and alterations in dose requirements should be anticipated (Filipsson and Johannsson 2009).

GH increases the peripheral conversion of triiodothyronine to thyroxine (T4) and treatment initiation may unmask preexisting central hypothyroidism. Agha et al. looked at 243 patients with severe GH deficiency due to hypothalamic-pituitary disorders, of whom 159 were treated for central hypothyroidism (treated group) and 84 were euthyroid prior to GH commencement (untreated group). Following GH initiation and dose titration over 3–6 months, 30/84 patients (36%) became hypothyroid and required initiation of T4 therapy. Moreover, 25/159 (16%) of patients in the treated group required increase in T4 dose (Agha et al. 2007). Commencement of T4 replacement is, therefore, recommended in patients with low normal serum T4 concentrations prior to GH initiation to provide a robust baseline from which to judge the clinical effects of GH replacement.

Oestrogen administered by the oral route impairs GH action, leading to higher dose requirements. Physiological non-oral route with transdermal patches or gel is preferable where possible (Wolthers et al. 2001; Phelan et al. 2012). Patients should be advised to update the endocrine clinic on any changes to oestrogen therapy, e.g., starting or stopping the oral contraceptive pill; IGF-1 should be checked for GH dose adjustment.

In adults with GH deficiency, there is an increased 11β-HCD type 1 activity which results in increased cortisol tissue exposure. This is reduced after initiating GH treatment (high GH and IGF-1 levels enhance conversion of cortisol to cortisone, i.e. lower levels of active cortisol), which can unmask central hypoadrenalism and predispose the patient to adrenal insufficiency (AI) and risk of adrenal crisis. Therefore, the assessment of the hypothalamic-pituitary-adrenal (HPA) axis to confirm or exclude AI is mandatory prior to starting GH replacement (Filipsson and Johannsson 2009; Giavoli et al. 2004). For patients on cortisol replacement, an increase in Hydrocortisone dose may be required after starting GH treatment.

25.12 New Developments in GH Treatment (Long-Acting GH)

Currently, treatment with subcutaneous injection of a biosynthetic recombinant human growth hormone (rhGH) requires daily administration. The treatment often enduring for many years increases the risk of poor adherence, i.e. patients admit being lax about taking injections. Long-acting GH (LAGH) preparation aims to improve adherence to treatment by decreasing the inconvenience of daily injections. LAGHs are expected to be as effective, safe, and cost-effective as the currently available rhGH brands. However, the problem of

Table 25.6 Long-acting GH (LAGH) formulations in advanced stages of clinical research

LG Life Sciences	**LB 03002**	GH embedded in sodium hyaluronate microparticles suspended in triglyceride	*Approved but not marketed in Europe Available in South Korea*
Ascendis Pharma A/S	**TransCon GH**	Transiently PEGylated GH prodrug	*Phase 3*
GeneScience	**Jintrolong**	Permanently PEGylated GH	*Available in China*
OPKO Health Inc	**MOD-4023**	GH fused with carboxyterminal peptides	*Phase 3*
Versatis Inc.	**VRS-317**	GH fused to half-life extension technology	*Phase 3*
Novo Nordisk	**NNC0195-0092**	Mutated GH attached to an albumin affinity tag	*Phase 2*
Hanmi Pharm	**LAPS-rhGH/ HM10560A**	GH fused to an Fc fragment	*Phase 3*

big molecules (modified GH) is that this may compromise tissue distribution (penetrance) and direct actions of GH on local IGF-1 production. LAGH should be small enough to permeate all tissues to achieve beneficial effects (for example QoL). Liver is favoured over peripheral tissue via fenestrated hepatic sinusoidal endothelium. There are still many safety considerations unique to LAGHs: (a) supraphysiological GH activity (can LAGH lead to acromegaly?); (b) fluctuating IGF-1 levels; (c) elevated IGF-1 in the absence of GH bioactivity; (d) tissue distribution (local IGF-1 production); (e) GH and LAGH bind to a common receptor, but they might have disparate effects on downstream signalling cascades.

Long action of GH can be achieved utilizing different development approaches (Sprogoe et al. 2017; Christiansen et al. 2016).

(a) **Unmodified GH**: half-life extension is achieved by the slow release of somatotropin from depot, crystal, or prodrug
(b) **Modified GH**: GH analogue has a longer half-life achieved by increasing molecular size

The LAGH formulations which are in advanced stages of clinical research are presented in Table 25.6.

25.12.1 Unmodified GH Superimposed on Inert Prolongation Technology

Sustained-release rhGH (LB03002) is a sustained-release GH formulation consisting of microparticles containing GH incorporated into sodium hyaluronate and dispersed in an oil base of medium-chain triglycerides. The first study with weekly depot formulation was performed in 155 adults with GH deficiency (Biller et al. 2011). LB03002 dose was adjusted to achieve a serum IGF-1 value between −0.5 and +1.5 SDS at 4 days post-dosing. Final dose of the GH weekly depot preparation was 4.31 ± 1.77 mg/week (men), 4.34 ± 1.64 mg/week (women without oral oestrogen), and 6.45 ± 2.44 mg/week (women on oral oestrogen).

TransCon GH. Sustained-release GH prodrug consisting of recombinant human GH transiently bound to a carrier molecule (methoxy polyethylene glycol-mPEG) via a proprietary TransCon linker. Over a 1-week period, TransCon frees fully active GH via auto-hydrolysis of TransCon linker (nonenzymatic cleavage). This allows PEG elimination from the body via renal filtration. GH-TransCon phase 2 trial in adults with GH deficiency is completed. A dose-dependent increase in GH peak exposure is shown without GH accumulation (Hoybye et al. 2017).

25.12.2 Active GH Analogues: Modified GH Molecule

Permanent pegylation-protein enlargement by attaching polyethylene glycol (PEG) to GH. Many PEGylated pharmacological compounds have been approved by regulatory agencies. Currently, the only available PEGylated-GH is Jintrolong which has been developed and approved in China (Hou et al. 2016). Major drawback is safety concern (PEGylated GH is taken up by reticuloendothelial cells and choroid plexus ependymal cells-vacuolation has been observed within cells

with GH receptors). Furthermore, local tolerability issues with permanently PEGylated GH were reported (including lipoatrophy).

MOD-4023 Conjugation of CTP to GH. Carboxy-terminus peptide (CTP) is a natural peptide created during evolution to enhance longevity of hormone hCG. CTP increases protein circulation time. MOD-4023 is a result of conjugation of CTP to GH. High dose of MOD 4023 has low affinity for GH receptor (eightfold). IGF1 was monitored every 2 weeks, 4 days after dose. Single weekly injection of MOD-4023 can replace 7 consecutive daily GH injections (Strasburger et al. 2017). The proposed MOD 4023 dose range is 1.23–5.6 mg/week. Data confirm safety.

GH fusion protein Somavartan (VRS-317) is a fusion protein produced in *Escherihia coli*. GH molecule is fused to two pharmacologically inactive naturally occurring hydrophilic amino acids (XTEN1, XTEN2) with an extended elimination time ($T½$ 110 h). Modification of GH reduces the affinity with receptors (for VRS-317 eleven-fold), but the prolonged exposure time achieved a greater potency. In a study in adults with GHD, higher doses of somavartan (VRS-317), male sex, and young age were all associated with greater IGF-1 responses (Yuen et al. 2013). In a phase 3 Velocity trial of somavartan twice monthly at 12 months, height velocity in children was 9.4 cm versus 10.7 cm for Genotropin daily, thus disappointingly missing the endpoint of noninferiority (Versatis press release September 2017).

Other formulations based on modified GH such as TV-1106 (GH fused to albumin) produced by Teva Pharmaceutical, LAPS-rhGH/HM 10560A (GH fused to an Fc fragment) produced by Hanmi Pharmaceutical, NNC0 195-0092 (Somapacitan-mutated GH attached to an albumin affinity tag binding reversibly to albumin) produced by Novo Nordisk are still under evaluation in phase 2 or phase 3 or are discontinued (TV-1106 due to high immunogenic potential).

25.13 Conclusions

This chapter presented an overview of causes and clinical presentation of hypopituitarism and hormone replacement therapy in patients with pituitary conditions. The reader is encouraged to refer to relevant chapters in the textbook regarding hormone deficiencies and replacement therapies. The second part of the chapters focused on GH deficiency and treatment for adult patients. New developments with long-acting GH formulations were also discussed. It is anticipated that long-acting GH compounds will improve adherence to GH replacement therapy. Long-term surveillance registries are needed to confirm the efficacy and address unique safety issues of these formulations. Clinical data are still very limited, and many questions remain to be answered.

Acknowledgments Special thanks to Pat McBride, Head of Patient and Family Services, The Pituitary Foundation (https://www.pituitary.org.uk), for her contribution to this chapter with case studies, patient resources, and information on the Patient Advocacy Group

References

Abdi L, Sahnoun-Fathallah M, Morange I, Albarel F, Castinetti F, Giorgi R, et al. A monocentric experience of growth hormone replacement therapy in adult patients. Ann Endocrinol. 2014;75(3):176.

Adelman DT, Liebert KJ, Nachtigall LB, Lamerson M, Bakker B. Acromegaly: the disease, its impact on patients, and managing the burden of long-term treatment. Int J Gen Med. 2013;6:31–8.

Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, et al. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. Clin Endocrinol (Oxf). 2007;66(1):72–7.

Ahmid M, Perry CG, Ahmed SF, Shaikh MG. Growth hormone deficiency during young adulthood and the benefits of growth hormone replacement. Endocr Connect. 2016a;5(3):R1–r11.

Ahmid M, Fisher V, Graveling AJ, McGeoch S, McNeil E, Roach J, et al. An audit of the management of childhood-onset growth hormone deficiency during young adulthood in Scotland. Int J Pediatr Endocrinol. 2016b;2016:6.

Aimaretti G, Attanasio R, Cannavo S, Nicoletti MC, Castello R, Di Somma C, et al. Growth hormone treatment of adolescents with growth hormone deficiency (GHD) during the transition period: results of a survey among adult and paediatric endocrinologists from Italy. Endorsed by SIEDP/ISPED, AME, SIE, SIMA. J Endocrinol Invest. 2015;38(3):377–82.

van Aken MO, Lamberts SW. Diagnosis and treatment of hypopituitarism: an update. Pituitary. 2005;8(3-4):183–91.

Andela CD, Scharloo M, Pereira AM, Kaptein AA, Biermasz NR. Quality of life (QoL) impairments in

patients with a pituitary adenoma: a systematic review of QoL studies. Pituitary. 2015;18(5):752–76.
Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.
Biller BM, Ji HJ, Ahn H, Savoy C, Siepl EC, Popovic V, et al. Effects of once-weekly sustained-release growth hormone: a double-blind, placebo-controlled study in adult growth hormone deficiency. J Clin Endocrinol Metab. 2011;96(6):1718–26.
Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B, et al. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 2010;72(3):297–304.
Brignardello E, Felicetti F, Castiglione A, Fortunati N, Matarazzo P, Biasin E, et al. GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. J Endocrinol Invest. 2014;38(2):171–6.
Burman P, Mattsson AF, Johannsson G, Hoybye C, Holmer H, Dahlqvist P, et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab. 2013;98(4):1466–75.
Burt MG, Ho KKY. Chapter 11 - Hypopituitarism and Growth Hormone Deficiency. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, et al., editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: W.B. Saunders; 2016. p. 188–208.e5.
Chapman SC, S L CP, Horne R. Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. Clin Endocrinol (Oxf). 2016;84:664–71.
Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. Eur J Endocrinol. 2016;174(6):C1–8.
Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152(2):165–70.
Cook DM, Ludlam WH, Cook MB. Route of estrogen administration helps to determine growth hormone (GH) replacement dose in GH-deficient adults. J Clin Endocrinol Metab. 1999;84(11):3956–60.
Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. NPJ Prim Care Respir Med. 2015;25:15026.
van der Meij N, van Leeuwaarde RS, Vervoort SCJM, Zelissen PMJ. Self-management support in patients with adrenal insufficiency. Clin Endocrinol. 2016; https://doi.org/10.1111/cen.13083.
Dwyer A, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis. 2014;9:83.
van Eck JP, Gobbens RJ, Beukers J, Geilvoet W, van der Lely AJ, Neggers SJ. Much to be desired in self-management of patients with adrenal insufficiency. Int J Nurs Pract. 2014; https://doi.org/10.1111/ijn.12368.
Ehrnborg C, Hakkaart-Van Roijen L, Jonsson B, Rutten FF, Bengtsson BA, Rosen T. Cost of illness in adult patients with hypopituitarism. Pharmacoeconomics. 2000;17(6):621–8.
Fernandez-Rodriguez E, Lopez-Raton M, Andujar P, Martinez-Silva IM, Cadarso-Suarez C, Casanueva FF, et al. Epidemiology, mortality rate and survival in a homogeneous population of hypopituitary patients. Clin Endocrinol (Oxf). 2013;78(2):278–84.
Filipsson H, Johannsson G. GH replacement in adults: interactions with other pituitary hormone deficiencies and replacement therapies. Eur J Endocrinol. 2009;161(Suppl 1):S85–95.
Flemming TG, Kristensen LO. Quality of self-care in patients on replacement therapy with hydrocortisone. J Intern Med. 1999;246(5):497–501.
Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(11):3888–921.
Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency - a worldwide patient survey. BMC Endocr Disord. 2012;12:8.
Gasco V, Prodam F, Grottoli S, Marzullo P, Longobardi S, Ghigo E, et al. GH therapy in adult GH deficiency: a review of treatment schedules and the evidence for low starting doses. Eur J Endocrinol. 2013;168(3):R55–66.
George J, Kong DC, Thoman R, Stewart K. Factors associated with medication nonadherence in patients with COPD. Chest. 2005;128(5):3198–204.
Giavoli C, Libé R, Corbetta S, Ferrante E, Lania A, Arosio M, et al. Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. J Clin Endocrinol Metabol. 2004;89(11):5397–401.
Gurel MH, Bruening PR, Rhodes C, Lomax KG. Patient perspectives on the impact of acromegaly: results from individual and group interviews. Patient Prefer Adherence. 2014;8:53–62.
Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. J Clin Endocrinol Metab. 2007;92(10):3912–22.
Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100(2):407–16.

Ho KK. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157(6):695–700.

Hou L, Chen ZH, Liu D, Cheng YG, Luo XP. Comparative pharmacokinetics and pharmacodynamics of a PEGylated recombinant human growth hormone and daily recombinant human growth hormone in growth hormone-deficient children. Drug Des Devel Ther. 2016;10:13–21.

Hoybye C, Pfeiffer AF, Ferone D, Christiansen JS, Gilfoyle D, Christoffersen ED, et al. A phase 2 trial of long-acting TransCon growth hormone in adult GH deficiency. Endocr Connect. 2017;6(3):129–38.

Janssen YJ, Helmerhorst F, Frolich M, Roelfsema F. A switch from oral (2 mg/day) to transdermal (50 microg/day) 17beta-estradiol therapy increases serum insulin-like growth factor-I levels in recombinant human growth hormone (GH)-substituted women with GH deficiency. J Clin Endocrinol Metab. 2000;85(1):464–7.

Jonsson B, Nilsson B. The impact of pituitary adenoma on morbidity. Increased sick leave and disability retirement in a cross-sectional analysis of Swedish national data. Pharmacoeconomics. 2000;18(1):73–81.

Kepicoglu H, Hatipoglu E, Bulut I, Darici E, Hizli N, Kadioglu P. Impact of treatment satisfaction on quality of life of patients with acromegaly. Pituitary. 2014;17(6):557–63.

Lee P, Ho K. Hypopituitarism and growth hormone deficiency. In: Jameson L, De Groot L, editors. Endocrinology: adult and pediatric. Neuroendocrinology and the Pituitary gland. 6th ed. Amsterdam: Elsevier Health Sciences; 2010.

Linn AJ, van Weert JC, van Dijk L, Horne R, Smit EG. The value of nurses' tailored communication when discussing medicines: Exploring the relationship between satisfaction, beliefs and adherence. J Health Psychol. 2016;21:798–807.

Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med. 1989;70(262):145–60.

Llahana S, Conway G. Knowledge of testosterone replacement therapy is significantly correlated with patient satisfaction suggesting greater need for education. 8th European Congress of Endocrinology, Glasgow, UK. Endocrine Abstracts 2006:11 P201.

Llahana S, Conway G, Mumuni A, Baldeweg S, Osz M, Horne R, editors. Patients' beliefs and concerns about growth hormone replacement therapy are associated with their satisfaction with treatment, medication side effects and quality of life. In: 18th International congress of endocrinology, 1–4 Dec 2018, Cape Town, South Africa; 2018.

Losa M, Scavini M, Gatti E, Rossini A, Madaschi S, Formenti I, et al. Long-term effects of growth hormone replacement therapy on thyroid function in adults with growth hormone deficiency. Thyroid. 2008;18(12):1249–54.

Mackenzie S, Craven T, Gattamaneni HR, Swindell R, Shalet SM, Brabant G. Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metabol. 2011;96(9):2756–61.

Martinez-Momblan MA, Gomez C, Santos A, Porta N, Esteve J, Ubeda I, et al. A specific nursing educational program in patients with Cushing's syndrome. Endocrine. 2016;53:199–209.

McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L, et al. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. Qual Life Res. 1999;8(4):373–83.

Melmed S. Idiopathic adult growth hormone deficiency. J Clin Endocrinol Metab. 2013;98(6):2187.

Melmed S, Jameson JL. Hypopituitarism, chapter 4. In: Jameson JL, editor. Harrison's endocrinology. 4th ed. New York: McGraw Hill Education; 2017. p. 25–34.

Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(6):1587–609.

NICE. Human growth hormone (somatropin) in adults with growth hormone deficiency. London: National Institute for Clinical Excellence; 2003.

Ntali G, Capatina C, Fazal-Sanderson V, Byrne JV, Cudlip S, Grossman AB, et al. Mortality in patients with nonfunctioning pituitary adenoma is increased: systematic analysis of 546 cases with long follow-up. Eur J Endocrinol. 2015;174(2):137–45.

Olsson DS, Nilsson AG, Bryngelsson IL, Trimpou P, Johannsson G, Andersson E. Excess mortality in women and young adults with nonfunctioning pituitary adenoma: a Swedish Nationwide Study. J Clin Endocrinol Metab. 2015;100(7):2651–8.

Omori K, Nomura K, Shimizu S, Omori N, Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. Endocr J. 2003;50(6):745–52.

Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab. 2015;100(4):1405–11.

Patterson BC, Chen Y, Sklar CA, Neglia J, Yasui Y, Mertens A, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report From the Childhood Cancer Survivor Study. J Clin Endocrinol Metabol. 2014;99(6):2030–7.

Peacey SR, Pope RM, Naik KS, Hardern RD, Page MD, Belchetz PE. Corticosteroid therapy and intercurrent illness: the need for continuing patient education. Postgrad Med J. 1993;69(810):282.

Pekic S, Popovic V. GH therapy and cancer risk in hypopituitarism: what we know from human studies. Eur J Endocrinol. 2013;169:R89–97.

Phelan N, Conway SH, Llahana S, Conway GS. Quantification of the adverse effect of ethinylestradiol containing oral contraceptive pills when used in conjunction with growth hormone replace-

ment in routine practice. Clin Endocrinol (Oxf). 2012;76(5):729–33.
Prabhakar VKB, Shalet SM. Aetiology, diagnosis, and management of hypopituitarism in adult life. Postgrad Med J. 2006;82(966):259–66.
Ragnarsson O, Mattsson AF, Monson JP, Filipsson Nystrom H, Akerblad AC, Koltowska-Haggstrom M, et al. The relationship between glucocorticoid replacement and quality of life in 2737 hypopituitary patients. Eur J Endocrinol. 2014;171(5):571–9.
Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol (Oxf). 2001;55(6):735–40.
Repping-Wuts HJWJ, Stikkelbroeck NMML, Noordzij A, Kerstens M, Hermus ARMM. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. Eur J Endocrinol. 2013;169(1):17–22.
Rosenfeld G, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract. 2008;14(2):143.
Ruiz MA, Pardo A, Rejas J, Soto J, Villasante F, Aranguren JL. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). Value Health. 2008;11(5):913–26.
Schoenfeld MJ, Shortridge E, Cui Z, Muram D. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims analysis. J Sex Med. 2013;10(5):1401.
Schulz J, Frey KR, Cooper M, Zopf K, Ventz M, Diederich S, et al. Reduction in daily hydrocortisone dose improves bone health in primary adrenal insufficiency. Eur J Endocrinol. 2016; https://doi.org/10.1530/eje-15-1096.
Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metabol. 2002;87(7):3136–41.
Sklar CA, Antal Z, Chemaitilly W, Cohen LE, Follin C, Meacham LR, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:2761–84.
Sprogoe K, Mortensen E, Karpf DB, Leff JA. The rationale and design of TransCon Growth Hormone for the treatment of growth hormone deficiency. Endocr Connect. 2017;6(8):R171–R81.
Stochholm K, Kiess W. Long-term safety of growth hormone-a combined registry analysis. Clin Endocrinol (Oxf). 2018;88(4):515–28.
Strasburger CJ, Vanuga P, Payer J, Pfeifer M, Popovic V, Bajnok L, et al. MOD-4023, a long-acting carboxy-terminal peptide-modified human growth hormone: results of a Phase 2 study in growth hormone-deficient adults. Eur J Endocrinol. 2017;176(3):283–94.
Tiemensma J, Andela D, Pereira M, Romijn A, Biermasz R, Kaptein A. Patients with adrenal insufficiency hate their medication: concerns and stronger beliefs about the necessity of hydrocortisone intake are associated with more negative illness perceptions. J Clin Endocrinol Metab. 2014;99(10):3668.
Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am. 2008;37(1):235–61. x
Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M, Ho KK. Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. Am J Physiol Endocrinol Metab. 2001;281(6):E1191–6.
Woodmansee WW, Zimmermann AG, Child CJ, Rong Q, Erfurth EM, Beck-Peccoz P, et al. Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS. Eur J Endocrinol. 2013;168(4):565–73.
Yuen CJ, Conway S, Popovic V, Merriam R, Bailey T, Hamrahian H, et al. A long-acting human growth hormone with delayed clearance (VRS-317): results of a double-blind, placebo-controlled, single ascending dose study in growth hormone-deficient adults. J Clin Endocrinol Metab. 2013;98(6):2595.
Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. Med Care. 2009;47(8):826–34.

Key Reading

1. Burt MG, Ho KKY. Chapter 11 - Hypopituitarism and growth hormone deficiency. In: Jameson JL, de Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, Potts JT, Weir GC, editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: W.B. Saunders; 2016.
2. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152:165–70.
3. Fleseriu M, Hashim IA, karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888–921.
4. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1587–609.
5. Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am. 2008;37:235–61.

Part IV

The Thyroid Gland

Violet Fazal-Sanderson

Thyroid Anatomy and Physiology

26

Chloe Broughton and Bushra Ahmad

Contents

26.1 **Anatomy** 499
26.1.1 Embryology and Development 499
26.1.2 Location 499
26.1.3 Blood and Nerve Supply 499

26.2 **Histology** 500

26.3 **Physiology** 500
26.3.1 Thyroid Hormone Synthesis, Storage, and Secretion 500
26.3.2 Peripheral Conversion of Thyroid Hormone 502
26.3.3 Thyroid Hormone Transport and Metabolism 502
26.3.4 Thyroid Hormone Action 502
26.3.5 Regulation of the Thyroid Axis 502

26.4 **Conclusions** 503

References 503

Abstract

The term anatomy can be defined as the study of structure and form of an organism including its body parts, while physiology refers to the study of how these structures function and work.

This chapter outlines the anatomy of the thyroid gland, including the embryology and development, location, blood and nerve supply, and histology. It then details thyroid hormone physiology including thyroid hormone synthesis and secretion, transport and metabolism, and mechanism of action. It concludes with discussion of the thyroid hormone axis.

Relevant knowledge and understanding is fundamental to the understanding of thyroid disorders and key to underpinning care in clinical decision-making. Applying accurate knowledge of thyroid anatomy and physiology enables clinical practitioners to care, treat, and manage patients with thyroid disorders more effectively.

C. Broughton
Specialist Registrar in Endocrinology and Diabetes, Southmead Hospital, North Bristol NHS Trust, Bristol, UK
e-mail: chloebroughton@nhs.net

B. Ahmad (✉)
Consultant Endocrinologist and Senior Honorary Clinical Lecturer, Bristol Royal Infirmary, University of Bristol, Bristol, UK
e-mail: bushra.ahmad@nhs.net

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_26

Keywords
Thyroxine (T4) · Triiodothyronine (T3) Anatomy · Thyroglobulin-iodine

Abbreviations

T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroid-binding globulin
TPO	Thyroperoxidase
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
TTR	Transthyretin

Key Terms

- **Calcitonin:** A protein hormone secreted by c cells in the thyroid gland.
- **Deiodinase:** An enzyme involved in the activation or deactivation of thyroid hormones.
- **Enzyme:** A substance that acts as a catalyst of a biochemical reaction.
- **Gland:** A group of cells secreting a particular chemical substance.
- **Hormone:** A chemical messenger that travels in the blood stream to target tissues or organs. It is produced by endocrine glands.
- **Hypothalamus:** A complex region of the brain lying above the pituitary gland.
- **Isthmus:** A small piece of thyroid tissue connecting the right and left lobes of the thyroid gland.
- **Pituitary gland:** A small gland located behind the eyes at the base of the brain. It secretes TSH, as well as other hormones.
- **Thyroglobulin:** A protein produced by the thyroid gland.
- **Thyroid:** An endocrine gland located in the anterior neck that produces thyroid hormones, thyroxine (T4) and triiodothyronine (T3).
- **Thyroid-stimulating hormone:** A hormone produced by the hypothalamus and secreted by the anterior pituitary gland. It stimulates the thyroid gland.
- **Thyroid-binding globulin:** A protein in the blood that binds with thyroxine (T4) and triiodothyronine (T3).
- **Thyroperoxidase:** An enzyme in the thyroid gland that plays an important role in the production of thyroid hormones.
- **Thyrotropin-releasing hormone:** A hormone that stimulates the release of TSH and prolactin by the pituitary gland.
- **Thyroxine:** The main hormone produced by the thyroid gland.
- **Transthyretin:** A protein in the blood that binds with thyroxine (T4) and triiodothyronine (T3).
- **Triiodothyronine:** The second hormone produced by the thyroid gland.

Key Points

- The thyroid gland develops as a diverticulum from the endoderm of the floor of the pharynx.
- The thyroid gland lies in the anterior neck. It is comprised of two lateral lobes joined in the midline by the isthmus. The thyroid gland is highly vascular and receives its arterial blood supply from the right and left superior and inferior thyroid arteries.
- Thyroid follicles are filled with colloid, the main constituent of which is thyroglobulin. Follicular cells surround the follicles and synthesise and secrete thyroid hormones. Parafollicular cells are found in-between follicles and secrete calcitonin.
- The primary function of the thyroid gland is the production of thyroid hormones: thyroxine (T4) and triiodothyronine (T3). The thyroid gland is the only source of T4 and secretes 20% of circulating T3. T4 and T3 act via nuclear receptors inside target cells.
- Thyroid hormones in the blood are tightly controlled by feedback mechanisms involving the hypothalamus-pituitary-thyroid axis.

26.1 Anatomy

The thyroid gland is one of the largest endocrine glands in the body, weighing between 10 and 20 g in adults (Pankow et al. 1985). It is larger in men than women and increases with age and body weight. It is one of the most vascular organs in the body.

26.1.1 Embryology and Development

The thyroid gland is the first endocrine gland to develop, with development occurring from the third week of gestation. It develops as a diverticulum from the endoderm of the floor of the pharynx. The diverticulum becomes bilobed; it descends down the neck and fuses with part of the fourth pharyngeal pouch. It is attached to the floor of the pharynx at this stage by the thyroglossal duct, which is usually obliterated after its decent. In about 55% of individuals, the distal portion persists as the pyramidal lobe. Other portions of the duct may persist as thyroglossal cysts. These present as a mass in the middle and can be excised surgically. By the seventh week of gestation, it has reached its final position anterior to the trachea.

The ultimobranchial body from the fifth pharyngeal pouch becomes infiltrated by neural crest cells and is incorporated into the developing thyroid gland. These cells migrate into the upper third of the thyroid lobes and are the source of the neuroendocrine parafollicular cells (C cells). The C cells make up 0.1% of the thyroid mass and are the source of calcitonin. They give rise to medullary thyroid cancer when they undergo malignant change.

The foetal thyroid begins to concentrate and organifies iodine by 10–12 weeks gestation. The foetal pituitary-thyroid axis is a functional unit distinct from that of the mother by 18–20 weeks gestation. The foetal production of thyroxine (T4) reaches a clinically significant level by 18–20 weeks gestation, but foetal triiodothyronine (T3) production remains low until 30 weeks gestation.

26.1.2 Location

The thyroid gland is located in the anterior neck. It sits just below the larynx and lies against the anterolateral portion of the trachea and oesophagus. It is bordered laterally by the carotid sheath, containing the carotid artery, internal jugular vein, vagus nerve, and deep cervical lymph nodes. Anteriorly, the sternocleidomastoid and the three strap muscles (sternohyoid, sternothyroid, and the superior belly of the omohyoid) overlie the gland.

The thyroid gland is often described as a butterfly-shaped structure. It is comprised of two lateral lobes joined in the midline by the isthmus. Each lobe is about 5 cm long, 3 cm wide, and 2 cm thick (Bliss et al. 2000). The isthmus is a narrow band of thyroid tissue overlying the second and third tracheal rings. A pyramidal lobe is often present (55% of cadaveric specimens (Braun et al. 2007)) projecting upwards from the isthmus.

26.1.3 Blood and Nerve Supply

The thyroid gland secretes thyroid hormones directly into the blood, and therefore, needs to be highly vascular. Each lobe of the thyroid gland receives its arterial blood supply from the right and left superior and inferior thyroid arteries. The superior thyroid artery arises from the external carotid artery and supplies the superior and anterior portions of the gland. The inferior thyroid artery is a branch of the thyrocervical trunk, which arises from the subclavian artery and supplies the posterior and inferior portions of the gland. There are three main veins draining the thyroid gland: superior, middle, and inferior thyroid veins (Fig. 26.1).

The thyroid gland receives parasympathetic nerve innervation from the recurrent laryngeal nerve and the superior laryngeal nerve. However, these nerves do not control endocrine secretion—this is under control of the pituitary gland. It is essential that these nerves are identified during surgery to prevent damage or ligation of the nerves, resulting in paresis or paralysis of the vocal cords.

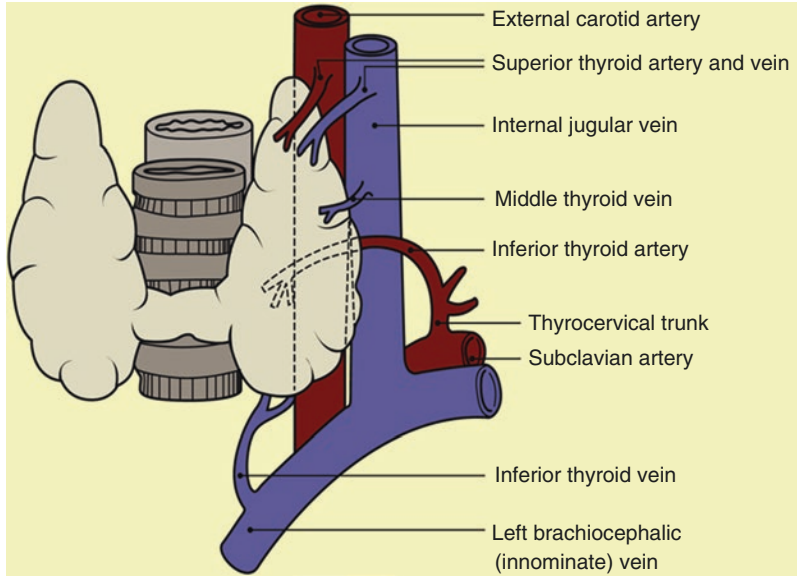


Fig. 26.1 The thyroid gland with its blood supply. From: Ritchie JE, Balasubramanian SP. Anatomy of the pituitary, thyroid, parathyroid, and adrenal glands. Surgery (Oxford) Volume 32, Issue 10, October 2014, Pages 499–503

26.2 Histology

Under the microscope, there are three main features of the thyroid gland: follicles, follicular cells, and parafollicular cells (Fawcett and Jensh 2002). Follicles are roughly spherical cavities filled with colloid, a proteinaceous deposit of thyroid hormone precursor. The major constituent of colloid is a large glycoprotein called thyroglobulin. Surrounding the follicles is a single layer of epithelial cells known as follicular cells. These cells are responsible for synthesising and secreting thyroid hormones (T3 and T4). Follicular cells are normally cuboidal in shape, but become columnar when stimulated and squamous when inactive. Parafollicular cells or C cells are found in between follicles and secrete the hormone calcitonin.

Increased thyroid activity over a period of time is usually associated with a decrease in colloid and a reduction in follicular volume. Follicular cells hypertrophy and increase in number; they also become columnar and may proliferate into the colloid. Decreased thyroid activity is associated with a flattening of the follicular cells.

26.3 Physiology

The primary function of the thyroid gland is the production of thyroid hormones. There are two biologically active thyroid hormones: thyroxine (T4) and triiodothyronine (T3).

26.3.1 Thyroid Hormone Synthesis, Storage, and Secretion

The following steps are involved in the synthesis, storage, and secretion of thyroid hormones (Fig. 26.2):

1. Thyroglobulin production by follicular cell and release into colloid by exocytosis.
2. Dietary iodine ingestion, iodine uptake by follicular cell from the blood and transferred to colloid.
3. Oxidation of iodine and iodination of thyroglobulin tyrosine residues (attachments of iodine to tyrosine on the thyroglobulin in colloid).
4. Coupling processes between the iodinated tyrosine molecules to form T4 and T3.

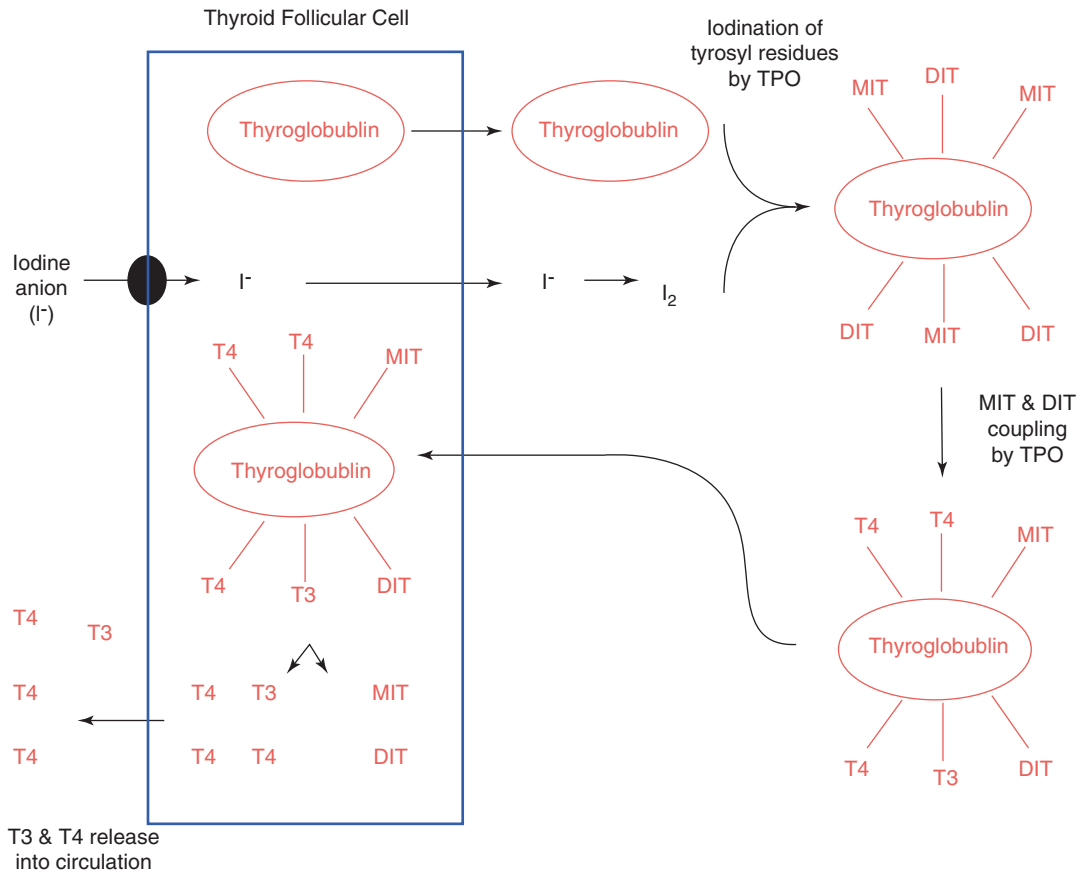


Fig. 26.2 Thyroid hormone synthesis, storage, and secretion

5. Secretion (upon stimulation) of T4 and T3 occurs by endocytosis of a piece of colloid, uncoupling of T4 and T3 and diffusion out of the follicular cell into the blood.

Iodine is essential for normal thyroid function and can be obtained only by consumption of food containing iodine or to which it is added. Iodine is present naturally in soil and seawater. The availability of iodine in food differs in various regions of the world. Iodine is found in seafood, kelp, dairy products and eggs, iodised salt, or dietary supplements as a trace mineral. The recommended minimum intake is 150 μg per day. Dietary iodine reaches the circulation as iodine anion (I^-). The thyroid gland transports I^- to the site of hormone synthesis. I^- accumulation in the thyroid is an active transport process that is stimulated by TSH.

Iodine anion must be oxidised to be able to iodinate tyrosyl residues of thyroglobulin. Iodination of the tyrosyl residues then forms monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are then coupled to form either T3 or T4. Both reactions are catalysed by TPO.

Thyroperoxidase (TPO) catalyses the oxidation steps involved in iodine anion activation, iodination of thyroglobulin tyrosyl residues, and coupling of iodotyrosyl residues. TPO has binding sites for iodine anion and thyroxine. Furthermore, TPO also uses H2O2 as the oxidate to activate iodine anion to hypoiodate (OI−), the iodination species.

T3 and T4 are synthesised and stored within the thyroglobulin molecule. Proteolysis is an essential step for releasing the hormones. To liberate T4 and T3, thyroglobulin is resorbed from

the follicular cells in the form of colloid droplets, which fuse with lysosomes to form phagolysosomes. Thyroglobulin is hydrolysed to T4 and T3, which are then secreted into the circulation.

26.3.2 Peripheral Conversion of Thyroid Hormone

The thyroid is the only source of T4. The thyroid secretes 20% of circulating T3. The remainder is generated in extra glandular tissues by the conversion of T4 to T3 by deiodinases. There are three iodothyroinine deiodinases (D1-D3) which regulate the availability of T3 to the cells. Type 1 deiodinase is located primarily in the thyroid, liver, and kidneys. This is considered responsible for the production of the majority of circulating T3. Type 2 deiodinase is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Type 1 and 2 deiodinase result in generation of T3, whereas D3 irreversible inactivates T4 and T3, resulting in production of rT3 and T2. The relative activities of D2 and D3 enzymes in T3 target cells regulate the availability of the active hormone T3 to the nucleus. Type 1 deiodinase has a relatively low affinity for T4, whereas type 2 deiodinase has a much higher affinity.

26.3.3 Thyroid Hormone Transport and Metabolism

About 20 times more T4 is secreted from the thyroid gland than T3. Both T4 and T3 are highly lipophilic, and once in the blood, immediately bind to proteins. 99.98% of T4 and 99.7% of T3 are protein-bound. 70–80% of T4 is bound to thyroid-binding globulin, a thyroid hormone-specific protein. The remainder is bound to transthyretin (TTR) and albumin (Benvenga 2005). T3 is bound 10–20 times less avidly by TBG. T3 is not bound significantly by TTR. Only free T4 and T3 hormones are biologically active and it's the free hormones that produce the effects of thyroid hormones on peripheral tissues and pituitary feedback mechanism. Therefore, free thyroid hormone concentration correlates more closely with the metabolic state rather than the total hormone concentration.

26.3.4 Thyroid Hormone Action

T4 and T3 enter cells by both passive diffusion and active transport via specific transporters, for example, monocarboxylate 8 (MCT8) transporter (Friesema et al. 2003). Once inside the cell, thyroid hormones act via nuclear receptors, thyroid hormone receptors (TR's) α and β (Flamant et al. 2006). The expression of TRα and TRβ varies between tissues, and hence, their roles are tissue-specific. TRα is expressed in the brain, kidneys, gonads, muscle, and heart and mediates effects of T3 in these tissues. TRβ is expressed in the hypothalamus, pituitary, and liver, and therefore, has a role in the feedback control of the hypothalamic pituitary-thyroid axis. The activated receptors can either stimulate or inhibit gene transcription.

26.3.5 Regulation of the Thyroid Axis

The thyroid axis is a classic example of an endocrine feedback loop (Fig. 26.3). Thyroid-releasing hormone (TRH) is secreted by the hypothalamus. This stimulates the pituitary to produce TSH. TSH stimulates the thyroid gland to synthesis and secrete thyroid hormones, mainly T4 but also T3. Thyroid hormones feedback at both the pituitary and hypothalamus to inhibit production of TRH and TSH, respectively, predominantly through thyroid hormone receptor β2. The levels of thyroid hormones in the blood are tightly controlled by these feedback mechanisms in the hypothalamic-pituitary-thyroid axis.

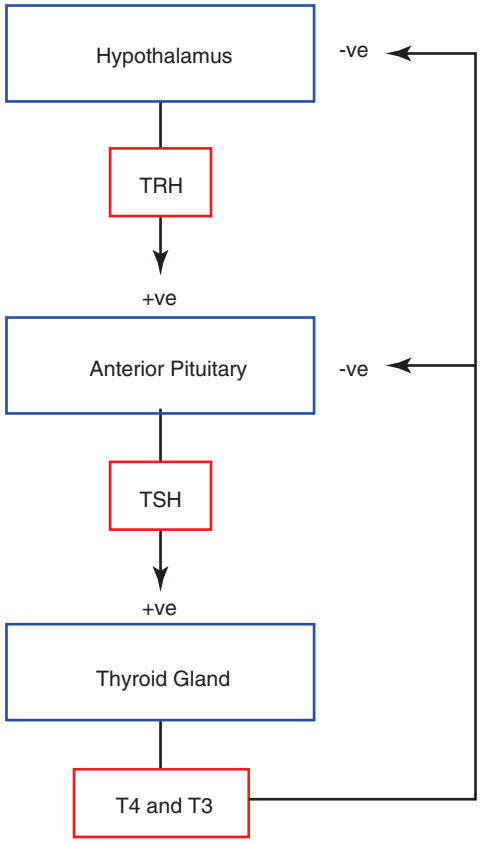


Fig. 26.3 Hypothalamic pituitary-thyroid axis

26.4 Conclusions

The thyroid gland is a butterfly-shaped gland located in the anterior neck. It is comprised of two lateral lobes joined in the midline by the isthmus and is highly vascular. Thyroid follicular cells synthesise and secrete thyroid hormones. There are two biologically active thyroid hormones: thyroxine (T4) and triiodothyronine (T3). T4 and T3 act via nuclear receptors within target cells to regulate metabolism. The levels of thyroid hormones in the blood are tightly controlled by these feedback mechanisms in the hypothalamic-pituitary-thyroid axis.

References

Benvenga S. Thyroid hormone transport proteins and the physiology of hormone binding. In: Braverman LE, Utiger RD, editors. The thyroid: fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 97.

Bliss RD, Gauger PG, Delbridge LW. Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. World J Surg. 2000;24:891.

Braun EM, Windisch G, Wolf G, et al. The pyramidal lobe: clinical anatomy and its importance in thyroid surgery. Surg Radiol Anat. 2007;29:21.

Fawcett D, Jensh R. Bloom & Fawcett's concise histology. New York: Arnold Publishers; 2002. p. 257–8. ISBN 0-340-80677-X.

Flamant F, Baxter JD, Forrest D, Refetoff S, Samuels H, Scanlan TS, Vennstrom B, Samarut J. International Union of Pharmacology. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. Pharmacol Rev. 2006;58(4):705–11.

Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem. 2003;278(41):40128–35.

Pankow BG, Michalak J, McGee MK. Adult human thyroid weight. Health Phys. 1985;49:1097.

Thyroid Investigations

27

Victoria J. Stokes, Rabia Arfan, Theingi Aung, and Violet Fazal-Sanderson

Contents

27.1 **Introduction** 508

27.2 **Clinical Assessment of a Patient with Thyroid Disease** 508

27.3 **Thyroid Hormones** 508
27.3.1 Thyroid Hormones and Homeostasis 508
27.3.2 Caution When Interpreting Thyroid Function Tests 510
27.3.3 Thyroid Autoantibodies 510

27.4 **Imaging** 511

27.5 **Ultrasound** 511
27.5.1 Characteristics of Nodules Used for Identifying Cancers 512
27.5.2 The Use of Ultrasound in Assessing for Fetal Thyroid Dysfunction 513

27.6 **Computed Tomography** 513

27.7 **Magnetic Resonance Imaging** 513

27.8 **Nuclear Imaging** 513

27.9 **Iodine-123 or Iodine-131** 513

V. J. Stokes
Endocrinology and Metabolism, Oxford Radcliffe Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, UK
e-mail: victoria.stokes4@nhs.net

R. Arfan
Thames Valley Deanary, Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK

T. Aung · V. Fazal-Sanderson (✉)
Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK
e-mail: Theingi.aung@royalberkshire.nhs.uk; Violet.sanderson@royalberkshire.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_27

27.10 **Technetium-99m Pertechnetate** 514
27.11 **Gallium-67** 514
27.12 **Role of Functional Imaging for Thyroiditis** 514
27.13 **Other Thyroid Investigations in Special Circumstances** 514
27.13.1 Heterophile Antibody Interference 514
27.13.2 Resistance to Thyrotropin (TSH) and Resistance to Thyrotropin-Releasing Hormone (TRH) 515
27.13.3 Resistance to Thyrotropin-Releasing Hormone (TRH) 515
27.14 **TSH-oma** 515
27.14.1 Dynamic Testing 516
27.14.2 Imaging 516
27.14.3 Treatment 516
27.15 **Conclusions** 516
References 517

Abstract

Thyroid dysfunction may result in inappropriate hormone secretion, mass effects, or a combination of both problems. Taking a relevant history and performing a thorough examination is the first step to reaching the correct diagnosis. Investigations should be selected according to the clinical findings and may be used to confirm clinical suspicions, to rule out serious pathology, and to establish the severity of the dysfunction. Blood tests are usually the first line, with biochemistry to confirm the functional status of the gland and, if appropriate, testing for autoantibodies to confirm autoimmunity. Ultrasound is the preferred method for detecting intra-thyroid lesions, with a sensitivity of 2 mm for cystic, and 3 mm for solid lesions. CT and MRI are of limited utility outside of tumour staging. Functional imaging is useful for differentiating thyroiditis and hyperthyroidism due to autoimmunity, toxic nodule, or multinodular goitre. This chapter describes the clinical features of different thyroid disorders; discusses thyroid investigations and their clinical utility; and highlights specific tests used for specific disorders.

Keywords

Thyroid hormone homeostasis · Imaging
Clinical assessment · Thyroid autoantibodies
TSH-oma

Abbreviations

bHCG	Beta human chorionic gonadotropin
CT	Computer tomography
FNA/C	Fine needle aspiration/cytology
fT3	Triiodothyronine
fT4	Thyroxine
MRI	Magnetic resonance imaging
RTSH	Resistance to thyroid stimulating hormone
TG Ab	Antithyroglobulin antibody
TIRADS	Thyroid imaging reporting and data system
TPOAbs	Antithyroid peroxidase antibody
TSH	Thyroid stimulating hormone
TSHoma	Thyroid stimulating hormone secreting pituitary adenoma
TSH receptor antibody	Thyroid stimulating hormone receptor antibody
US	Ultrasound

Key Terms

- **CT:** Computed tomography is a useful imaging technique that is used, for example, to evaluate any thyroid retrosternal or retro-tracheal extension of an enlarged thyroid, and also can be used to look for thyroid cancer spread into distant organs.
- **FNAB:** Fine needle aspiration biopsy is a procedure by which a fine needle is inserted into a mass, for example, a thyroid nodule/s, and is used to draw tissue cells for diagnostic purposes.
- **MRI:** Magnetic resonance is a useful imaging technique that gives a more detailed image of the body's soft tissue, for example, can be used to look for cancer of the thyroid gland and distant spread.
- **TG Ab:** Thyroglobulin antibody blood test. Thyroglobulin is a thyroid glycosylated iodoprotein secreted by the thyroid follicular cells and involved in the production of active thyroid hormone. In the presence of autoimmune disease, antibodies attack the thyroid and disrupt thyroglobulin production, resulting in increased antiTPO antibodies. Also used as a tumour marker in thyroid cancers.
- **TPO Ab:** Thyroid peroxidase antibody. Thyroid peroxidase is an enzyme found in the thyroid gland and involved in thyroid hormone production. A TPO antibody blood test is used to detect antibodies against TPO, and the presence of antibodies usually suggests an autoimmune thyroid disease.
- **TRH:** Thyroid-releasing hormone. A thyrotropin-releasing factor (thyroliberin), a neurohormone produced by the hypothalamus that stimulates the anterior pituitary to release TSH hormone.
- **TSH-oma:** Thyroid stimulating hormone (TSH) or thyrotropinoma. A benign pituitary tumour that secretes excess TSH. Characterized by high levels of circulating TSH, fT4, and fT3.
- **TSH-R ab:** TSH receptor antibody. Thyroid stimulating hormone receptor is a G-protein coupled receptor expressed in the thyroid and important for cell activation. TSH-R abs are associated with thyroid pathogenesis and the cause of autoimmune thyrotoxicosis such as Graves' disease. Antibodies bind to the TSH receptor and cause production of thyroid hormone, growth, and vascularization of the thyroid gland.

Key Points

- Relevant history combined with thorough clinical examination is a important first step for diagnosis of thyroid disorder supported by appropriate investigations. TSH, FT3, and FT4 results must be interpreted with caution taking into account of assay variation and possible interference.
- TSH receptor antibody is a reliable, sensitive, and specific test in diagnosis of Graves disease and if TSH receptor antibody is a positive, uptake scan is not indicated to confirm Graves' disease. TPO Abs is most sensitive test for autoimmune thyroiditis and in post-partum thyroiditis.
- Ultrasound is the most sensitive method for diagnosing thyroid nodule or intra-thyroid lesions. Current methods of ultrasonography allow identification of 2 mm cystic lesions and 3 mm solid intra-thyroid lesions. FNAC is indicated for single or multiple nodules for excluding malignancies after the US feature analysis.
- CT scanning is useful in evaluating lymphadenopathy, local tumour extension, extension into the mediastinum and retro-tracheal region and metastasis disease staging.
- Thyroid uptake scan has particular role of functional status of the gland differentiating between hot and cold nodules and Graves' hyperthyroid vs. thyroiditis. Differentiating Graves' disease and thyroiditis is crucial as the management is different.

27.1 Introduction

Thyroid dysfunction may be due to biochemical abnormalities, i.e. dysregulated secretion of thyroid hormones resulting in hyper- or hypothyroidism, changes in the physical characteristics of the gland itself, such as the development of a lump or diffuse enlargement that may produce mass effects or a combination of both biochemical and structural changes. Thyroid investigations can be used as a tool to screen for these problems, i.e. to test for dysfunction in a patient suspected of having thyroid disease or to obtain further information about a known thyroid problem. The information provided from the results of investigations is only as useful as the clinician's interpretation of them. Before ordering a particular test it is important to know what questions are being asked, and how the answers are going to inform the management of the patient. In a patient who is suspected of having thyroid dysfunction it is important to know:

- Is there any hormonal dysfunction, i.e. hyper- or hypothyroidism?
- What is causing the hormonal dysfunction? i.e. autoimmunity? "hot nodules"? or medications?
- Is there a problem due to mass effect from the thyroid itself?
- How severe is the problem?

27.2 Clinical Assessment of a Patient with Thyroid Disease

The thyroid hormones, thyroxine (T4), and triiodothyronine (T3), act on almost every cell in the body to alter the metabolic rate, affect growth, and maturation and to increase sensitivity to catecholamines, therefore over- or under-production of these hormones may result in a vast array of symptoms determined by the history, and signs found on clinical examination.

Symptoms are often highly variable between patients, for example, it is not uncommon for hyperthyroid patients to feel tired (this may be related to poor sleep), and hypothyroid patients may lose weight. Patients may also experience or describe symptoms in different ways, e.g. one person may experience the neurological effects of hypothyroidism as a "fuzzy head", another as "tiredness" and another as "lethargy and depression". The timing and onset of symptoms can also be informative. For example, the onset of hyperthyroid symptoms shortly after delivery suggests post-partum thyroiditis, and the onset of a tender gland and hyperthyroid symptoms shortly after a viral illness suggests De Quervain's thyroiditis. These are important diagnoses to make as they are often self-limiting and are therefore managed differently to Graves' disease. Similarly, a small smooth thyroid nodule that has been present and stable for many years suggests a benign thyroid adenoma, this is far less concerning than a short history of a hard and irregular rapidly enlarging thyroid nodule which may suggest a thyroid carcinoma, and therefore requires more urgent investigation.

The thyroid gland is anatomically close to the larynx, trachea, oesophagus, and jugular veins and an enlarging thyroid gland, or a thyroid nodule, may compress any of these structures and cause local mass effects (Table 27.5), all of which are "red flag" symptoms that indicate the presence of potentially serious pathology (Table 27.1). Most patients are very sensitive to a sense of fullness in the neck, and patients may experience symptoms of a sore throat, dysphagia, or dysphonia with only minimal thyroid gland enlargement on examination. Conversely, occasionally patients with a very large goitre that has been present for many years will be relatively asymptomatic.

27.3 Thyroid Hormones

27.3.1 Thyroid Hormones and Homeostasis

The thyroid gland produces two hormones, thyroxine (T4), which is weakly biologically active, and triiodothyronine (T3), which is 3–5 times

Table 27.1 History and examination findings: Red flag symptoms and signs

System	Symptoms	Signs
Neuro	Anxiety Poor sleep May feel more impatient/angry than usual Difficulty relaxing May experience abnormal thoughts	Appears anxious, tired, agitated Fine peripheral tremor Pressure of speech Occasionally psychosis
CVS	Palpitations Breathlessness Reduced exercise tolerance	Tachycardia Atrial fibrillation Heart failure
GIS	Diarrhoea Borborygmi Weight loss often despite good appetite	Signs of weight loss
Other	Heat intolerance	Dressed inappropriately for the conditions Sweating Warm peripheries Lid retraction Lid lag

Table 27.2 Findings associated with thyroid hormone excess

System	Symptoms	Signs
Neuro	Anxiety Poor sleep May feel more impatient/angry than usual Difficulty relaxing May experience abnormal thoughts	Appears anxious, tired, agitated Fine peripheral tremor Pressure of speech Occasionally psychosis
CVS	Palpitations Breathlessness Reduced exercise tolerance	Tachycardia Atrial fibrillation Heart failure
GIS	Diarrhoea Borborygmi Weight loss often despite good appetite	Signs of weight loss
Other	Heat intolerance	Dressed inappropriately for the conditions Sweating Warm peripheries Lid retraction Lid lag

more potent than T4. T4 and T3 are released into the circulation at a ratio of 14–20:1, and T4 is converted into the more active T3 within cells (Wiersinga 2001) T4 has a much longer half-life than T3, largely due to being strongly bound to plasma thyroid hormone-binding proteins (Schussler 2000), so acts as a "pool" of thyroid hormone to help maintain homeostasis (Table 27.2). As the majority of circulating T4 and T3 is protein-bound, and therefore not biologically active, free T4 (FT4) and free T3 (FT3) are measured in clinical practice. The production of T4 and T3 is maintained within tight limits to maintain normal functioning of the body tissues. This homeostasis is maintained through the hypothalamic-pituitary-thyroid axis. The hypothalamus produces thyrotropin-releasing hormone (TRH) in response to low circulating levels of T4 and T3. TRH stimulates the pituitary to produce thyroid stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce more T4 and T3. TRH is not routinely measured in clinical practice. As the levels of T4 and T3 rise, they exert negative feedback on both the hypothalamus and pituitary, the production of TRH and TSH attenuate, and the thyroid reduces the production of T4 and T3 (Sec.4. Chap. 27).

The vast majority of patients with thyroid hormone dysfunction will have a problem arising in the thyroid gland itself, so the hypothalamus and pituitary can be assumed to be reacting appropriately to the prevailing thyroid hormone levels. Therefore, in most situations, a TSH level within normal limits suggests that the levels of T4 and T3 are normal. For this reason, some laboratories will measure only TSH as a screening test, rather than TSH, FT3, and FT4. If the thyroid gland over-secretes T4 and T3 (e.g. in Graves' disease), the hypothalamus and pituitary detect these high levels and appropriately reduce production of TRH and TSH. Conversely, if the thyroid gland fails to make enough T4 and T3 (e.g. in autoimmune hypothyroidism), these low levels are detected by the hypothalamus and pituitary, TRH secretion increases appropriately and therefore the pituitary increases TSH secretion appropriately.

Table 27.3 Findings associated with thyroid hormone deficit

System	Symptoms	Signs
Neuro	Tiredness Mental fogginess Lethargy Depression	Appears tired Slow speech
CVS	Breathlessness	Bradycardia Signs of heart failure Pleural effusion
GIS	Constipation Weight gain despite constant/reduced food intake	Constipation Ascites
Other	Cold intolerance	Dressed inappropriately for the conditions Cool peripheries Deepening of voice Hypothyroid facies

Rarely, the primary defect is outside of the thyroid gland and the TSH level may be misleading. These conditions are rare but should be considered where the patient's symptoms and signs do not fit with the TSH result, or if there is clinical suspicion of a condition affecting the pituitary or hypothalamus. Central hypothyroidism is usually due to a problem with the pituitary gland that prevents it from responding to TRH, T4 and T3, and from secreting adequate amounts of TSH. Causes include compression of the gland by a tumour, apoplexy, surgery, radiotherapy, autoimmune hypophysitis (primary or drug related), and infection. In this situation, T4 and T3 levels fall and the patient develops symptoms of hypothyroidism, but will have either a low TSH or TSH at the lower end of the normal range that is inappropriate for the circulating low levels of T4 and T3. The pituitary gland is involved in the regulation of many other hormonal axes in addition to the thyroid axis, so patients with pituitary damage may well have symptoms of other hormonal deficits including hypoadrenalism and hypogonadism (Table 27.3). Very rarely, the pituitary may develop an adenoma that autonomously secretes TSH resulting in central hyperthyroidism. These adenomas are called TSH-omas. Dysfunction of the hypothalamus is very rare and is usually apparent before symptoms and signs of thyroid dysfunction develop.

27.3.2 Caution When Interpreting Thyroid Function Tests

When thyroid hormone levels are measured, they are usually reported by the lab with "normal reference ranges". These ranges are derived from a healthy population (i.e. where the hypothalamus, pituitary, and thyroid gland are working normally). Results at the extremes, i.e. the highest and lowest 2.5% of this "normal" population are excluded, so the "normal reference range" is the range of results that can be expected in 95% of healthy individuals. Therefore, 5% of healthy individuals will have an "abnormal result" at any one time (2.5% below the lower limit of the reference range, and 2.5% above the upper limit of the reference range). It should also be noted that occasionally individuals who are developing thyroid dysfunction may have blood test results within the normal range, for example, at the onset of hyperthyroidism, TSH may begin to drop and T4 may begin to rise but still be in the normal range. It is therefore unusual to start treatment based on the results of one abnormal blood test and good practice to have at least one repeat result and to interpret blood test results in the context of the overall clinical picture.

27.3.3 Thyroid Autoantibodies

The presence of thyroid autoantibodies can help to confirm whether the aetiology of thyroid dysfunction is autoimmune. The thyroid autoantibodies most commonly tested for are antithyroid peroxidase antibody (TPO Ab), antithyroglobulin antibody (TG Ab), and TSH receptor antibody (TSH-R Ab).

TPO Abs are the most sensitive antibody for autoimmune thyroiditis. They are elevated in virtually all cases of Hashimoto's thyroiditis and up to 65% of cases of Graves' disease. However, they have a low specificity, with a prevalence of between 8.6 and 11.3% in the normal population (Hollowell et al. 2002; Deshpande et al. 2016). TG Ab may also be elevated in autoimmune thy-

Table 27.4 Findings associated with an autoimmune aetiology

Graves' disease	Hashimoto's
Graves' eye disease—proptosis, difficulty closing eye, periorbital oedema, squint, injected cornea, corneal ulceration, reduced visual acuity	Pretibial myxoedema
Thyroid acropachy	

Table 27.5 Findings associated with mass effects

Laryngeal compression	Change in quality of the voice Stridor
Oesophageal compression	Dysphagia to solids than liquids
SVC obstruction	Flushed face Distended veins on chest and neck Sensation of stuffiness/fullness in head Change in vision/consciousness on bending forwards, coughing, raising arms above head headache
Other	Tethering Rapid growth Irregular surface Hard

roiditis, but also has a low specificity, present in 10.4% of patients without thyroid dysfunction, and it is therefore for not routinely tested for in thyroid hormone dysfunction. TSH Abs are formed against the TSH receptors in the thyroid gland, and activate them abnormally, resulting in an inappropriately elevated TSH secretion. They are both sensitive and specific for Graves' disease (Tozzoli et al. 2012).

Patients with autoimmune thyroid disease may, therefore, have a combination of these autoantibodies, for example, a patient with Graves' disease may have positive TPO Ab, TSH-R Ab, and TG Ab. As these antibodies are present in the normal healthy population, their presence does not necessarily indicate that the patient has thyroid dysfunction (Table 27.4). Therefore, in practice, they are usually only assessed after thyroid dysfunction has been established to help determine the dysfunction or to guide treatment decisions in the setting of subclinical hypothyroidism (Table 27.5).

27.4 Imaging

The role of plain radiography in the evaluation of thyroid disease is limited. Plain radiographs can show soft tissue masses, tracheal deviation, a retrosternal extension of goitre, calcification in thyroid tumours and metastatic lung disease, but are neither sensitive nor specific. The patterns of calcification from thyroid cancer seen on plain X-ray overlap with those of benign disease, tracheal deviation/stenosis can result from causes other than retrosternal and goitre extension, metastasis in lungs or bone may arise from several primary sites.

27.5 Ultrasound

Ultrasound (US) is the most sensitive method for diagnosing intra-thyroid lesions. Current methods of ultrasonography allow identification of 2 mm cystic lesions and 3 mm solid intra-thyroid lesions (Mandel 2004; Miki et al. 1993). Doppler US helps in estimating overall and regional blood flow to thyroid. However, caution should be taken when relying on the US features alone as results do not correlate perfectly with histopathologic findings. Solid nodules are described as isoechoic if their texture closely resembles that of normal thyroid tissue, hyperechoic if more echogenic and hypoechoic if less echogenic.

The main clinical uses of ultrasonography are:

- To assess the anatomic features of thyroid nodules
- To monitor nodular thyroid disease
- To assist in interventional procedures such as fine needle aspiration (FNA) of thyroid, cervical lymph nodes and thyroid ablation
- To assist in the planning of thyroid cancer surgery
- To assist in surveillance for recurrence in patients with thyroid cancer
- To screen for presence of thyroid nodules in high-risk groups
- To assess fetal goitre

Ultrasound should be performed on all patients with nodules incidentally noted on other imaging studies as non-palpable nodules have approximately the same risk of malignancy as palpable nodules. US may be the only investigation required for haemorrhagic cysts due to their characteristic appearance. Clots may be hyperechoic and after liquefaction may become hypoechoic. A haemorrhagic nodule which looks part cystic and part solid is called a complex nodule.

Ultrasonography also plays an important role in detecting cervical lymphadenopathy in a patient with a thyroid nodule or newly diagnosed thyroid cancer. The US guided aspiration biopsy of enlarged cervical lymph nodes for cytological and immunohistological analysis can differentiate metastasis from thyroid cancer and inflammatory lymphadenopathy. US is also the most frequently used imaging procedure for long-term monitoring of patients with thyroid cancer for recurrence in the thyroid bed after total thyroidectomy or lobectomy. A major advantage of US over functional imaging is that the procedure can be performed without discontinuing thyroxine therapy, therefore, avoiding the risk of hypothyroidism.

27.5.1 Characteristics of Nodules Used for Identifying Cancers

- ***Vascularity:*** US evidence of vascular invasion may be a most reliable predictor of malignancy but is an uncommon finding.
- ***The intensity of echoes:*** Malignant thyroid nodules often have a hypoechoic appearance on the US but many benign nodules are less echogenic than surrounding normal thyroid tissue. The sensitivity and specificity of a hypoechoic appearance are approximately 53% and 73%, respectively.
- ***The sharpness of border:*** Typically, 96% benign lesions are well defined and malignant lesions are mostly with irregular margins. However, the sharpness of the nodule border has a lower diagnostic value, and an ill-defined edge of nodule may be a marker of aggressive characteristics of papillary thyroid cancer.
- ***Halo:*** The "halo" is the name given to the interface between thyroid tissue and nodule which is less echogenic than either of two. The partition could be a capsule, or compressed or atrophied thyroid tissue. An incomplete or absent halo has been reported as a feature of malignancy with poor sensitivity and specificity (Daumerie et al. 1998).
- ***Calcifications:*** Calcifications are often present in both benign and malignant nodules. Punctate calcifications in the range of 1 mm are uncommonly seen and suggest microscopic psammoma bodies in papillary carcinomas. Peripheral or egg shell calcification is indicative of chronicity and seen in benign lesions (Brunese et al. 2008; Jakobsen 2001; Kwak et al. 2007). Coarse scattered calcification may be seen in haemorrhagic benign or malignant nodules. Large areas of calcification may be a feature of medullary thyroid cancer.
- ***Internal structure:*** A layered appearance of the echo pattern described as "spongiform" is a useful predictor of benign lesions (Bonavita et al. 2009). The uniformity of internal structure of nodule is not a useful indicator for diagnosis of cancer.
- ***The shape of nodule:*** Cancers frequently have a tall and narrow shape. An anteroposterior and transverse diameter ratio greater than 1 in combination with other suspicious characteristic has better predictive value (Bonavita et al. 2009; Cappelli et al. 2005).
- ***Nodule size:*** Large nodule diameter or size and volume may be predictive of the likelihood of thyroid cancer and prognosis (Kiernan and Solórzano 2017; Cavallo et al. 2017).

No single US criterion is reliable in differentiating benign thyroid nodules from malignant ones in isolation (Cappelli et al. 2007; Sipos 2009). The American college of Radiology has proposed a risk stratification system for the ultrasonic appearance of thyroid lesions called Thyroid Imaging Reporting and Data System (TIRADS). Five characteristics of the thyroid mass (composition, echogenicity, shape, margin, and echogenic foci) are graded individually,

and then the information is combined to provide an overall score that is predictive for the risk of malignancy. These are TIRADS 1: normal thyroid, TIRADS 2: benign lesions, TIRADS 3: probably benign lesions, TIRADS 4: suspicious lesions, TIRADS 5: probably malignant lesions and TIRADS 6: biopsy proved lesions (Singaporewalla et al. 2017).

27.5.2 The Use of Ultrasound in Assessing for Fetal Thyroid Dysfunction

Ultrasonography is also used to assess the fetal thyroid gland, diagnose fetal goitre, or thyroid dysfunction and to facilitate therapy. Thus, it can reduce obstetric complications and contribute to neonatal health. In mothers with Graves' disease, US by an experienced ultrasonographer is an excellent diagnostic tool which can facilitate assessment of fetal thyroid function (Luton et al. 2005; Cohen et al. 2003). The detection of a fetal goitre on US in conjunction with clinical features such as fetal tachycardia, intrauterine growth retardation, and occasionally cord blood sample showing high levels of free T3, free T4 and suppressed fetal TSH levels indicate fetal thyrotoxicosis. Conversely, fetal goitre without clinical manifestation of fetal thyrotoxicosis may suggest overtreatment of the mother with anti-thyroid drugs and prompt a dose reduction.

27.6 Computed Tomography

CT is not a sensitive technique for demonstrating intra-thyroid lesions. However, it may be useful in evaluating lymphadenopathy, local tumour extension, extension into the mediastinum and retro-tracheal region, and for tumour staging. Thyroid cancer is suggested by certain patterns of calcification within a thyroid mass and when extension into surrounding structures is visualized. Regional lymphadenopathy in association with a thyroid mass is also suggestive of thyroid malignancy. However, thyroid cancers can be missed on CT scans in the presence of multinodular goitre.

27.7 Magnetic Resonance Imaging

MRI is useful in detecting local extension of thyroid neoplasm, spread of disease in the mediastinum or retro-tracheal region, and to assess lymphadenopathy.

Magnetic resonance spectroscopy may be of value in assessing the malignancy of follicular thyroid specimens, taken either through fine needle aspiration or surgery, where differentiation is difficult on basis of cytology. Performing hydrogen spectroscopy at 360 MHz has demonstrated the ratio of peaks at 1.7 and 0.9 ppm, and it can be used to differentiate benign from malignant lesions. Values higher than a ratio of 1.1 is normal and ratios lower than 1.1 indicate malignancy. Normal tissue can be differentiated from papillary and medullary carcinoma with a sensitivity of approximately 95%.

27.8 Nuclear Imaging

Nuclear imaging provides information on both the function and anatomy of the gland. It is contraindicated in patients who are pregnant because of the risk of exposing the fetus to radiation and is not recommended for breast-feeding women. In the past, radionuclide imaging was performed to differentiate malignant from benign lesions; however, 4% of hot nodules are shown to contain tumour compared with 16% of cold nodules (Daumerie et al. 1998). Thus, radionuclide imaging is unreliable in excluding or confirming the presence of cancer.

27.9 Iodine-123 or Iodine-131

Radioactive iodine has many advantages. The short 13.3-h half-life, the 159-keV principal photon and the absence of particulate emission allow for good imaging with modest patient radiation exposure. Metastatic cancer is imaged well because ½ of papillary carcinoma and 2/3 of fol-

licular carcinoma are sufficiently iodine avid to allow their visualization. However, this isotope is cyclotron produced and therefore relatively expensive. In addition, its short half-life necessitates frequent shipment from the producer adding to the cost.

27.10 Technetium-99m Pertechnetate

Technetium-99m is commonly used as it is an inexpensive and readily available isotope which delivers a low dose radiation because of its short 6-h half-life and favourable decay scheme without particulate emission. A gamma camera using a 140-keV photon is used for imaging. However, disadvantages include decreased sensitivity within the mediastinum due to uptake in the oesophagus, poor image quality when uptake is low and, as it is trapped but not organified, it cannot be used to assess organification defects.

27.11 Gallium-67

Gallium-67 may be useful when thyroid lymphoma is suspected, but generally is of limited utility as it does not enable sufficient differentiation between malignant and benign lesions.

27.12 Role of Functional Imaging for Thyroiditis

Subacute thyroiditis is a clinical syndrome that manifests as transient thyrotoxicosis followed by transient hypothyroidism. The thyroid uptake scan reveals markedly decreased glandular activity which helps to differentiate subacute thyroiditis from Graves' disease. Such a distinction is crucial because the management of these thyroid disorders differs significantly. Thyrotoxicosis from subacute thyroiditis will resolve spontaneously and should not be treated with anti-thyroid medication.

27.13 Other Thyroid Investigations in Special Circumstances

27.13.1 Heterophile Antibody Interference

Heterophile antibodies are endogenous antibodies in human serum that may interfere with immunoassays causing a false positive, or falsely elevated, test result. Awareness of the possibility of interference by heterophile antibodies is important to prevent inappropriate management on the basis of erroneous laboratory results.

Heterophile antibodies are common, naturally occurring antibodies with low affinities. Medical researchers have proposed that heterophile antibodies bind and remove foreign antigens from the intestinal tract and help to maintain self-tolerance (Levinson and Miller 2002). They are inherently produced from B cells prior to antigen exposure and are made up of a random combination of genes encoding the heavy and light chain variable regions. These antibodies react with many antigens including a wide variety of chemical structures, self-antigens, and variable regions of other antibodies (anti-idiotypic antibodies) (Warren et al. 2005; Bjerner et al. 2005). Heterophilic antibodies are typically not strong enough to interfere with competitive binding assays (Levinson and Miller 2002; Kaplan and Levinson 1999) clinical practice, if a patient has heterophilic antibodies that are causing interference with one particular type of assay, these same antibodies will only react poorly, if at all, with another type of assay. Therefore, switching the assay kit to one from a different manufacturer, or to a different in-house preparation may reduce or eliminate the interference. The use of nonimmune globulin, serum from several animal species or commercially available preparations, such as heterophile blocking reagents and immunoglobulin inhibiting reagents, can significantly reduce heterophile interference (Levinson and Miller 2002; Preissner et al. 2005). Heterophile antibodies should be suspected in patients that have FT4 and TSH results in which the concentrations

together are considered discordant, i.e. an elevated TSH with an elevated FT4, where an alternative cause is statistically unlikely, or does not fit with the clinical picture.

27.13.2 Resistance to Thyrotropin (TSH) and Resistance to Thyrotropin-Releasing Hormone (TRH)

Resistance to TSH (RTSH) is defined as high serum TSH of normal biological activity in the absence of goitre. Affected individuals have normal or hypoplastic thyroid glands, high serum TSH concentrations, and normal or low serum T4 and T3 concentrations. They are often identified at birth through neonatal screening for congenital hypothyroidism. RTSH should be suspected in patients, particularly infants, who have high serum TSH concentrations, normal or low serum-free T4 and T3 concentrations, and a normally located thyroid gland. The differential diagnosis includes all conditions that impair thyroid secretion. TSH is the predominant regulator of thyroid growth and T4 and T3 synthesis and secretion. Because of the important role of TSH in promoting thyroid growth, RTSH is unlikely if the patient has a goitre or ectopically located thyroid tissue.

Three phenotypes of resistance to TSH representing different degrees of resistance to TSH.

1. **Fully Compensated defect:** The impaired response to TSH is compensated by hypersecretion of TSH; this overcomes the resistance, resulting in euthyroid hyperthyrotropinaemia (high TSH). In an individual patient with a genetic mutation causing resistance to TSH, the phenotype tends to be stable over time. This course contrasts to that of acquired subclinical hypothyroidism due to autoimmune thyroiditis, which tends to worsen over time.
2. **Partially compensated defect:** Affected individuals have mild hypothyroidism as the high serum TSH cannot fully compensate for the defect.
3. **Uncompensated defect:** Complete lack of TSH receptor function results in severe hypothyroidism. This most often occurs when both alleles carry mutant TSH receptors with a complete lack of function (Abramowicz et al. 1997; Gagné et al. 1998; Tiosano et al. 1999).

Individuals with fully compensated RTSH are euthyroid and need no treatment. There is no evidence that in the absence of other risk factors, persistent elevation of serum TSH levels produces TSH-secreting pituitary adenomas or thyroid neoplasia. Individuals with partially compensated or uncompensated RTSH should be treated with L-T4, like any other hypothyroid patient. Because these individuals have normal responsiveness to thyroid hormone, the goal is to normalize their serum TSH concentration.

27.13.3 Resistance to Thyrotropin-Releasing Hormone (TRH)

Resistance to thyrotropin-releasing hormone (TRH) is a rare disorder that is transmitted as an autosomal recessive trait. It is due to an inactivating mutation in the TRH receptor.

Patients with resistance to TRH present with findings of central hypothyroidism, i.e. normal serum TSH, low T4 and T3 concentrations, and no serum TSH or prolactin responses to the administration of TRH.

27.14 TSH-oma

The thyrotropin (TSH)-secreting pituitary adenomas (TSH-omas) are a rare cause of hyperthyroidism. It includes autonomous secretion of TSH which is refractory to the negative feedback of thyroid hormones and TSH itself is responsible for the hyper stimulation of the thyroid gland and the consequent hypersecretion of T4 and T3(Beck-Peccoz et al. 1996; Beck-Peccoz et al. 2015). If FT4 and FT3 concentrations are elevated in the presence of measurable TSH levels, it is important to exclude methodological interference first, due to the presence

of circulating autoantibodies or heterophilic antibodies. A similar biochemical picture may also be seen in patients on L-T4 replacement therapy. The finding of measurable TSH in the presence of high FT4/FT3 levels may be due to poor compliance or to an incorrect high L-T4 dosage, probably administered before blood sampling.

In patients with a confirmed TSH-oma, clinical features of hyperthyroidism are usually present, but may be milder than expected for the level of thyroid hormones, probably due to their long-standing duration. The presence of a goiter is the rule, even in the patients with previous partial thyroidectomy, since thyroid residue may regrow as a consequence of TSH hyperstimulation. (Abs et al. 1994). The monitoring of the thyroid nodule(s) and the execution of fine needle aspiration biopsy (FNAB) are indicated in TSH-omas since differentiated thyroid carcinomas have been documented in several patients (Beck-Peccoz et al. 1996; Kishida et al. 2000; Nguyen et al. 2010; Gasparoni et al. 1998; Poggi et al. 2009; Perticone et al. 2015).

Patients with TSH-omas may also hypersecrete other pituitary hormones. Hyperthyroid features can be overshadowed by those of acromegaly in the patients with mixed TSH/GH adenomas (Malchiodi et al. 2014; Beck-Peccoz et al. 1986; Losa et al. 1996), thus emphasizing the importance of systematic measurement of TSH and FT4 in patients with pituitary a tumour. Dysfunction of the gonadal axis is not rare and occurs mainly in the mixed TSH/PRL adenomas. As a consequence of tumour suprasellar extension or invasiveness, signs and symptoms of expanding tumour mass predominate in many patients. Partial or total hypopituitarism was seen in about 1/4 cases, headache reported in 20–25% of patients, and visual field defects are present in about 50% of cases.

About 30% of TSH-oma patients with an intact thyroid showed TSH levels within the normal range; TSH levels in patients previously treated with thyroid ablation were sixfold higher than in untreated patients though free thyroid hormone levels were still in the hyperthyroid range (Beck-Peccoz et al. 1996).

27.14.1 Dynamic Testing

Both stimulatory and inhibitory tests have been proposed for the diagnosis of TSH-oma, but neither option is of clear-cut diagnostic value. The tests proposed include T3 suppression test, TRH test, response to native somatostatin and its analogue.

27.14.2 Imaging

MRI is considered the first choice for visualization however when contraindicated, high-resolution computed tomography (HRCT) is an alternative. Pituitary scintigraphy with radiolabeled octreotide (octreoscan) has been shown to successfully localize TSH-omas expressing somatostatin receptors (Brucker-Davis et al. 1999; Losa et al. 1997). However, the specificity of octreoscan is low since positive scans can be seen in other types of pituitary mass, both secreting or non-secreting.

27.14.3 Treatment

Surgical resection is the recommended therapy for TSH-secreting pituitary tumours as stated in a guideline by the European Thyroid Association (Beck-Peccoz et al. 2013). This involves highly invasive, surgical removal or debulking of the tumour by transsphenoidal or subfrontal adenomectomy, depending on the tumour volume and its suprasellar extension.

If surgery is contraindicated or declined, or is unsuccessful, pituitary radiotherapy and/or medical treatment with somatostatin analogues are two valid alternatives (Beck-Peccoz et al. 2013).

27.15 Conclusions

Thyroid investigations are paramount towards reaching a correct diagnosis and thyroid blood tests such as TSH, fT4, and fT3 are usually the first line of investigations, together with biochemistry to confirm the functional status of the gland.

To avoid unnecessary thyroid investigations, a structured approach is required that combines taking relevant patient history and performing a thorough examination with selective investigations according to the clinical findings. This not only serves as cost effective within the health service but more importantly benefits and enhances patient recover.

References

Abramowicz MJ, Duprez L, Parma J, et al. Familial congenital hypothyroidism due to inactivating mutation of the thyrotropin receptor causing profound hypoplasia of the thyroid gland. J Clin Invest. 1997;99:3018.

Abs R, Stevenaert A, Beckers A. Autonomously functioning thyroid nodules in a patient with a thyrotropin-secreting pituitary adenoma: possible cause-effect relationship. Eur J Endocrinol. 1994;131:355–8.

Beck-Peccoz P, Piscitelli G, Amr S, Ballabio M, Bassetti M, Giannattasio G, Spada A, Nissim M, Weintraub BD, Faglia G. Endocrine, biochemical, and morphological studies of a pituitary adenoma secreting growth hormone, thyrotropin (TSH), and a-subunit: evidence for secretion of TSH with increased bioactivity. J Clin Endocrinol Metab. 1986;62:704–11.

Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev. 1996;17:610–38.

Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2(2):76–82.

Beck-Peccoz P, Lania A, Persani L. Chapter 24. TSH-producing adenomas. In: Jameson JL, DeGroot LJ, editors. Endocrinology. 7th ed. Philadelphia: W.B. Saunders; 2015. p. 266–74.

Bjerner J, Olsen KH, Bormer OP, Nustad K. Human heterophilic antibodies display specificity for murine IgG subclasses. Clin Biochem. 2005;38(5):465–72.

Bonavita JA, Mayo J, Babb J, et al. Pattern recognition of benign nodules at ultrasound of the thyroid: which nodules can be left alone? AJR Am J Roentgenol. 2009;193:207.

Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub BD. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab. 1999;84:476–86.

Brunese L, Romeo A, Iorio S, et al. A new marker for diagnosis of thyroid papillary cancer: B-flow twinkling sign. J Ultrasound Med. 2008;27:1187.

Cappelli C, Pirola I, Cumetti D, et al. Is the anteroposterior and transverse diameter ratio of nonpalpable thyroid nodules a sonographic criteria for recommending fine-needle aspiration cytology? Clin Endocrinol (Oxf). 2005;63:689.

Cappelli C, Castellano M, Pirola I, et al. The predictive value of ultrasound findings in the management of thyroid nodules. QJM. 2007;100:29.

Cavallo A, Johnson DN, White MG, et al. Thyroid nodule size at ultrasound as a predictor of malignancy and final pathologic size. Thyroid. 2017;27:641.

Cohen O, Pinhas-Hamiel O, Sivan E, et al. Serial in utero ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy. Prenat Diagn. 2003;23:740.

Daumerie C, Ayoubi S, Rahier J, et al. [Prevalence of thyroid cancer in hot nodules]. Ann Chir. 1998;52(5):444–8.

Deshpande P, Lucas M, Brunt S, Lucas A, Hollingsworth P, Bundell C. Low level autoantibodies can be frequently detected in the general Australian population. Pathology. 2016;48(5):483–90.

Gagné N, Parma J, Deal C, et al. Apparent congenital athyreosis contrasting with normal plasma thyroglobulin levels and associated with inactivating mutations in the thyrotropin receptor gene: are athyreosis and ectopic thyroid distinct entities? J Clin Endocrinol Metab. 1998;83:1771.

Gasparoni P, Rubello D, Persani L, Beck-Peccoz P. Unusual association between a thyrotropin-secreting pituitary adenoma and a papillary thyroid carcinoma. Thyroid. 1998;8:181–3.

Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489–99.

Jakobsen JA. Ultrasound contrast agents: clinical applications. Eur Radiol. 2001;11:1329.

Kaplan IV, Levinson SS. When is a heterophile antibody not a heterophile antibody? When it is an antibody against a specific immunogen. Clin Chem. 1999;45(5):616–8.

Kiernan CM, Solórzano CC. Bethesda category III, IV, and V thyroid nodules: can nodule size help predict malignancy? J Am Coll Surg. 2017;225:77–82.

Kishida M, Otsuka F, Kataoka H, Yokota K, Oishi T, Yamauchi T, Doihara H, Tamiya T, Mimura Y, Ogura T, Makino H. Hyperthyroidism in a patient with TSH-producing pituitary adenoma coexisting with thyroid papillary adenocarcinoma. Endocr J. 2000;47:731–8.

Kwak JY, Kim EK, Son EJ, et al. Papillary thyroid carcinoma manifested solely as microcalcifications on sonography. AJR Am J Roentgenol. 2007;189:227.

Levinson SS, Miller JJ. Towards a better understanding of heterophile (and the like) antibody interference with modern immunoassays. Clin Chim Acta. 2002;325(1–2):1–15.

Losa M, Giovanelli M, Persani L, Mortini P, Faglia G, Beck-Peccoz P. Criteria of cure and follow-up of

central hyperthyroidism due to thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab. 1996;81:3086–90.

Losa M, Magnani P, Mortini P, Persani L, Acerno S, Giugni E, Fazio F, Beck-Peccoz P, Giovanelli M. Indium-111 pentetreotide single-photon emission tomography in patients with TSH-secreting pituitary adenomas: correlation with the effect of a single administration of octreotide on serum TSH levels. Eur J Nucl Med. 1997;24:728–31.

Luton D, Le Gac I, Vuillard E, et al. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. J Clin Endocrinol Metab. 2005;90:6093.

Malchiodi E, Profka E, Ferrante E, Sala E, Verrua E, Campi I, Lania AG, Arosio M, Locatelli M, Mortini P, Losa M, Beck-Peccoz P, Spada A, Mantovani G. Thyrotropin-secreting pituitary adenomas: outcome of pituitary surgery and irradiation. J Clin Endocrinol Metab. 2014;99(6):2069–76.

Mandel SJ. Diagnostic use of ultrasonography in patients with nodular thyroid disease. Endocr Pract. 2004;10(3):246–52.

Miki H, Oshimo K, Inoue H, et al. Incidence of ultrasonographically-detected thyroid nodules in healthy adults. Tokushima J Exp Med. 1993;40(1-2):43–6.

Nguyen HD, Galitz MS, Mai VQ, Clyde PW, Glister BC, Shakir MK. Management of coexisting thyrotropin/growth-hormone-secreting pituitary adenoma and papillary thyroid carcinoma: a therapeutic challenge. Thyroid. 2010;20(1):99–103.

Perticone F, Pigliaru F, Mariotti S, Deiana L, Furlani L, Mortini P, Losa M. Is the incidence of differentiated thyroid cancer increased in patients with thyrotropin-secreting adenomas? Report of three cases from a large consecutive series. Thyroid. 2015;25(4):417–24.

Poggi M, Monti S, Pascucci C, Toscano V. A rare case of follicular thyroid carcinoma in a patient with thyrotropin-secreting pituitary adenoma. Am J Med Sci. 2009;337(6):462–5.

Preissner CM, Dodge LA, O'Kane DJ, Singh RJ, Grebe SK. Prevalence of heterophilic antibody interference in eight automated tumor marker immunoassays. Clin Chem. 2005;51(1):208–10.

Schussler GC. The thyroxine-binding proteins. Thyroid. 2000;10(2):141–9.

Singaporewalla RM, Hwee J, Lang TU, Desai V. Clinico-pathological correlation of thyroid nodule ultrasound and cytology using the TIRADS and Bethesda Classifications. World J Surg. 2017;41:1807–11.

Sipos JA. Advances in ultrasound for the diagnosis and management of thyroid cancer. Thyroid. 2009;19:1363.

Tiosano D, Pannain S, Vassart G, et al. The hypothyroidism in an inbred kindred with congenital thyroid hormone and glucocorticoid deficiency is due to a mutation producing a truncated thyrotropin receptor. Thyroid. 1999;9:887.

Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N. TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. Autoimmun Rev. 2012;12(2):107–13.

Warren DJ, Bjerner J, Paus E, Bormer OP, Nustad K. Use of an in vivo biotinylated singlechain antibody as capture reagent in an immunometric assay to decrease the incidence of interference from heterophilic antibodies. Clinl chem. 2005;51(5):830–8.

Wiersinga WM. Thyroid hormone replacement therapy. Hormone Res. 2001;56(Suppl 1):74–81.

Hyperthyroidism in Adults

28

Violet Fazal-Sanderson, Niki Karavitaki, and Radu Mihai

Contents

28.1 **Section A: Hyperthyroidism** 521
28.1.1 Introduction 521
28.1.2 Hyperthyroidism 521
28.1.3 Causes of Hyperthyroidism 524
28.1.4 Graves' Disease 524
28.1.5 Toxic Adenoma/Toxic Multinodular Goitre 527
28.1.6 Thyroiditis 530
28.1.7 Struma Ovarii 536
28.1.8 Anti-thyroid Drug Therapy 536

28.2 **Section B: Radioiodine Therapy (1-131)** 544
28.2.1 Radioactive Iodine Treatment (I-131) 544

28.3 **Section C: Thyroid Surgery** 547
28.3.1 Preoperative Medical Control of Hyperthyroidism (With Reference at Previous Sections) 547
28.3.2 Thyroid Lobectomy for 'Hot' Nodule 547
28.3.3 Total Thyroidectomy for Graves' Disease 548

28.4 **Conclusions** 550

Useful Resources 551

V. Fazal-Sanderson (✉)
Department of Endocrinology, Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Berkshire, UK
e-mail: violet.sanderson@royalberkshire.nhs.uk; Violetsanderson@royalberkshire.nhs.uk

N. Karavitaki
Institute of Metabolism and Systems Research, University of Birmingham and Queen Elizabeth Hospital, Birmingham, UK
e-mail: n.karavitaki@bham.ac.uk

R. Mihai
Department of Endocrine Surgery, Churchill Cancer Centre, Oxford University Hospitals Foundation Trust, Oxford, UK
e-mail: Radu.Mihai@ouh.nhs.uk

Abstract

In the UK, the prevalence of hyperthyroidism is estimated to be around 2% in women and 0.2% in men. In Europe, the prevalence of overt hyperthyroidism is in the region of 0.6–16% and in the USA, prevalence is reported to be approximately 1.2%.

Hyperthyroidism refers to conditions that cause increased secretion of thyroid hormones from the thyroid gland leading to thyrotoxicosis. Thyrotoxicosis occurs as a result of elevated circulating thyroid hormones, of either free thyroxine or free triiodothyronine, (or both) and can

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_28

affect almost every organ in the body triggering many symptoms including agitation, rapid weight loss, heat intolerance, and increased heart rate. Left untreated, thyrotoxicosis can have serious health implications on a patient's well being. A specialist clinical practitioners role is to identify the signs and symptoms of thyrotoxicosis through the undertaking of a detailed patient history, assessment, and physical examination in this way a tailored approach for treatment can be implemented safely, efficiently, and cost-effectively with positive outcomes.

The conditions most commonly associated with hyperthyroidism include Graves' disease, multinodular goitre, toxic adenoma, thyroiditis (such as subacute and post-partum), and subclinical thyrotoxicosis. These are briefly outlined in this chapter and provide an overview of related definitions, pathologies, and clinical features including diagnosis and treatments, such as medical therapy, radioiodine, and surgery. Furthermore, it also aims to equip and enhance relevant evidence-based knowledge and understanding of the hyperthyroid disorders seen in the endocrine clinical practice, with a view to provide specialist practitioners useful tips and guidance of how to diagnosis, manage, and treat some of the most common hyperthyroid conditions seen in many endocrinology departments.

Keywords

Hyperthyroidism · Graves' disease · Toxic nodular goitre · Thyroiditis · Anti-thyroid drug therapy · Radioiodine · Thyroid surgery

Abbreviations

ATA	American Thyroid Association
ATDs	Anti-thyroid drugs
BTA	British Thyroid Association
BTF	British Thyroid Foundation
BD	Twice daily
BRLN	Bilateral recurrent laryngeal nerve
CKS	Clinical knowledge summaries
FT3	Free triiodothyronine
FT4	Free thyroxine
HT	Hashimoto's thyroiditis
NICE	National Institution for Health and Care Excellence
OD	Daily
PPT	Post-partum thyroiditis
RAI/RAIU	Radioiodine/Radioiodine uptake
SH	Subclinical hyperthyroidism
TA	Toxic adenoma
TDS	Three times daily
TED	Thyroid eye disease
TFT	Thyroid function test
TMNG	Toxic multinodular goitre
TSH	Thyroid stimulating hormones
TSHRAb	Thyroid stimulating hormone receptor antibody
UK	United Kingdom
USA	United States of America

Key Terms

- **Primary hyperthyroidism**: a disorder of the thyroid gland that causes thyrotoxicosis such as Graves' disease, nodular goitre, or various types of thyroiditis
- **Secondary hyperthyroidism**: is caused by excess extra-thyroidal stimulation of the thyroid by a thyroid stimulating hormone (TSH) secreting pituitary adenoma
- **Thyrotoxicosis:** is caused by an excess of circulating thyroid hormones, either free thyroxine (FT4) or free triiodothyronine (FT3), or both
- **Graves' disease:** is an autoimmune condition in which thyrotropin receptor antibodies stimulate TSH receptors, and as a result, there are increased levels of circulating of thyroid hormone.

Key Points

- Hyperthyroidism refers to conditions that cause increased secretion of thyroid hormones (either free thyroxine or free triiodithyronine, or both), with suppressed thyroid stimulating hormone.
- The classic symptoms of thyrotoxicosis include agitation, palpitations, weight loss, fine hand tremor, heat intolerance, and frequency of bowel movements.

- Common conditions caused by hyperthyroidism include Graves' disease, then toxic adenoma, multinodular goitre and less common, various forms of thyroiditis.
- Investigations such as thyroid radioiodine uptake scan can differentiate thyroid disorders such as Graves' disease by an increased and diffuse uptake, toxic multinodular goitre by focal areas of normal to increased uptake, and thyroiditis by a low uptake.
- Thyroid antibodies are useful indicators for determining thyroid disease, for example, thyroid autoantibodies to thyroglobulin and thyroid peroxidase can show those at risk to developing autoimmune thyroid disease.
- Appropriate diagnosis is critical to formulating a more specific and tailored approach in enhancing patient recovery.
- Thionamides such as Carbimazole and Propylthiouracil are anti-thyroid drugs treatments used in the management of hyperthyroidism, in preparation for thyroidectomy in hyperthyroidism and as prescribed as therapy prior and post-radioiodine treatment.

28.1 Section A: Hyperthyroidism

28.1.1 Introduction

Thyroid hormones are essential for cellular metabolism, normal skeletal growth, and cerebral development (Visser 2011; Harvey et al. 2002). Adequate iodine intake is paramount for normal thyroid function and can be obtained from foods such as white fish, milk, and dairy products (Bath 2016). Deficiency of iodine can lead to impaired thyroid hormone production that can have serious implications on both cognitive function and growth (Vanderpump 2011). The balance of thyroid hormones within the body are controlled through a negative feedback on the hypothalamus and pituitary gland (Visser 2011; Harvey et al. 2002)

Box 28.1 Thyrotoxicosis Associated with Hyperthyroidism, Thyroiditis, and Non-thyroidal Disorders

Thyrotoxicosis and hyperthyroidism in adults

- Graves' disease
- Toxic adenoma
- Multinodular goitre
- Iodine induced
- TSH secreting tumour

Thyrotoxicosis and thyroiditis

- Subacute thyroiditis
- Silent thyroiditis
- Amiodarone induced (type 2)

Thyrotoxicosis of non-thyroidal origin

- Thyroid hormone intoxication
- Dermoid tumours (Struma ovarii)
- Metastatic thyroid cancer

Excess circulating thyroid hormones causes thyrotoxicosis and can be associated with hyperthyroidism, thyroiditis, or non-thyroidal disorder (Box 28.1).

28.1.2 Hyperthyroidism

Hyperthyroidism refers to conditions that cause increased secretion of thyroid hormones from the thyroid gland that leads to thyrotoxicosis, whilst **thyrotoxicosis** is termed as a clinical syndrome that results from elevated circulating thyroid hormones, of either free thyroxine (FT4) or free triiodothyronine (FT3), or both (British Thyroid Association-BTA 2006; Franklyn and Boelaert 2012; American Thyroid Association – ATA 2016).

High levels of circulating thyroid hormones can effect almost every organ in the body and trigger numerous unpleasant signs and symptoms including palpitations, weight loss, fine hand tremor, heat intolerance, frequency of bowel movement, etc. (Fig. 28.1), and if left

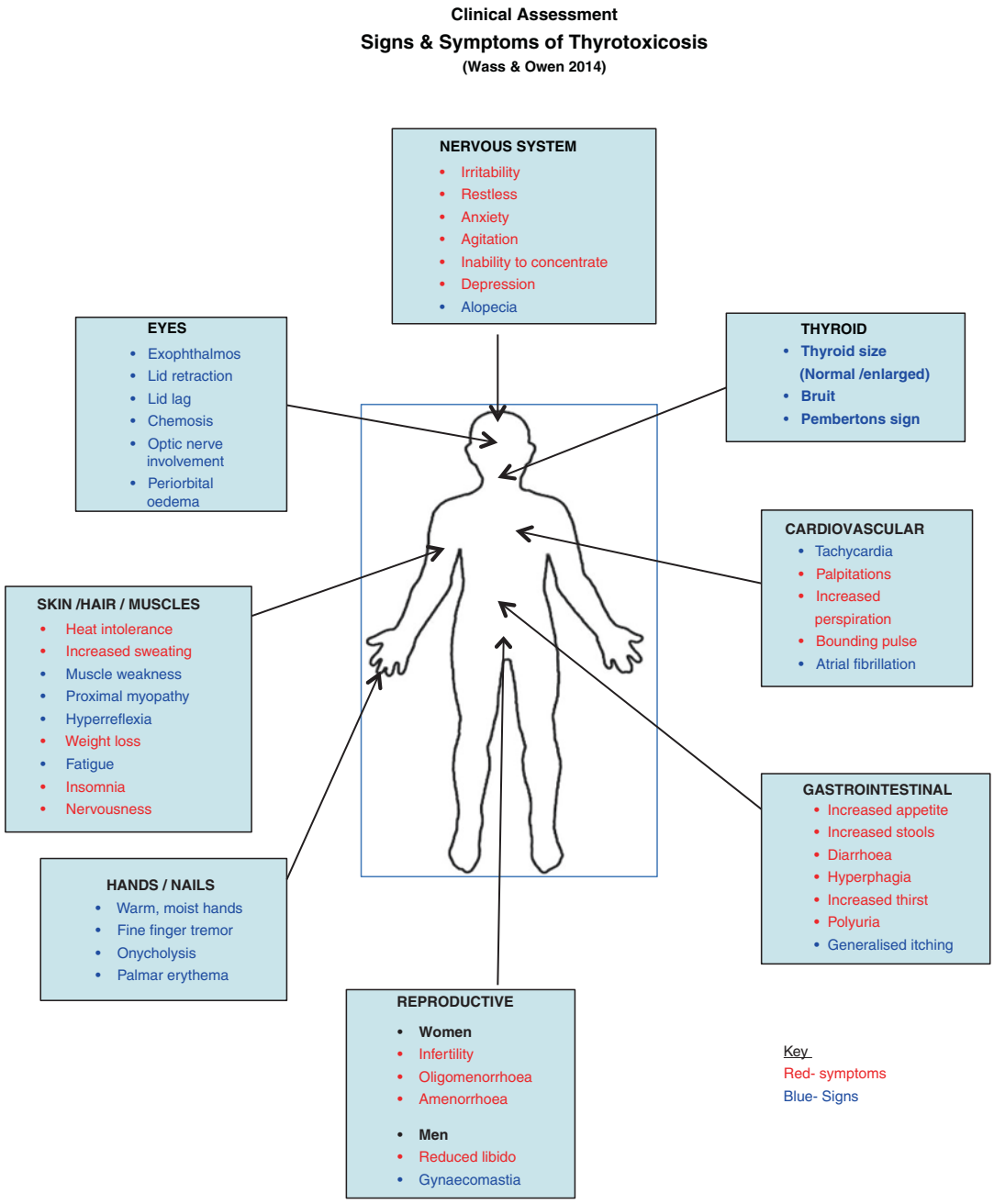


Fig. 28.1 Clinical assessment—signs and symptoms of thyrotoxicosis

untreated, can have serious health implications on a patients' well-being (British Thyroid Association-BTA 2006; Franklyn and Boelaert 2012; American Thyroid Association – ATA 2016; Goichot et al. 2015).

Primary hyperthyroidism refers to disorder of the thyroid gland that causes thyrotoxicosis such as in Graves' disease, nodular goitre, or various types of thyroiditis, whilst **Secondary hyperthyroidism** is caused by extra-thyroidal stimulation of the thyroid gland, for example, a thyroid stimulating hormone (TSH) secreting pituitary adenoma that causes thyrotoxicosis (Weetman 2010).

The prevalence of hyperthyroidism in the United Kingdom (UK) is reported to be around 2% in women and 0.2% in men (Tunbridge et al.

1977; Franklyn and Boelaert 2012). Furthermore, in Europe, the prevalence of endogenous subclinical hyperthyroidism is estimated to be around 0.6–16% (Bondi et al. 2015; Canaris et al. 2000; Bülow Pedersen et al. 2002; Marqusee et al. 1998). The incidence of hyperthyroidism is mostly found in regions of iodine deficiency and in the elderly population. In the United States of America (USA), the prevalence of hyperthyroidism is estimated to be in the region of 1.2% (American Thyroid Association – ATA 2016; Singer et al. 1995).

Overt hyperthyroidism is diagnostic of primary hyperthyroidism, for example, by a low TSH, and high FT4 and FT3 hormone concentrations (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016).

In patients with overt Graves' or nodular goitre, serum FT3 levels are often reported to be higher than serum FT4 and termed as FT3-toxicosis (Ross 2016; Laurberg et al. 2007). However, T4-toxicosis can suggest a concurrent non-thyroidal illness demonstrated by a low serum TSH, high serum FT4, and normal serum FT3, due to decreased extra-thyroidal conversion of T4 to T3 (Caplan 1980).

In a TSH secreting pituitary adenoma, the serum TSH is increased as well as serum FT4 and FT3, indicating not only overt hyperthyroid but also diagnostic of secondary hyperthyroidism.

Subclinical hyperthyroidism (SH) is defined by a low biochemical or an undetectable TSH, with both FT4 and FT3 values within the normal reference range, and in the absence of the following diseases (Franklyn 2011; Cooper and Biondi 2012; European Thyroid Association 2015):

- Hypothalamic disease or pituitary disease
- Non-thyroidal illness
- Ingestion of drugs that inhibit TSH secretion, e.g. glucocorticoids and dopamine

SH is frequently found in men and women over the age of 65 years and can give rise to risks for developing osteoporotic fractures from the increased bone turnover as well as coronary heart disease and atrial fibrillation (Cappola et al. 2006; Wirth et al. 2014; Ross 2017a; Blum et al. 2015).

Patients treated with either radioiodine (RAI) or thyroid surgery for underlying hyperthyroid disorders such as Graves' disease or toxic nodular goitre, often require Thyroxine to normalise thyroid function; patients should therefore be warned of the risks associated with SH and aim therefore always to have the thyroid hormones within the normal reference range (Franklyn 2011).

However, there remains an ongoing debate as to whether to treat or not to treat with Thyroxine replacement, for example, there appears to be very little evidence that demonstrate whether there are any related long-term side effects. In these circumstances, a multidisciplinary approach should be practised if treatment is to be considered. However, recurrent guidelines suggest, all patients with SH over the age of 65 are at risk of developing osteoporosis and atrial fibrillation and the use of Thyroxine would benefit such patient (British Thyroid Association-BTA 2006; Franklyn 2011). Furthermore SH can also occur as a result of non-thyroid reasons, for example, major illness, iodine agents, pregnancy, and also drug therapies including Dopamine and Glucocorticosteroids.

A number of risk factors are thought to be associated with hyperthyroidism (Box 28.2).

Box 28.2 Hyperthyroidism Risk Factors (Adapted from BTA 2006; Vaidya and Pearce 2014)

- Age: elderly over the age of 60 and Graves' disease between ages of 40 and 60
- Gender: women more commonly effected
- In recent pregnancy
- In autoimmune diseases such as type 1 diabetes
- Genetics: Family history of thyroid disease
- Iodine deficiency
- Iodine excess
- Ethnicity
- Medical: common viral infections
- Smoking

28.1.3 Causes of Hyperthyroidism

Hyperthyroidism can occur from a variety of thyroidal or non-thyroidal causes, and therefore it is essential that the condition is determined both accurately and promptly.

In-depth knowledge related to thyroid anatomy and physiology is key towards providing appropriate care to patients (Sect. 4, Chap. 26). For example, an astute clinical practitioner will be able to identify the signs and symptoms of thyrotoxicosis through the undertaking of a detailed patient history, assessment, and physical examination. In doing so, this in turn not only provides the pathway for a preliminary diagnosis to be made, but also accelerates a more tailored approach to implementing specific investigations and a treatment plan whilst waiting for a more formal confirmed validated diagnostic test to return (e.g. thyroid receptor antibody or uptake scan results). Moreover, this can benefit the health service in terms of cost-effectiveness as well as enhance patient recovery.

In most endocrinology departments, conditions more commonly associated with hyperthyroidism include Graves' disease, multinodular goitre, toxic adenoma, various types of thyroiditis (subacute and post-partum), and subclinical thyrotoxicosis (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016). These common conditions were also evident from a thyroid nurse-led clinic outcomes audit undertaken in Oxford for example the audit showed that out of 134 patients seen over a year, 112 were managed for Graves' disease, 10 with toxic nodular goitre, 10 with thyroiditis (subacute and post-partum), and 2 with subclinical thyrotoxicosis (Fazal-Sanderson et al. 2017).

Other rare hyperthyroid conditions include a TSH secreting adenoma, human chorionic gonadotropin-dependent hyperthyroidism, trophoblastic tumours, hyperemesis gravidarum, familial gestational hyperthyroidism, fetal and neonatal transfer hyperthyroidism, non-autoimmune congenital and familial hyperthyroidism (Latrofa et al. 2011).

Conditions associated with hyperthyroidism and thyrotoxicosis are highlighted below.

28.1.4 Graves' Disease

Graves' disease originally derives its name from an Irish Physician called Joseph Graves (1796–1853) who first associated the disease with thyroid gland enlargement and its association with palpitations (Volpe and Sawin 2011; Smith 2018).

The actual cause of Graves is unknown, although it mostly affects women, often runs in families and thought to be linked to a genetic component, stress, smoking, and pregnancy (Box 28.2). Smoking has also been an associated as a risk factor for developing thyroid eye disease (TED) (Sect. 4, Chap. 31).

In the UK, Graves' disease affects around 75% of patients with overt hyperthyroidism and occurs more frequently in women than in men. Around 30% of these cases are reported to develop Graves' orbitopathy or thyroid eye disease [Vaidya and Pearce 2014; Thyroid Eye Disease Committee Team (TEDct) 2018].

Active TED comprises of an inflammatory process that can lead to eye signs including conjunctival injection, chemosis, visual field defect, double vision, and can ultimately affect the extraocular muscle and related cranial nerves (Perros et al. 2015). If left untreated, major eye complications can occur damaging both external and internal orbital soft tissue structures. Body image becomes a huge problem in these patients, as well as depression and low self-esteem (TEDct 2018). Patients with active TED should therefore be referred promptly to a specialist ophthalmologist for appropriate assessment and management (Sect. 4, Chap. 33).

28.1.4.1 Definition

Graves' disease is an autoimmune condition in which thyrotropin receptor antibodies stimulate TSH receptors, and as a result, there are increased levels of circulating of thyroid hormone. The autoantibodies produced mimic the action of thyroid stimulating hormone on follicular cells within the thyroid gland. As a result of continual stimulation of thyroid hormones, fT4 and fT3 are increased in the circulation causing loss of feedback mechanism to the pituitary. Consequently,

the TSH becomes suppressed and exerts its effects on the follicular cell of the thyroid causing thyroid enlargement and lymphocytic infiltration (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016).

28.1.4.2 Aetiology

Thyroid stimulating immunoglobulin binds to and stimulates the thyroid.

28.1.4.3 Pathogenesis

There is diffuse hyperplasia and hypertrophy of the thyroid follicular cells.

28.1.4.4 Specific Clinical Features

Thyroid gland: The classical hallmarks features of Graves disease includes thyroid gland enlargement, which is usually smooth, soft, diffuse and often symmetrical on palpation, however, a few cases have been diagnosed with accompanying nodules thought to be linked to pre-existing nodule/s or from a longstanding disease (American Thyroid Association – ATA 2016; Berghout et al. 1990).

Signs and symptoms: Patients can present with a range of signs and symptoms relating to overt hyperthyroidism (Fig. 28.1). The severity of symptoms requires a thorough assessment with a full clinical history and physical examination for the purpose of managing symptom effectively and restoration of normal thyroid function.

Graves' ophthalmopathy: All patients with Graves' disease should have a thorough eye assessment as part of the clinical assessment. Eye signs including lid lag and retraction, signs of proptosis, and extraocular movements should be recorded and monitored at every follow-up. Any active signs of TED should prompt a referral to an ophthalmologist for treatment and regular follow-up (Perros et al. 2015) (Sect. 4, Chap. 31).

Smoking: This is considered as a serious risk factor for developing Graves' ophthalmopathy (Perros et al. 2015). Health promotion leaflets should be provided for patients to stop smoking and the consequences for developing TED must be explained (British Thyroid Association-BTA 2006; Thyroid Eye Disease Committee Team 2018; Perros et al. 2015).

Pretibial myxoedema: This is also known as Graves' dermopathy, thyroid dermopathy, or infiltrative dermopathy.

Pretibial myxoedema is a rare condition and can be found in around 5% of cases with Graves' hyperthyroidism. It is also associated with Graves' disease with ophthalmopathy.

Pretibial myxoedema is usually located in the pretibial region just below the knees but also has been associated with ankles, and dorsum of the foot, hands, elbows, upper back, face, and neck (Davis 2017).

The combination of lymphocytic infiltration with cytokines causes pathologic changes that give rise to mucinous oedema within the papillary, reticular dermis and deep beyond into tissue. This results in non-pitting oedema and lesions of the dermis together with high levels of circulating TSHRAb. The lesions are usually raised and the skin appears thick and discoloured often with no pain or symptoms, thus no treatment is required and resolves spontaneously over time. However, in cases where pain and tenderness is experienced, treatment comprises of topical steroids and compression bandages (Schwartz et al. 2002).

28.1.4.5 Biochemical and Imaging Features

A thyroid function test: This is the gold standard diagnostic test for hyperthyroidism and is confirmed by a suppressed TSH, elevated fT4 and fT3.

TSHRAbs: reported to have 98% sensitivity and 99% specificity for testing positive in the diagnosis of Graves' hyperthyroidism (Tozzoli et al. 2012).

Radionuclide thyroid uptake: provides formal confirmation of Graves' disease with increased uptake and when TSHRAb test is inconclusive.

28.1.4.6 Diagnosis

- Thyroid function test shows a supressed serum TSH, increased serum fT3 and fT4.
- Positive TSHRAb test and thyroid peroxidase antibodies (antithyroglobulin and anti-thyroid peroxidase antibodies are markers of autoimmune disease).

- A thyroid uptake scan that shows increased uptake confirms Graves' disease.
- Fine needle aspiration (FNA) thyroid biopsy may be required to exclude thyroid malignancy if a nodule is discovered in presence of Graves' hyperthyroidism.
- Eye signs related to hyperthyroidism that have not settled following normalisation of thyroid hormones should prompt an ophthalmology referral for opinion.

28.1.4.7 Treatment

Hospital policy and protocols vary in countries although guidelines are provided with the most up-to-date evidence-based recommendations (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; Schwartz et al. 2002). Many endocrine centres use the guidelines to form their own policies and care pathways.

Anti-thyroid drugs: In the UK, Europe, China, and Japan, primary treatment for Graves' hyperthyroidism comprises of 6–18 month course of anti-thyroid medications such as Carbimazole. Studies have demonstrated that the duration of treatment in excess of 18 months does not improve remission rates. Furthermore, findings have also suggested that remission is improved if restoration of euthyroid state is achieved independent of drug dose and type. To date, the remission rate in Graves' disease varies in countries and is reported to be around 40–70% (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; Organzi and Bournard 2011). A thyroid nurse-led clinic audit (Oxford, UK) of long-term follow-up patients with Graves' hyperthyroidism showed the remission rate to be around 33%, and inturn suggesting that definitive treatment could be a future consideration for primary treatment for Graves' disease rather than patients enduring a lengthy course of medical therapy (Sanderson et al. 2012). This not only can have cost-benefits to the health service but also enhances a more rapid restoration of normal thyroid hormone function and patient recovery. In the USA, radioiodine is offered as the first-line treatment for Graves' hyperthyroidism and thought to be due to the high rate of relapse with anti-thyroid medications.

Definitive treatments radioiodine or thyroid surgery: In the UK, patients who have relapsed following a 12–18 month course of anti-thyroid drugs (ATDs) such as Carbimazole and Propylthiouracil are offered, provided the patients suitability has been assessed (Sect. 4, Chap. 28 B-RAI & C-Thyroid surgery). Both treatments aim to prevent future relapse of Graves' hyperthyroidism (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

Lifelong thyroxine: is usually required following definitive treatment with either radioiodine or thyroid surgery, and therefore normalisation of thyroid hormones is essential prior to discharge (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

Following discharge from secondary care: all patients should seek have regular 6–12 monthly thyroid function test, or earlier if thyroid symptoms return (with their assigned General Practitioner (GP), or healthcare provider), to ensure that long-term stability of thyroid status is maintained (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016) (Box 28.3).

Thyroid eye disease: Treatment for active TED requires specialist treatment under the care and supervision of an ophthalmologist. Treatment may include steroidal medication, series of eye drops, visual field assessment, orthoptic services, or even orbital surgery (TEDct 2018; Perros et al. 2015) (Sect. 4, Chap. 31).

Box 28.3 Case Study 1. Graves' Disease and a Case of Neutropenia: A Matter of Urgency!

Graves' disease is an autoimmune disorder accounting for about 80% of the cases of hyperthyroidism and affecting predominantly females. In the UK, Carbimazole is the first choice of anti-thyroid medication and is associated with a risk of agranulocy-

tosis (reported in 0.2–0.5% of the patients) and severe infections. In such cases, immediate discontinuation of Carbimazole is needed and alternative management options should be considered. In a Thyroid Nurse-led Clinic in Oxford, most patients opt for an 18-month course of Carbimazole, despite there being only a 30% remission rate. This case study demonstrates the management of Graves' disease and the matter of urgency required for prompt action in cases of neutropenia.

Case study—A 26-year-old female was diagnosed with Graves' disease and opted for an18-months course of Carbimazole. She completed the course of treatment and 1 month after stopping the anti-thyroid medication she was diagnosed with relapse of the Graves'. She responded to treatment well and by month 6, her daily dose was reduced to 5 mg. At this time, she developed a fever and consequently a FBC taken which showed low white cell count of 3.57 and low neutrophil count of 0.84. Carbimazole was stopped and 2 weeks later, the neutrophil count was restored. Swift arrangement was made for an urgent thyroidectomy. She was later discharged on Thyroxine with normal thyroid hormones.

28.1.5 Toxic Adenoma/Toxic Multinodular Goitre

The term goitre refers to an abnormal growth of the thyroid gland that can result either as diffuse or nodular, and effect thyroid hormones production (Ross 2017b). The most common cause of goitre worldwide is reported to be due to iodine deficiency (Vanderpump 2011).

An enlarged goitre usually implies iodine deficiency. It can occur at any age, for example, when iodine intake falls, TSH from the pituitary rises and maximises the availability of iodine from the thyroid gland causing diffuse enlargement. Overtime, and in light of low iodine intake, nodules develop, the commonest being multinodular goitre, mostly found in the elderly population (Zimmerman 2012).

The incidence of thyroid nodules is reported to be more common in females compared to male population. In the UK, toxic nodular goitre accounts for 15% of hyperthyroid cases and is also reported to be associated with the elderly population in regions of iodine deficiency (Franklyn and Boelaert 2012). Around 5% of nodules are picked up on neck palpation during a clinical assessment (Bomeli et al. 2010).

28.1.5.1 Definition

Toxic adenoma (TA) can be described as a single autonomously functioning nodule within the thyroid gland that secretes thyroid hormones from thyrocyte cells (Latrofa et al. 2011). These are benign tumours that can cause mild to overt hyperthyroidism mostly associated with iodine deficiency (Vaidya and Pearce 2014).

Toxic multinodular goitre (TMG) is usually a heterogeneous disorder of the thyroid gland, comprising of multiple autonomous functioning nodules, also known as Plummer's disease (Weiner and DeVries 1979). Additional nodules may also be present and appear as normal or with reduced uptake on radioiodine uptake imaging.

28.1.5.2 Aetiology

TA comprises of monoclonal autonomously secreting benign tumour, whilst TMG is reported as multiple monoclonal autonomously secreting benign thyroid tumours.

28.1.5.3 Pathogenesis

These nodules are usually benign follicular adenomas. Adenomas are reported to consist of uniform structures containing mitoses that are encompassed by a fibrous capsule formed by the surrounding compressed thyroid tissue. The autonomous function from within the thyroid nodule follicular cells is independent to that regulated by the thyroid stimulating hormone, and in the absence of TSH-receptor stimulating antibodies. The continual autonomous production of thyroid hormones over time can progress from a subclinical state to overt hyperthyroidism.

Unregulated thyroid hormones initially suppress the TSH, and in the presence of overt hyperthyroidism cause tissue atrophy around the adenoma (Fuhrer and Lazarus 2011).

28.1.5.4 Biochemical and Imaging Features

- Measurements of thyroid function tests are essential for diagnosis and confirmed by a suppressed serum TSH, and elevated serum fT4 and fT3.
- T3 toxicosis is often found in TAs (Laurberg et al. 2007).
- A thyroid ultrasonography and scintiscanning identifying nodular activity shows increased uptake with suppression of uptake in the surrounding extranodular thyroid tissue, thus provides a formal diagnosis (Fuhrer and Lazarus 2011).
- Ultrasound scanning of the neck gives information of nodule size and identifies the presence of other existing cold nodules.
- Ultrasound elastography is useful for identifying benign from malignant nodules.

28.1.5.5 Clinical Features

- Signs and symptoms that patients present with are any of those relating to overt hyperthyroidism (Fig. 28.1), and severity of these requires a thorough patient assessment that includes a full clinical history and physical examination for the purpose of symptom relief and management.
- Examination of thyroid anatomy will help to determine the presence of a single or multiple nodules. Furthermore, given that such nodules are commonly found in the elderly population, a thorough assessment of the thyroid is recommended using skills of observation, palpation, auscultation, and percussion. The size, consistency, symmetry, and texture including any tenderness should also be noted. Attention to any signs of obstruction compromising blood flow, or air entry due to thyroid gland enlargement or tracheal deviation should be addressed as a matter of urgency to the medical team.
- Head and neck lymph node examination is also essential noting size, tenderness, consistency, including whether any are mobile or fixed for the purpose of detecting any associated malignancy (Hogan-Quigley et al. 2012). Although TAs are benign and very rarely malignant, other malignancies can be picked up.
- Ophthalmopathy and other stigmata of Graves' disease, including anti-thyroid antibodies, are usually absent.

28.1.5.6 Diagnosis

- Thyroid function tests confirm hyperthyroidism (low TSH, high fT4, and high fT3) in both TA and in TMNG.
- Thyroid ultrasonography and scintiscanning provides a formal diagnosis of single nodule—TA, or multiple nodules—TMG with increased uptake.
- Thyroid peroxidase Abs are usually absent (TA and TMG).
- Fine needle aspiration biopsy is recommended for nodules greater than 1 cm in diameter or according to local hospital policy. Although the risk of malignancy thought to be low in cases of toxic nodular goitre, occasional cases of malignancy have been reported in TMNG (Cerci et al. 2007).
- Computer tomography (CT) scans or X-ray imaging may be required to assess tracheal compression from a large toxic nodular goitre. However, the use of iodine containing contrasts with CT scanning can exacerbated existing hyperthyroidism, and thus should be avoided; furthermore, caution should be practised with similar agents, for example, barium swallow test to evaluate oesophageal pressure effects.

28.1.5.7 Treatment

The treatment for TA and MNG is aimed to restore normal thyroid function. The treatment options depend on patients' age, severity of hyperthyroidism, size of goitre, and underlying medical illnesses.

28.1.5.7.1 Anti-Thyroid Medication: Carbimazole

In the UK, anti-thyroid drugs (ATDs) such as Carbimazole (CBZ) and Propylthiouracil (PTU)

are effective treatments used to control thyroid function in TA or TMNG (CBZ being first choice due to its association with less side effects compared to PTU). Although an ATD is not a curative treatment for an autonomously functioning TA or TMNG, they are used primarily to stabilise thyroid function in preparation for definitive treatment such as radioiodine or thyroid surgery (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016).

Beta blockade drugs: Propranolol is an effective treatment for symptom relief, and can be prescribed in combination with Carbimazole. Once euthyroidism has been achieved, Propranolol should be weaned off gradually as per local hospital policy(British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; British National Formulary 2018a).

TFT monitoring on ATDs: This comprises of 4–6 weekly TFTs monitoring until euthyroidism is achieved on the minimal dose of anti-thyroid medication, for example, a starting dose of Carbimazole 20–40 mg daily is titrated against TFTs, and as TFTs improve every 4–6 weeks, Carbimazole is gradually weaned until maintenance dose of 5 mg daily is achieved in preparation for a definitive treatment(British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

28.1.5.7.2 Definitive Thyroid Surgery

Partial or complete thyroidectomy: surgery aims to remove the entire autonomously functioning nodule. In the case of a large multinodular goitre that compromises a patient's airway, or where surrounding structures cause compression and interfere with swallowing, surgery is usually favourable and often successful in the hands of an expert thyroid surgeon (Sect. 4, Chap. 28 (C) Thyroid Surgery).

Pregnancy: In hyperthyroidism associated with pregnancy, surgery is usually restricted from the first to third trimester(American Thyroid Association – ATA 2016) during which time anti-thyroid medication such as Propylthiouracil is administered to restore normal thyroid function within the safe and specific parameters recommended in pregnancy (American Thyroid Association – ATA 2016) (Sect. 4, Chap. 33).

Monitoring of thyroid function post surgery: TFTs should be monitored 4–6 weekly post-thyroid surgery with the aim to achieve euthyroidism on lifelong Thyroxine replacement.

Checks to ensure thyroidectomy site is adequately healed, calcium level within normal reference range, and importance of taking lifelong Thyroxine replacement are essential prior to discharge from secondary care. Information leaflets can also be made accessible to patients via relevant website (British Thyroid Foundation 2015a).

28.1.5.7.3 Definitive Radioiodine-RAI Treatment

The treatment of TA and TMNG with RAI avoids surgery thus is managed conservatively. In the UK, RAI 131 is prescribed within the safe recommendations of hospital guidelines (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

It not only ablates hyperthyroidism but has also shown to reduce nodular size. Patients are likely to become hypothyroid and therefore close monitoring of thyroid hormones are paramount in the early stages to avoid the side effects of hypothyroidism.

Monitoring of thyroid function post-RAI: TFTs should be monitored 4–6 weekly to avoid occurrence of hypothyroidism. In this way, ATD can be gradually weaned off until euthyroidism is achieved, with or without Thyroxine replacement.

The effects of RAI for achieving euthyroidism approximates from 6 weeks to 3 month, sometimes even up to 6–8 months (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

Second dose of RAI: Patients who remain hyperthyroid beyond 6–8 months following first dose of RAI, and still requiring Carbimazole, are usually offered a second dose of RAI, which usually renders the patient euthyroid.

Pregnancy: RAI is contraindicated in pregnancy (see chapter). Females receiving RAI treatment should avoid pregnancy for up to 6 weeks and suggested to seek contraceptive cover.

Long-term monitoring: after successful treatment and restoration of normal thyroid function with or without Thyroxine replacement, long-term monitoring of thyroid function is essential. Healthcare providers such as general practitioners (GPs) should be advised to monitor TFTs 6–12 monthly to avoid potential long-term effects of hypothyroidism. In this way euthyroidism can be maintained with or without Thyroxine replacement (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

28.1.6 Thyroiditis

The term thyroiditis comes under an umbrella of a variety type of thyroid disorders. It is generally associated with inflammation of the thyroid gland, and often causes transient thyrotoxicosis, followed by temporary hypothyroidism, resulting with either restoration of normal thyroid function or permanent hypothyroidism.

Thyroiditis can also be referred to as painful (Box 28.4) or painless (Box 28.5) thyroiditis, and can occur as a result of drug therapies or through radiation (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016).

Acquiring relevant knowledge and understanding of the distinctive features associated with the various types of thyroiditis disorders can contribute significantly towards establishing the correct diagnoses, provide the most appropriate treatment and in turn enables the nurse practitioner to manage patients promptly, efficiently and cost-effectively.

Box 28.4 Thyroiditis with Pain/Tenderness

- Subacute thyroiditis
- Infectious thyroiditis
- Radiation thyroiditis
- Palpation
- Trauma induced thyroiditis

Box 28.5 Thyroiditis with Absence of Pain/Tenderness

- Painless thyroiditis
- Post-partum thyroiditis
- Drug induced thyroiditis
- Chronic Hashimoto's thyroiditis
- Struma Ovarii (Dermoid)

Some of the common conditions related to thyroiditis are discussed and include subacute infectious, post-partum, and silent thyroiditis.

28.1.6.1 Subacute Thyroiditis (Infectious)

28.1.6.1.1 Definition

Subacute thyroiditis (or infectious thyroiditis) is a self-limiting inflammatory disorder of the thyroid that can last for several weeks or months. It characterised by transient thyrotoxicosis, followed by hypothyroidism and then returns to normal thyroid function in the majority of patients. It is also known as 'De Quervains' named after Fritz De Quervains, a Swiss surgeon who in 1904 first described granulomatous changes as giant cells in the pathology of thyroiditis (Engkakul et al. 2011; Kaplan et al. 2011; Hennessey 2015).

Subacute thyroiditis is the most common cause of painful thyroiditis in which women, aged 20–50 years, are more frequently affected compared to men.

It is usually triggered by a viral infection, for example, mumps or flu, with highest incidence often occurring around the summer season (Hennessey 2015).

28.1.6.1.2 Aetiology

Inflammation of the thyroid gland (possibly caused by a virus) results with the release of preformed stores of thyroid hormone, including thyroglobulin and iodinated compounds, causing a rise in circulating thyroid hormones fT4 and fT3,

and suppression of TSH. This phase lasts for around 1–3 months before going into spontaneous remission as colloid is depleted from the thyroid gland. In the majority of patients this results in hypothyroidism, lasting for around 3–6 months during which time the thyroid follicles begin to regenerate and return to a euthyroid state in the majority of patients.

28.1.6.1.3 Pathogenesis

In subacute thyroiditis there is destruction of follicular epithelium and loss of follicular integrity. These can appear as granulomatous with either partial or complete loss of colloid tissue forming giant cells or granulomatous thyroiditis and consistent in viral infection. On recovery, the inflammation recedes and recovery is generally complete.

28.1.6.1.4 Clinical Features

- Subacute thyroiditis starts with prolonged phase of myalgia, malaise, and fatigue.
- History of frequent upper respiratory infection.
- Fever may be present.
- Moderate to severe pain in the neck, jaw, throat, or ear. Patients can usually localise pain to thyroid region.
- Transient vocal cord paresis.
- Symptoms can be related to transient overt hyperthyroidism (Fig. 28.1) or hypothyroidism (Sect. 4, Chap. 30).
- The thyroid gland is often enlarged, firm to hard on palpation, with tenderness focused in one area spreading to other areas of the thyroid gland.

28.1.6.1.5 Diagnosis

- TFTs usually show transient thyrotoxicosis at onset lasting for around 3–6 weeks (suppressed TSH and elevated fT4 and fT3), followed by hypothyroidism usually lasting for approximately 6 months.
- Clinical features include moderate to severe pain in the neck, jaw, throat, or ear and symptoms at early onset relate to thyrotoxicosis, followed by those related to hypothyroidism.
- Raised erythrocyte sedimentation rate and raised C-reactive protein helps to confirm the diagnosis (usually resolves around 6 months).
- Full blood count may show mild anaemia.
- White blood cell count is usually elevated.
- Radioactive iodine uptake scan RAIU uptake appearance is low or undetectable.
- Thyroid peroxidase and thyroglobulin antibodies are usually low or absent.

28.1.6.1.6 Treatment

Anti-thyroid medication is usually not necessary because no new hormones are being made and due to its transient nature, normal thyroid function is restored return to normal thyroid function.

Beta-blockers such as Propranolol can be prescribed for symptom relief in transient cases of thyrotoxicosis. ATDs are not recommended due to the transient presence associated with subacute thyrotoxicosis and furthermore, Thyroxine therapy is often not required in the short hypothyroid phase; however, it can be prescribed in the very symptomatic patients for up to 3–6 months (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; British National Formulary 2018a; Shreshtha and Hennessey 2015).

Analgesia: Paracetamol, Aspirin, or non-steroidal anti-inflammatory including Ibuprofen can all provide effective pain relief (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; Hennessey 2015; British National Formulary 2018b).

Corticosteroids: If analgesia or non-steroidal anti-inflammatory drugs (NSAID) fail to work, corticosteroids can be used and are effective, for example, prednisolone 15–40 mg daily can be prescribed for 1–2 weeks, followed by reduction of 5 mg over 2–4 weeks (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; Hennessey 2015; British National Formulary 2018b).

In subacute thyroiditis, the transient phase of thyrotoxicosis is usually 1–3 months, followed by the hypothyroid phase 3–6 months, leading to complete recovery by 12 months from onset. On recov-

Box 28.6 Case 2. A Case of Subacute Thyroiditis

A 27-year-old woman was referred by her GP to the Thyroid Nurse-Led Clinic (TNLC). She presented with a recent history of a swelling and pain of the neck, shortness of breath, feeling flushed, shaky, and anxious. These symptoms developed after an upper respiratory tract infection. Blood tests by the GP showed thyrotoxicosis [TSH <0.01 mU/L (0.35–5.5), fT4 34.6 pmol/L (10.5–20), and fT3 8.6 pmol/L (3.5–6.5)] who started Carbimazole 20 mg od. She was referred to the TNLC at a tertiary centre and assessed. Her symptoms were settling, although on palpating her neck, a very small, non-tender, soft, and symmetrical goitre was noted. Other than mild fine hand tremor, she had no other manifestations of thyrotoxicosis and there were no signs of thyroid eye disease. Investigations showed her TSH receptor Abs to be negative and TFTs: TSH 0.09, fT4 15.2, and fT3 3.5. The thyroid uptake scan showed no uptake. The Carbimazole treatment was then stopped and around 1 month later, her TFTs showed TSH 10.90, fT4 13.9, and fT3 4.3. No Levothyroxine was started and within 3 months she became biochemically euthyroid. She remained stable in the next few weeks and she was discharged back to her GP.

ery, patients should be warned of future repeated relapses that can occur especially following upper respiratory infections, and the possibility of becoming permanently hypothyroid, requiring long-term Thyroxine replacement (Box 28.6).

28.1.6.2 Post-Partum Thyroiditis

Post-partum thyroiditis (PPT) is also referred to as painless thyroiditis. In the USA, the incidence is reported to be around 10% in pregnancies. It usually occurs within the first year following childbirth or within 6 months after pregnancy (Amino and Kubota 2011; Pearce et al. 2003). The immune system essentially attacks the thyroid gland causing temporary thyrotoxicosis (1–6 months), followed by hypothyroidism (3 months) as the thyroid gland becomes depleted of thyroid hormone, to then becoming fully recovered to euthyroid state within 12 months after childbirth. There are, however, reported cases in which some women fail to recover from the hypothyroid phase and end up requiring Thyroxine replacement (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; Latrofa et al. 2011).

PPT is often preceded by subclinical autoimmune thyroiditis. For example, immune activation causes transition of subclinical to overt autoimmune thyroid disease. During the post-partum period in patients with previous history of Graves' disease or Hashimoto's thyroiditis, immune activation results in relapse after parturition.

PPT is also seen in women with type 1 diabetes.

28.1.6.2.1 Definition

PPT thyroiditis is defined as an exacerbation of autoimmune thyroiditis during the first post-partum year and characterised by transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by transient hypothyroidism after which most women return to a state of euthyroidism at 1-year post-partum (Stagnaro-Green 2002).

28.1.6.2.2 Aetiology

The exacerbation of the underlying autoimmune thyroiditis in PPT is reported to be aggravated by auto-immunological rebound that follows the partial immunosuppression of pregnancy (Stagnaro-Green 2002).

28.1.6.2.3 Pathogenesis

Lymphocytic infiltration into thyroid causes destruction of thyroid gland (similar changes occur in both Hashimoto's and painless thyroiditis). Autoimmune lymphocytic infiltration of the thyroid results in release of stored thyroid hormone (Stagnaro-Green 2002).

28.1.6.2.4 Clinical Features

- Patient may or may not be symptomatic in subclinical thyrotoxicosis. In overt thyrotoxicosis, patients are more likely to experience moderate to severe symptoms such as sweating, palpitations, and fine hand tremor (Fig. 28.1). This phase can occur between 2 and 10 month. Patients entering the hypothyroid phase will experience related symptoms such as cold intolerance, reduced concentration, and constipation (Sect. 4, Chap. 30).
- In some cases, patients may show signs of post-partum depression.
- Graves' eye disease and myxoedema may be present.

28.1.6.2.5 Diagnosis

- Abnormal thyroid dysfunction occurs depending on the phase of PPT, for example, TFTs may indicate subclinical thyrotoxicosis, overt thyrotoxicosis, or hypothyroidism.
- Overt hyperthyroid should be differentiated from post-partum Graves' (e.g. time of onset 2–10 month) and destructive thyrotoxicosis (e.g. onset 1–3 month).
- Elevated (positive) antithyroglobulin antibodies or anti-thyroid peroxidase antibodies.
- RAIU is either low or undetectable.
- Positive TSHRAbs in early pregnancy may indicate risk to developing post-partum Graves' disease and can be confirmed by the presence of a pronounced goitre with bruit, Graves' ophthalmopathy, and increased RAIU.

28.1.6.2.6 Treatment

Untreated hyperthyroidism in post-partum destructive thyrotoxicosis usually resolves spontaneously within 2–3 months, thus the use of anti-thyroid medication is ineffective. However, in patients whose quality of life is disrupted with the burdensome symptoms of hyperthyroidism, use of beta-blockers such as Propranolol or Metoprolol can be prescribed for effective relief. Furthermore, during the hypothyroid phase-related symptoms can be managed with Thyroxine under the guidance of an obstetrician and local hospital policy and guidelines.

Box 28.7 Case 3. Post-Partum Thyroiditis

A 42-year-old mother was referred by her GP feeling unwell with a range of symptoms including tiredness, anxiety, tearfulness, exhaustion, and irritability. Her symptoms started around 6 months after the birth of her baby. Blood tests by her GP showed mild thyrotoxicosis [TSH <0.01 mU/L (0.35–5.5), fT4 24.8 pmol/L (10.5–20), fT3 8.4 pmol/L (3.5–6.9)], and GP commenced anti-thyroid medication. She was referred to the thyroid nurse-led clinic at a tertiary centre 2 months later. Blood tests showed hypothyroidism [TSH 10.99 mU/L (0.35–5.5), fT4 8.7 pmol/L (10.5–20), fT3 4.7 pmol/L (3.5–6.9)] and the medical treatment was stopped. TSH receptor Abs were negative and her anti-TPO Abs were elevated. She was monitored for 6 months, recovered and remained euthyroid and was discharged back to her GP. She was informed that in case of another pregnancy, there was a risk of a future relapse of the post-partum thyroiditis.

In post-partum Graves' disease, if usual course of thyroiditis fails to recover, treatment can be managed with the use of anti-thyroid drugs, radioiodine, or thyroid surgery (Box 28.7).

28.1.6.3 Silent Thyroiditis

Silent thyroiditis is also known as painless thyroiditis. It has a low genetic predisposition and is more common in women than in men.

28.1.6.3.1 Definition

Painless or silent thyroiditis is characterised by an autoimmune-mediated lymphocytic inflammation of the thyroid gland that leads to destructive thyroiditis. This occurs through the release of thyroid hormone, triggering transient thyrotoxicosis that is often followed by a hypothyroid phase, progressing to full recovery by 12–18 months. However, some of these patients will go on to develop early permanent hypothyroidism,

whilst in others, long-term hypothyroidism can also occur many years later.

Silent thyroiditis has similarities to post-partum thyroiditis and also to a form of the autoimmune thyroid disorder called Hashimoto's thyroiditis (Sect. 28.1.6.4).

It can also develop from an enlarging existing goitre, or occur as a result of treatments such as radiotherapy, drug induced therapies containing iodine, lithium, interleukin-2 and interferon (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; Latrofa et al. 2011; Kaplan et al. 2011; Pearce et al. 2003).

Hyperthyroidism is an autoimmune disease and in the majority of patients, manifested by positive anti-thyroid peroxidase and antithyroglobulin antibodies.

28.1.6.3.2 Aetiology

Autoimmune lymphocytic infiltration essentially causes release of stored thyroid hormones resulting in destruction of thyroidal tissue.

28.1.6.3.3 Pathogenesis

Thyroid tissue changes take place as a result of chronic lymphocytic infiltration. For example, the follicular cells within the thyroid gland undergo metaplasia, resulting as larger eosinophilic cells known as Hurthle cells. These contain mitochondria that can progress to fibrosis, and occupy focal regions within the thyroid or affect the entire thyroid gland.

28.1.6.3.4 Clinical Features

- Non-tender goitre, absence of fever, malaise and neck pain
- Asymptomatic although, some patient may experience symptoms-related thyrotoxicosis (Fig. 28.1) or hypothyroidism (Sect. 4, Chap. 30).

28.1.6.3.5 Diagnosis

- Anti-thyroid peroxidase and antithyroglobulin antibodies are usually high (positive)
- Hallmark of silent thyroiditis is the absence of thyroid pain and RAIU of the thyroid is usually low or undetectable.
- A positive TSHRAb test, presence of a goitre, and increased RAIU, is likely to be associated it with a variant of Graves' disease with cytotoxic properties resulting in a form of Hashimoto's thyroiditis.
- Painless thyroiditis is rarely associated with Graves' ophthalmopathy (Latrofa et al. 2011).
- FNA: may be required if a pre-existing goitre enlarges.

28.1.6.3.6 Treatment

In the initial phase of silent thyroiditis, there is usually transient self-limiting thyrotoxicosis followed by hypothyroidism that recovers spontaneously. There is no role for the use of ATDs; however, symptomatic patients can be prescribed beta-blockers such as Propranolol that can be weaned off when the transient phase passes.

If the phase of thyrotoxicosis is so severe, corticosteroids can be administered according to hospital policy.

TFT are usually monitored 4–6 weekly aiming to maintain euthyroidism. The recovery period can take 12–18 months; however, few patients may develop permanent hypothyroidism and require long-term treatment with Thyroxine and regular follow-up as per local guidelines.

28.1.6.4 Autoimmune Hashimoto's Thyroiditis

28.1.6.4.1 Definition

Hashimoto's thyroiditis (HT) is an autoimmune condition, named after a Japanese surgeon, Dr. Hakaru Hashimoto, who in 1912 first associated the histology of thyroid with lymphocytic infiltration, parenchymal atrophy, fibrosis, and eosinophilic changes (Pearce et al. 2003; Akamizu and Amino 2018; Hiromatsu et al. 2013).

HT occurs in all ages but mostly seen in young and middle-aged women. The disorder often can run in families and reported to have a genetic predisposition. It has also been referred to as painless thyroiditis, similar to that associated with silent thyroiditis and post-partum described previously (Pearce et al. 2003; Burman 2017).

In addition, HT can also be associated with other autoimmune conditions including

insulin-dependent diabetes mellitus, vitiligo, pernicious anaemia, and Addison's disease.

28.1.6.4.2 Pathology

The follicular tissue is affected within the thyroid gland and becomes occupied by lymphoid tissue. Over time, lymphocytic infiltration and follicular cells changes occur leading to the formation of fibrotic tissue that can effects a local area of the thyroid or occupy the entire gland (Kaplan et al. 2011; Pearce et al. 2003; Akamizu and Amino 2018).

In some patients, lymphoma has been reported in HT although this is extremely rare (Pearce et al. 2003).

28.1.6.4.3 Clinical Features

- HT is mostly seen in middle-aged women and often picked up on routine clinical assessment or incidental finding.
- Patient may report of neck enlargement over years or sudden onset of rapid enlargement.
- There may be signs of local compression, affecting swallowing or compromising airway (this may be accompanied by a vague ache or tenderness).
- On palpation, the goitre is usually symmetrical, can vary in size, and has a soft-to-firm consistency, with an irregular surface (Kaplan et al. 2011).
- Patient may be asymptomatic if euthyroid, or present with symptoms related to hypothyroidism (Sect. 4, Chap. 30) (very occasionally, some patients with HT can present with mild thyrotoxicosis in the very early stage of disease).
- Fine needle aspiration (FNA) may be required in cases where a thyroid nodule may be present.
- Lymph nodes of the head and neck may be enlarged and should be assessed and evaluated accordingly (e.g., noting location, size, mobility) in case of malignancy (Hogan-Quigley et al. 2012).
- Ophthalmology in HT may also be present and evaluated in case an ophthalmology referral is required (Sect. 4, Chap. 31).

28.1.6.4.4 Biochemical and Imaging Features

- Thyroid hormone findings are usually within normal range or may result with permanent hypothyroidism; however, some patients develop mild thyrotoxicosis also known as hashi-toxicosis.
- Imaging in HT usually shows an enlarged thymus.
- RAIU appears low and patchy on uptake and is only useful in identifying a toxic nodule where the uptake will be increased, and then evaluated by an ultrasound.

28.1.6.4.5 Diagnosis

- The hallmark for diagnosis of HT is increased anti-thyroid peroxide and antithyroglobulin antibodies.
- FNA may be required to exclude any nodule malignancy if a goitre presents with a toxic nodule.

28.1.6.4.6 Treatment

Most cases of HT do not require treatment due to the presence of a small goitre and no symptoms (Vickery and Hamlin 1961). Patients who make good recovery are often prone to frequent future relapse and should therefore be made aware of becoming permanently hypothyroid, requiring lifelong Thyroxine replacement.

Patients with hypothyroidism are usually treated with Thyroxine replacement, calculated under medical supervision according to local guidelines or hospital policy.

TFTs are usually monitored 4–6 weekly, and the goal is to achieve normalisation of thyroid hormones. TFTs checks thereafter can be monitored 6–12 monthly in case adjustment is required.

Special attention should be practised when prescribing Thyroxine replacement in any patient over the age of 60 years, for example, gradual incremental doses of 25 μg daily is suggested to avoid any cardiovascular risks.

Thyroxine replacement is also reported to have a beneficial effect on reducing the size of a large goitre; however, in the elderly, reduction in

size is thought to be delayed due to the fibrotic changes within the thyroid gland.

28.1.7 Struma Ovarii

Struma ovarii (SO) was first described by Dr. Richard Boettlin who discovered the presence of thyroid follicular tissue in ovaries (Boettlin 1889).

Most of the published data for SO are based on case study findings.

28.1.7.1 Definition

SO is defined as a type of dermoid tumour (germ cell) (Young 1993) and account for 1% of all ovarian tumours and 2–5% of ovarian teratomas (Yoo et al. 2008; Kondi-Parfit et al. 2011).

These tumours comprise over 50% of mature thyroid tissue and although this makes it uniquely termed as struma ovarii, thyrotoxicosis is found in less than 10% of cases making SO often very difficult to diagnose (Yassa et al. 2008; Kraemer et al. 2011).

SO effects women aged between 40 and 60 years (Yoo et al. 2008; Kondi-Parfit et al. 2011). Most cases of SO are benign; however, the potential for malignancy has been found on occasions, the most common being associated with papillary thyroid cancer (Yoo et al. 2008; Kraemer et al. 2011; Makani et al. 2004; DeSimone et al. 2003).

28.1.7.2 Pathogenesis

The histology of SO more often shows the presence of benign thyroid follicular and colloid cells; however, pathological changes can also take place causing hyperfunction of thyroid gland (Szyfelbein et al. 1994; Dunzendorfer et al. 1999). Malignancies can be associated with papillary thyroid carcinoma (Kraemer et al. 2011; Makani et al. 2004).

28.1.7.3 Clinical Features

(Clinical features may or may not be present)

- Hyperthyroid symptoms can occur in less than 10% of cases (Fig. 28.1)
- Lower abdominal pain
- Palpable lower abdominal mass
- Abnormal vaginal bleeding
- Abdominal ascites (Mui et al. 2009)

28.1.7.4 Biochemical and Imaging Investigations

- Hyperthyroidism (although rare): suppressed TSH, raised fT4 and fT3
- Imaging with Radioiodine (I)-whole body scan shows pelvic mass, with thyroid involvement
- Ultrasonography shows ovarian mass
- Antithyroglobulin antibodies usually elevated

28.1.7.5 Diagnosis

- RAIU of thyroid is usually low to undetectable.
- Elevated serum thyroglobulin.
- RAIU in pelvis is increased (not in thyroid gland) and extra-thyroidal struma ovarii suspected.
- Histology and pathology findings reveal thyroid tissue as the major component.

28.1.7.6 Treatment

Surgical resection of mass is the approach for benign disease, including regular serum thyroglobulin level checks used as a marker for recurrence at follow-up.

Surgery with adjuvant radioiodine therapy has been shown to be successful in treating metastatic and recurrent disease (Yoo et al. 2008).

28.1.8 Anti-thyroid Drug Therapy

Thionamides are group of chemically related compounds used as anti-thyroid drug (ATD) treatments for managing hyperthyroidism. They are used in preparation for thyroidectomy in hyperthyroidism or prescribed as therapy prior to and post-radioiodine treatment (British Thyroid Association-BTA 2006; British National Formulary 2018a).

28.1.8.1 Carbimazole and Propylthiouracil

The most commonly used ATD treatment in the UK is Carbimazole (CBZ). Propylthiouracil

(PTU) is also available although this can sometimes be used if patients develop adverse effects to CBZ such as rash, stomach upset, nauseas, and occasionally hair loss (British National Formulary 2018a; Tidy 2014). PTU is usually reserved for pregnancy and is usually administered during the first trimester as it is reported to minimise the potential side effects of fetal malformation that have been associated with Carbimazole in pregnancy (American Thyroid Association – ATA 2016; Cooper and Laurberg 2013; Bowman et al. 2012) (Sect. 4, Chap. 33) (Box 28.8).

CBZ and PTU exert their action on thyroid tissue by inhibiting iodination of thyroglobulin thereby gradually diminishing thyroid hormone secretion, thereby rendering the patient euthyroid and controlling hyperthyroidism in the majority of patients (Laurberg 2006; Cooper 2005). However, the rate of relapse following an 18-month course of ATD treatment is reported to be around 40–60% (Bartelena 2008; Benker et al. 1998; Hedley et al. 1998).

The use and availability of CBZ is known in many parts of Europe. However, in the USA, anti-thyroid treatments used are Methimazole (considered the equivalent of CBZ) and PTU.

The use of healthcare guidelines from reputable organisations often provides an itinerary of recommendations of the most up-to-date evidence-based related research for use in clinical practice. The following governing bodies from the UK, Europe, and the USA have published advice and suggestions for managing patients with hyperthyroidism (Box 28.8).

Anti-thyroid drugs have a number of benefits for managing thyrotoxicosis. The aim of these medications includes:

- Control of symptoms related to hyperthyroidism with the aim to restore normal thyroid function
- To induce remission in Graves' hyperthyroidism
- To achieve euthyroidism in hyperthyroid disorders such as toxic goitre, in preparation for treatment with radioiodine or thyroid surgery
- To manage hyperthyroidism in cases of recurrence of Graves' disease
- To maintain normal thyroid function in long-term treatment in the elderly

Box 28.8 A Consensus of Guideline Recommendations for Managing Hyperthyroidism

- UK guidelines are available for the management of thyroid function tests in thyroid disease published by the Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation (British Thyroid Association-BTA 2006).
- The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism (Bondi et al. 2015).
- US evidence-based guidelines on hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists (American Thyroid Association – ATA 2016).

Expert opinion in review articles (Weetman, 2013 & Vaidya and Pearce, 2014). Advice on symptoms suggesting adverse effects (Vaidya and Pearce 2014; Weetman 2013).

28.1.8.2 Anti-thyroid Drug Regimes

28.1.8.2.1 Graves' Hyperthyroidism

Titration block regime: In the UK, titration with CBZ is used as primary treatment.

Titration method involves the measurement of thyroid hormones TSH and fT4.

Drug dose regime: This varies according to the severity of hyperthyroidism. In overt hyperthyroidism, many hospital policies adopt a high dose treatment, for example, CBZ 30–40 mg daily for the first 2–3 months (British

Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

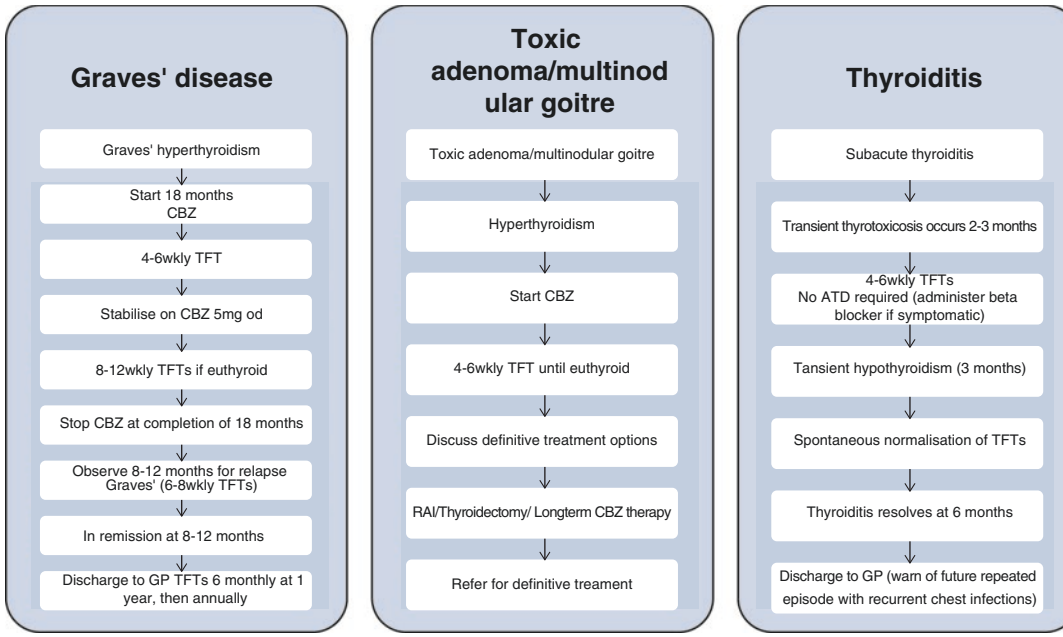
Thyroid function tests: TSH, fT3, and FT4 monitoring is recommended 4–6 weekly after initiation of ATD (e.g. CBZ or PTU) and during dose titration until euthyroidism is achieved. For example, in Graves' hyperthyroidism, normalisation of thyroid hormones in compliant patients can take around 2–6 months through gradual weaning to a minimal maintenance dose of CBZ 5 mg daily. Thereafter, TFTs can be monitored every 3–4 months until treatment is discontinued at around 18 months or according to local hospital policy (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016; Bartelena 2008) (Flow Chart 28.1). The steady weaning process is also thought to decrease thyroid stimulating antibody (TSAb) and TSH-binding inhibitor immunoglobulin (TBII), and furthermore reported to be a reliable predictor of remission in Graves' hyperthyroidism (Takasu et al. 2000).

Duration of treatment for potential remission: The mechanism behind the remission is thought to be due to the immunosuppressive action of the ATD (McGregor et al. 1980). In the UK, treatment for Graves' hyperthyroidism usually comprises an 18 month ATD therapy (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016; Bartelena 2008), or according to national or local hospital guidelines. Beyond this time serves no additional benefit (Abraham et al. 2010).

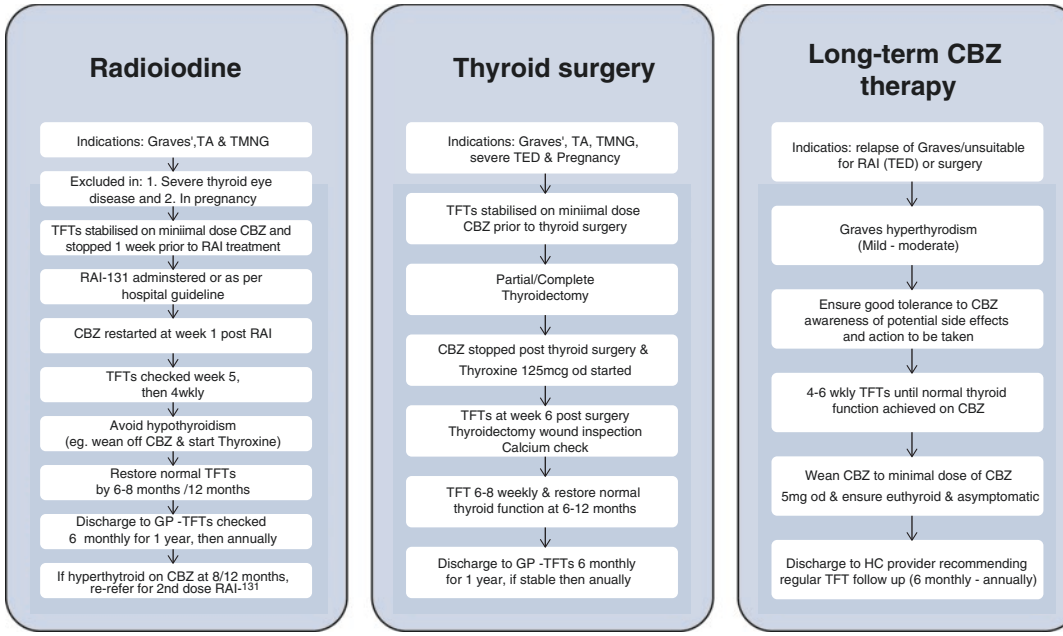
Furthermore, the measurement of TSHRAb levels prior to discontinuation of ATD therapy is thought to be useful in predicting those patients who will have a better chance of achieving remission.

At completion of the 18-month course of ATD treatment, TFTs can be monitored 4–6 weekly. If patient remains euthyroid, the time interval for TFTs monitoring can be extended to 2, 3, and then 6 months. If patient continues to remain euthyroid and in remission by 8–12 months, plans can be made to discharge back to healthcare provider with follow-up instructions (Flow Charts 28.1 and 28.2 Graves').

Block and replace regime: In the UK, this regime is less commonly used compared to the



Flow Chart 28.1 Hyperthyroid conditions and ATD summarised



Flow Chart 28.2 Definitive (radioiodine and thyroid surgery) and long-term ATD therapy

preferred ATD titration option (Bartelena 2008), and avoided in pregnancy (Cooper 2005; Burch and Cooper 2015; British Thyroid Foundation 2015b). Furthermore, the rate of remission in Graves' hyperthyroidism with this method is no different when compared to dose titration option (Vaidya and Pearce 2014).

Block and replace comprises a combination of CBZ and Thyroxine. CBZ is used to block thyroid hormones synthesis, whilst Thyroxine works by replacing thyroid hormones thought to not only stabilise the thyroid but also minimise the chances of becoming resistant to medication. This regime is used in Graves' disease, and the recommended course of treatment is around 6–12 months (or according to the supervising endocrinologist, national or hospital guidelines). The advantages of this regime is that the patient often requires less frequent patient hospital visits and few drug dose adjustments compared to the titration method; however, poor compliancy to medication may serve as a disadvantage due to the number of tablets the patient has to take on a daily basis (Bartelena 2008), and so caution must be practised when following this regime.

Drug dose regime: This starts with CBZ 20–40 mg daily for the first 4–6 weekly until fT4 has normalised on this dose. Thereafter, Thyroxine 125 μg daily is only then commenced (British Thyroid Association-BTA 2006; National Institute for Health and Care Excellence-NICE 2016).

Thyroid function tests: These should be monitored 4–6 weekly and adjustments only made to the dose of Thyroxine if indicated. When TFTs have normalised, the dose of anti-thyroid drug and Thyroxine usually remains unchanged. TFT monitoring can then be done less frequent as 3–6 monthly or as per local hospital guideline (British Thyroid Association-BTA 2006).

28.1.8.2.2 Toxic Adenoma or Toxic Multinodular Goitre

CBZ or equivalent in TA and TMNG is only used as a short-term measure to control hyperthyroidism, as remission is highly unlikely (Flow Charts 28.1 and 28.2 Nodule/s). When normal thyroid function is achieved, CBZ is continued to maintain control of hyperthyroidism until preparation for a more definitive treatment (radioiodine or

thyroid surgery) is arranged (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016).

28.1.8.2.3 Thyroiditis

Antithyroid drugs are rarely used in thyroiditis given its transient nature, for example, the temporary spill of thyroid hormones into the circulation results in transient thyrotoxicosis, followed by hypothyroidism, thereafter returning to euthyroid state and fully recovered by 8–12 months (Kaplan et al. 2011) (Flow Chart 28.1 Thyroiditis).

Very occasionally, the use of CBZ can sometimes be indicated in symptomatic cases of postpartum thyroiditis having a previous history of Graves' disease.

28.1.8.2.4 Pregnancy

Treatment of hyperthyroidism in pregnancy reduces the risk for fetal complications, however, following the recommended national or local guidelines can help avoid miscarriage and fetal abnormalities (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016) (Sect. 4, Chap. 33).

28.1.8.3 Agranulocytosis

Granulocytes are neutrophils (a type of white cell) that help to fight infection and are manufactured in bone marrow.

One of the rare side effects of ATDs such as CBZ, PTU, and Methimazole is agranulocytosis (Vicente et al. 2017). Agranulocytosis is the term used when the bone marrow fails to produce sufficient amount of granulocytes resulting in decreased neutrophils leading to neutropenia.

Neutropenia in bone marrow suppression can lead to serious life-threatening risk to infection and consequently be detrimental to a patient's well-being.

In the UK, CBZ is the preferred choice of ATD therapy compared to PTU as it has a reduced risk of serious liver damage and reported to be around 1 in 10,000 adults (Cooper and Rivkees 2009).

Healthcare practitioners starting patients on ATDs should always inform and warn patients of the potential side effect of agranulocytosis, and the procedure to take should this occur (Box 28.9).

In circumstances when ATD treatment is discontinued due to low neutrophil count, Propranolol or a similar alternative can be used in place until neutrophils are restored. In addition to this, an urgent referral should be initiated for a

Box 28.9 Side Effects of CBZ and PTU (Signs of Bone Marrow Suppression)

Neutropenia

- Sore throat
- Fever or chills
- Bruising
- Mouth ulcers
- Infection
- Sinusitis/otitis
- Swollen or tender gums
- Cough dyspnoea

Agranulocytosis
Sudden onset of:

- Malaise
- Fever (>40 °C) and chills
- Rapid pulse and respiration
- Pharyngitis with difficulty with swallowing
- Painful ulcers and oral cavity

Action taken for any side effects

- **STOP CBZ or PTU**
- Full blood count should be taken straight away.
- Results should be processed and evaluated within 24 h.
- If neutrophils are within normal range, it is safe for CBZ or PTU to be restarted.

If neutrophils are below normal range, patient should remain off CBZ or PTU, and definitive treatment options discussed with an urgent referral for either RAI or thyroid surgery. (Propranolol or alternative can be used in place of CBZ or PTU until neutrophils are restored)

suitable definitive treatment option (radioiodine or thyroid surgery).

28.1.8.4 Thyroid Function Monitoring and Discharge Instructions

28.1.8.4.1 Thyroid Function Monitoring

- Serum FT4 and TSH should be measured in all patients receiving thionamides.
- In most cases, the FT4 result will be the marker of choice to guide therapy.
- 4–6 weekly TFT monitoring is recommended at initiation of ATD until euthyroidism is achieved; then time interval can be extended according to hospital policy guidelines.
- A fall in FT4 to low normal or to below the normal range should prompt reduction in ATD dosage.
- A rise in serum TSH above normal reference range indicates the development of hypothyroidism and the need for dose reduction.
- A persistent suppression of serum TSH may not always indicate a need to increase ATD and should be discussed with senior practitioner for advice.

28.1.8.4.2 Discharge Instructions from Secondary Care to Healthcare Provider

The healthcare provider is recommended to monitor TFTs 6 monthly for the first year, and if the patient remains euthyroid, TFTs can be monitored annually thereafter (or earlier should symptoms of hyperthyroidism re-occur).

If Graves' hyperthyroidism re-occurs, HCP restarts ATD treatment and re-refers the patient back to endocrine services to discuss definitive treatment options (RAI or thyroid surgery).

28.1.8.5 Propranolol and Potassium Iodide

28.1.8.5.1 Propranolol

Propranolol is a beta-adrenoceptor antagonist also known as a beta-blocker (British National Formulary 2018a).

Action

In hyperthyroidism, there is an increased beta-adrenergic activity as a result of the symptoms caused by high levels of circulating thyroid hormones. For this reason, Propranolol works well to rapidly reduce symptoms such as palpitations, heat intolerance, tachycardia anxiety (British National Formulary 2018a; Marcocci et al. 2011). Furthermore, it also works by inhibiting extra-thyroidal conversion of T4 to T3, and although the reduction in T3 is limited, it is considered as an effective short-term treatment for managing thyrotoxicosis especially in the absence of CBZ and PTU (British National Formulary 2018a).

Uses

- When ATD such as CBZ or PTU cannot be used because the patient has developed side effects.
- As a temporary measure until a diagnosis and referral is made for definitive treatment (RAI or thyroid surgery).
- In some cases of thyroiditis where symptom control is required in transient phase of thyrotoxicosis.

Propranolol is effective in reducing many of the clinical features of hyperthyroidism, for example, palpitations, heat intolerance, anxiety, and tremor (Fig. 28.1). Although Propranolol does not completely abolish the symptoms of thyrotoxicosis compared to CBZ or PTU, patients can be relieved of some troublesome symptoms until a suitable treatment pathway is established.

Dosage

- The starting dose of Propranolol for mild to moderate thyrotoxicosis is usually 10 mg/20 mg/40 mg tds.
- In severe cases, Propranolol can be prescribed up to 80–120 mg daily.

Caution

- Beta-blockers should be avoided in patients with history of asthma and chronic obstructive airways disease. In cases of neutropenia due to the use of anti-thyroid drugs such as CBZ or PTU, beta-blockers are often the only available treatment and sometimes can be administered under the close supervision by a senior medical endocrine practitioner (British National Formulary 2018a).

- Dose reduction of Propranolol is required in renal and liver impairment.
- Care should be taken in breastfeeding as small amounts are contained in breast milk.

Contraindicated
- Avoided with Verapamil

Side Effects
- These are rare and can be found in the most up-to-date national guidelines (National Institute for Health and Care Excellence-NICE 2016; British National Formulary 2018a).

Weaning Off Propranolol
- Gradual weaning of Propranolol is recommended according to local hospital/guidelines. This avoids the potential occurrence of myocardial ischaemia.

28.1.8.5.2 Potassium Iodide

Potassium Iodide (KI) is a thyroid-blocking agent (Ross 2017c; Wass and Owen 2014; Electronic Medical Com 2016). It is also known as Lugol's solution, which was discovered in 1829 by a French physician called Jean Guillaume August Lugol. This was used for treating tuberculosis and as a disinfectant for various procedures including dental, histologic preparations, etc.

In around the 1920s, it was being used as a preoperative measure for controlling hyperthyroidism (Callissendorf and Falhammar 2017; Plummer 1924). In the UK, Potassium Iodide is used as a preoperative measure in patients with controlled or uncontrolled hyperthyroidism requiring thyroid surgery (British Thyroid Association-BTA 2006; Wass and Owen 2014).

Mechanism of Action

It works by decreasing thyroidal iodide uptake and blocks the release of thyroid hormones. It also is reported to decrease the thyroidal blood flow by shrinking the thyroid blood vessels, making surgery less risky especially when operating on a very large goitre (American Thyroid Association – ATA 2016; Paul et al. 1988).

Uses and Procedure
- In the UK, ATDs are initially used to achieve euthyroidism prior to thyroid surgery and when RAI is not suitable. In cases where ATDs cannot be used due to agranulocytosis, the use of beta blockade drugs such as Propranolol can be substituted as a temporary measure to stabilise thyroid hormones as best as possible with the necessary precautions in place.
- In patients with uncontrolled hyperthyroidism and when urgent thyroid surgery is required, patients can be prescribed Potassium Iodide 60 mg tds orally that can be given preoperatively for up to 10 days. Thyroid surgery must take place no later than during this time to avoid exacerbation of thyrotoxicosis (Wass and Owen 2014).

Drug information should be thoroughly checked at all times prior to prescribing medications to patients, whilst at the same time ensuring it complies with the most up-to-date, evidence-based recommendations from reputable resources (British Thyroid Association-BTA 2006; American Thyroid Association – ATA 2016; National Institute for Health and Care Excellence-NICE 2016; Electronic Medical Com 2016; British National Formulary 2018c) or local hospital policies and guidelines.

28.1.8.6 Long-Term Anti-Thyroid Drug Therapy

In Graves' hyperthyroidism, ATDs are commonly used to stabilise the thyroid hormones with a view to achieve euthyroid state and remission. However, considering that relapse rate of Graves' hyperthyroidism is high following a 12–18-month course of ATD and remission low (Bartelena 2008; Benker et al. 1998; Hedley et al. 1998), most patients go on to have definitive treatment such as thyroid surgery or radioiodine treatment.

The use of long-term therapy with ATD such as CBZ is considered to be safe and effective in achieving permanent remission (Barrio et al. 2005; Leger et al. 2012).

Therefore, in some patients, it may be appropriate to prescribe long-term control with minimal dose of ATD, for example, Carbimazole 5 mg daily

or Propylthiouracil 50 mg equivalent. Caution for safe prescribing of such medications is paramount for example side effects explained and the appropriate action to be taken (Box 28.9), as well as the importance of maintaining normal thyroid function with regular blood checks (Flow Chart 28.2. Long-term Carbimazole therapy). The following principles should therefore be considered carefully for all patients prior to commencing long-term ATD treatment (Organzi and Bournard 2011).

- Suitable in cases with mild–moderate Graves' hyperthyroidism
- Euthyroid state achieved on minimal ATD, e.g. Carbimazole 5 mg daily (or equivalent)
- Has good tolerance to Carbimazole
- In those with a small goitre (absence of a large goitre)
- Patients who are asymptomatic
- Healthcare provider and patients committed to regular annual follow-up to ensure thyroid hormones remain within normal reference range.

Summary of recommendations for the management of hyperthyroidism with antithyroid medication (Box 28.10).

Box 28.10 Specialist Nurse Recommendations on Initial Management of Hyperthyroidism and ATD Therapy

- **Rapport:** is essential between the clinical specialist and the patient. It helps create a climate of trust and cooperation for establishing a successful treatment outcome and positive patient experience.
- **Clear explanation:** patients require clear, understandable explanation of their thyroid condition. Use of diagrams, information leaflets and websites such as BTF (http://www.btf-thyroid.org/), BTA (https://www.british-thyroid-association.org/), and TEDct (http://tedct.org.uk/) are useful sources of evidence-based information.
- **History taking and physical assessment**
  - **O**nset: of neck complaint (e.g. swelling)
  - **L**ocation: of neck swelling (e.g. right or left lobe or both lobes)
  - **D**uration: how long has the swelling been present (e.g over days/months/year/or sudden)
  - **C**haracteristics: of neck swelling (e.g. smooth, irregular, soft, or firm)
  - **A**ssociated characteristics: pain and fever (e.g. sharp/dull/aching or redness/hot)
  - **R**elief strategy: of neck swelling and pain (e.g. Paracetamol for pain relief)
  - **T**reatment: by healthcare provider (e.g. TFTs indicate thyrotoxicosis and referred to endocrinology in secondary care)
  - ***Review of systems****:* including cardiac, respiratory, renal, abdominal, neuroperipheral.
  - ***Eye evaluation for Graves'****:* ophthalmopathy and plan to refer to ophthalmologist
  - ***Past medical and surgical history****:* e.g. Asthma and avoiding use of Propranolol
  - ***Social*****:** e.g. smoking and evaluation and health promotion to discourage smoking
  - ***Medication history****:* noting any potential medications that might interact with anti-thyroid medication
  - **Allergies**: especially if there is a previous history of adverse effects with ATD
- **Females and pregnancy:** Females of childbearing age should avoid pregnancy during ATD. If pregnancy occurs, the Carbimazole should be switched to PTU especially during the first trimester. The doses of PTU should not exceed 200 mg daily. Referral should be made to the endocrine combined obstetrics specialist

services. Specialist nurse monitoring continues after child delivery to manage the thyroid disorder. TFT monitoring 4 weekly or as hospital policy.

- **Baseline blood investigations and vital signs**: This allows to establish diagnosis of hyperthyroidism and any differential diagnosis
  - TFTs, Thyroid TSH receptor, and peroxidase Abs
  - FBC, U & Es, LFT
  - Blood pressure, heart rate, pulse, respiration, weight
- **Side effects of ATD**: Obtain medical history and ensure compatibility with ATD, or if there is a previous history of adverse events with ATD, use of Propranolol or equivalent may be necessary until diagnosis made (such patients would warrant an urgent referral for definitive treatment (e.g. radioiodine or thyroid surgery)
- **Agranulocytosis:** Provide related patient information, e.g. warn patients about the rare side effects of ATD and the importance of stopping CBZ/PTU should a sore throat, fever, mouth ulcers, or any bruising develop. Furthermore to have a FBC followed up within 24 h and to determine whether anti-thyroid drug should be continued or not.
- **Contact details:** Ensure patient has telephone support line and email details of nurse-led clinic/endocrinology services (Benner 1984; BTA 2018; BTF 2018; TEDct 2018; Hogan-Quigley et al. 2012).

28.2 Section B: Radioiodine Therapy (1-131)

28.2.1 Radioactive Iodine Treatment (I-131)

Radioactive iodine has been used in the treatment of hyperthyroidism since the early 1940s. It is offered orally as a capsule or liquid form. The radioactive iodine is taken up by the thyroid and gradually destroys the cells in the gland.

28.2.1.1 Indications for Offering I-131 in Benign Thyroid Disease

- Graves' disease (in the UK, first-line treatment after recurrence)
- Toxic adenoma
- Toxic multinodular goitre

28.2.1.2 Contraindications for Radioiodine 1-131

- Pregnancy
- Breastfeeding
- Planning pregnancy
- Active moderate to severe or sight-threatening Graves' ophthalmopathy
- Inability to comply with radiation safety recommendations
- In patients with thyroid nodules suspicious for or proven (following fine needle aspiration) thyroid cancer

Graves' ophthalmopathy: Patients with mild active Graves' ophthalmopathy, I-131 administration should be followed by prophylactic steroid treatment. Factors related with worsening of the ophthalmopathy after I-131 include smoking, high pre-treatment T3 levels, high TSH-receptor antibody titres, and untreated hypothyroidism after the I-131 (See chapter).

28.2.1.3 Treatment Protocol

Anti-thyroid medication: There is no consensus on the necessity for pre-treating with anti-thyroid medications before the administration of RAI I-131 in terms of protecting against exacerbation of thyrotoxicosis. Nonetheless, anti-thyroid medications would be recommended in the elderly, patients with comorbidities (especially cardiovascular) and cases with severe thyrotoxicosis.

It has also been suggested that pre-treatment with anti-thyroid medications (particularly propylthiouracil) is related with increased risk of treatment failure after the RAI I-131. The anti-thyroid drugs are discontinued 1 week prior to administration of RAI I-131 and are usually

restarted 1 week after this. Beta-blocker may be needed if the patient is very symptomatic.

The dose of RAI I-131 can be fixed or calculated based on the radioactive uptake by the thyroid.

Radiation protection rules: Each treatment centre should have relevant detailed information leaflets.

- Advice on transport after the administration of RAI I-131
- Avoid close contact with adults, children. and pregnant women
- Refrain from fathering a child for 4–6 months or conceiving for 6 months
- Recommendations for near future travel plans

Thyroid function: TFTs should be checked 1–2 months after the RAI I-131 and thereafter every 4–6 weeks, until the patient is euthyroid or hypothyroid (off anti-thyroid drugs).

28.2.1.4 Outcomes and Risks of Treatment

Thyroid activity: This will reduce over weeks and the timing of response is variable. Around 60% of the patients will become hypothyroid after 12 months and after this, hypothyroidism can develop at a rate of 3% per year.

Thyroxine replacement: Replacement with Levothyroxine should be offered as soon as hypothyroidism is diagnosed. It should be noted that hypothyroidism might be transient in a small number of patients. Thyroid gland shrinkage may also occur.

Lifelong monitoring: In all patients, lifelong monitoring of the thyroid hormones is required. In cases of treatment failure, a second dose of I-131 can be offered 6–12 months after the previous one.

Factors predicting the outcome of treatment include dose of RAI I-131, size of goitre, female gender, pre-treatment fT4 levels.

RAI 1-131 Risks: These include worsening of thyroid eye disease, acute thyroiditis (in 1% of the patients, lasts a few weeks and is managed with non-steroidal anti-inflammatory drugs and beta-blockers, or, in severe cases, with steroids), acute enlargement in multinodular goitre (caution in severe trachea compression). It has been proposed that cancer incidence is slightly higher in hyperthyroid patients compared with euthyroid people, but is not associated with the type of thyroid treatment.

Summary of recommendations for the management of hyperthyroidism and radioiodine therapy (Box 28.11).

Box 28.11 Specialist Nurse Recommendations for Pre- and Post-radioiodine Management

Pre-radioiodine

- Explanation regarding information of and safety aspect of radioiodine (RAI) therapy is paramount to dispel fear as some patients worry about the effects of radiation and cancer.
- Avoid radioiodine in patients with thyroid eye disease as it may cause progression of the condition (or seek ophthalmology referral for assessment and opinion), and discuss referral for thyroid surgery (Sect. 4, Chap. 28 (C) Thyroid Surgery).
- RAI treatment is contraindicated in pregnancy and in women who are breastfeeding.
- Women should avoid pregnancy for at least 6 months after RAI treatment.
- Men should avoid fathering children for at least 4 months after radioiodine treatment.
- Aim to achieve euthyroidism prior to administering RAI.
- Referral of patient from nurse-led clinic (NLC) services for RAI assessment includes:
  - Interview with endocrinologist
  - RAI procedure explained
  - Consent obtained
  - Protocol provided for post-RAI, NLC, thyroid function test (TFT) monitoring as per hospital protocol
- Assessment with radiologist consultant includes:
  - Detailed RAI protection rules explained

- Leaflets provided with clear instructions as per hospital protocol
- Date provided for RAI treatment

Post-radioiodine considerations for TFT monitoring

- Serum FT4 and TSH should be checked every 4–6 weeks for 6 months after administration of 131 iodine-RAI.
- The frequency of TFT testing may be reduced when the FT4 remains within the reference range, then annually.
- A fall in serum FT4 to below normal, or rise in TSH should prompt a reduction in dose or withdrawal of any thionamide administered post-RAI therapy.
- A more marked or persistent rise in serum TSH (>20 mU/L for more than 1 month), especially if associated with symptoms, should prompt thyroxine prescription.
- Persistent elevation of FT4 at around 6 months after RAI therapy indicates lack of cure and the need for considering a second dose.
- If FT4 is normal (off thionamides) approximately 6 months after radioiodine, the frequency of testing may be reduced to 3 monthly and then 6 monthly.

After an interval of euthyroidism (normal serum FT4) of more than 12 months after RAI therapy, the patient may be transferred to annual testing.

Second dose radioiodine

- Persistent elevation of FT4 6 months after RAI therapy indicates lack of cure and need for consideration of re-dosing.
- Discuss second dose of RAI, and re-refer for assessment with endocrinologist and radio-nuclear physicist (procedure as for first dose of RAI).
- TFT monitoring is required 4 weekly post-RAI treatment until euthyroidism is achieved (off antithyroid drug or on Thyroxine replacement). Then plans to discharge patient from NLC hospital services to healthcare provider or general practitioner.

Discharge Suggestions to Healthcare Provider Following Radioiodine

- Stable TFTs either with or without Thyroxine requires 6 monthly monitoring of TFTs. If stable, for the first year, monitoring can be transferred to annual checks thereafter, or earlier should the patient experience any symptoms related to thyroid dysfunction.
- Patients should be advised to keep up to date with all aspects of thyroid news that may be pertinent to their needs. Access to websites such as British thyroid Association: https://www.british-thyroid-association.org/, British thyroid foundation: http://www.btf-thyroid.org/ and Thyroid eye disease committee: http://tedct.org.uk/ are recommended, as well as attending 'patient information meetings'.
- Healthcare provider may have to adjust Thyroxine dose as required for several months or years following patient discharge.
- Patients previously euthyroid, without Thyroxine, who develop **hypothyroidism** will require Thyroxine replacement with 4–6 weekly TFT monitoring until euthyroidism is achieved, then have less frequent checks at 3, 6, and 12 months monitoring to maintain euthyroidism.
- Patients previously euthyroid, without Thyroxine, who develop recurrence of **hyperthyroidism**, should be re-referred back to endocrinologist for definitive treatment discussion and restoration of normal thyroid function (BTA 2006; NICE 2016; ATA 2016; TEDct 2018).

28.3 Section C: Thyroid Surgery

28.3.1 Preoperative Medical Control of Hyperthyroidism (With Reference at Previous Sections)

28.3.1.1 Length of Treatment

There is significant variation in the length of treatment with anti-thyroid medication before patients are being offered definitive treatment with either thyroid surgery or radioactive iodine ablation. The general consensus is that after 12–18 months of effective blockade with Carbimazole (or Propylthiouracil) medication should be stopped and patients monitored to identify those with recurrent thyrotoxicosis. Recurrence is expected in at least 50% of patients, more likely in smokers and patients with large goitres. If recurrence is suspected clinically and/or demonstrated on biochemical testing, medical control of thyrotoxicosis has to be restarted and patients considered for definitive therapy (i.e. radioactive iodine ablation-RIA or total thyroidectomy).

Despite this expected timeline, in clinical practice most patients who present for thyroid surgery declare that they have been on medical treatment for many years (rather than 12–18 months).

28.3.1.2 Urgent Control of Hyperthyroidism

This can be necessary in patients who develop agranulocytosis whilst on Carbimazole (or PTU) treatment. These patients should be managed through close collaboration between medical and surgical team. A date of the operation should be fixed as soon as feasible and from that date one decides 10 days backwards to start the acute blockade of thyroid function using high iodine intake (e.g. Lugol's drops 10 drops tds or potassium iodide 60 mg tds) and propranolol (40 mg tds, titrating it towards higher doses based on how well tachycardia is controlled). Dexamethasone 1–2 mg daily could be added for 2–3 days prior to surgery.

28.3.1.3 Control of Pre-Op Hyperthyroidism and Post-Op Thyrotoxic Storm

It is imperative to control hyperthyroidism before proceeding with thyroid surgery in order to avoid post-operative thyrotoxic storm. This is a condition rarely seen in today's clinical practice but often discussed in postgraduate exams for anaesthetists and surgeons. It can be triggered by stress (e.g. emergency non-thyroid operations performed on thyrotoxic patients, fractures, road traffic accidents, thyroid surgery) or excessive iodine intake (e.g. use of contrast IV agents for CT scanning). It can be life-threatening hence it requires a low threshold of suspicion. The symptoms and signs of thyroid storm are usually recognisable by the endocrine specialist (6).

28.3.1.3.1 Symptoms and Signs Specific to Thyroid Storm

- Pyrexia (>38.5 °C)
- Tachycardia
- Hypertension
- Tremor
- Confusion
- Nausea and vomiting
- High output cardiac failure

Treatment: Management of hyperthyroidism must be instituted rapidly, with timely involvement of endocrine specialists and critical care physicians. If it occurs after total thyroidectomy, the treatment is supportive and involves cooling, beta blockade (e.g. with propranolol 80 mg), supplemented by dexamethasone. If it occurs in other scenarios, the production of thyroid hormones should be blocked rapidly with Methimazole and Lugol's iodine.

28.3.2 Thyroid Lobectomy for 'Hot' Nodule

A hot nodule (Plummer's adenoma) demonstrated on radioactive uptake scans can be treated with radioactive iodine ablation (if <3 cm and no

contraindications for RIA) or offered thyroid lobectomy.

28.3.2.1 Indications

- Large nodules (>3–4 cm)
- Children (in order to avoid exposure to radioactive treatment)
- Patients who need neck exploration for other indications (e.g. parathyroidectomy)
- Patients with ipsilateral or contralateral thyroid nodules with suspicious appearance of ultrasound assessment

Hot nodules should not be assessed with fine needle aspiration (FNA) biopsy because all are follicular adenomas hence FNA would lead to a THY3 cytological appearance (Sect. 4, Chap. 27 and Sect. 4, Chap. 29), which could raise inadvertent concerns/suspicion of malignancy. It is exceedingly rare for a patient presenting with thyrotoxicosis to have a follicular carcinoma.

28.3.3 Total Thyroidectomy for Graves' Disease

28.3.3.1 Indications

Patients have to make an informed decision regarding the choice between RIA and thyroid surgery for Graves' disease.

Definitive indications for thyroid surgery

- Large goitres
- Severe Graves' ophthalmopathy
- Small children
- Patient's fears about radioactive treatment

28.3.3.2 Contraindications

- Patients with pre-existent recurrent laryngeal nerve injury
- Patients with history of neck radiotherapy
- Frail patients who would be better managed on long-term medical therapy

28.3.3.3 Extent of Surgery

In the 1980s, Australian surgeons were the first to demonstrate that total thyroidectomy is the ideal operation for Graves' disease. Subtotal thyroidectomy caries a high risk of recurrent hyperthyroidism and has been abandoned in centres where total thyroidectomy can be performed with low risk of complications (*vide infra*). The only exception from this 'rule' is the treatment of people whose employment does not allow being on thyroxine replacement (e.g. army/air force personnel).

28.3.3.4 Surgical Technique

The 'classical' technique for thyroid surgery has been established in the early twentieth century through the work of famous surgeons like Dr. Theodor Kocker and the principles established in the era are easily recognisable in the way the operation is performed in modern practice.

Around the world there are different degrees of interest in adopting more radical techniques for thyroid surgery and include:

Minimally invasive video-assisted thyroid surgery: This was introduced by Italian surgeons. It relies on the use of a small cervical skin incision (2 cm) through which small instruments and a video camera are introduced to allow dissection of tissue planes under direct vision. The technique is feasible only if the volume of the thyroid is small (so that it can be retrieved through the small skin incision).

Robotic thyroid surgery: This was initially promoted by South Korean surgeons, but in recent years the use of the Da Vinci robot for thyroid surgery has been restricted in many countries (e.g. in the USA insurance companies are not covering the costs of the procedure). The technique avoids an incision in the neck instead access to the thyroid is secured though a long 'tunnel' created from the arm pit in front of the pectoralis major).

Face-lift approach: This relies on a cervical incision away from the thyroid bed, in the hairline, with the dissection under platysma muscle and over the sternocleidomastoidian muscle.

Transoral thyroidectomy: This has been developed by German surgeons by making small incisions on the oral mucosa in front of the mandible and creating a working space for laparoscopic or robotic instruments.

28.3.3.5 Complications

Immediate complications after thyroid surgery can be life-threatening; hence patients have to be looked after on a ward environment where nurses are familiar with such complication and where rigorous protocols are in place for timely recognition of these complications that prompt intervention.

Post-operative bleeding: With the airway compromise, post-operative bleeding is the most dangerous complication that occurs usually in the first 6 h after the operation (though it has been reported up to 24 h post-op). It requires urgent opening of the neck in order to avoid further venous congestion that triggers the mucosal oedema and intraluminal laryngeal obstruction. In extreme situations, the sutures will have to be removed on the ward (i.e. the subcuticular skin sutures and the muscular sutures between the strap muscles so that the haematoma is fully released) before return to theatre for formal neck exploration to identify the source bleeding. The emergency management of neck haematoma could require opening of the neck on the ward. This is freely available as an educational video demonstration using the mnemonic 'SCOOP' (Endocrine Surgery Oxford 2018):-

S: Steristrips - remove

C: Cut - subcuticular suture & push fingers into wound

O: Open - skin to expose strap muscle

O: Open - strap muscle to expose trachea

P: Pack - wound

Bilateral recurrent laryngeal nerve (BRLN) injury: With acute airway compromise is an exceedingly rare complication. Its incidence should be mitigated by the use of intraoperative nerve monitoring that should alert the surgeon if the recurrent laryngeal nerve is injured after completing the first side of the operation hence a decision could be taken to not proceed with bilateral surgery (hence avoiding a BRLN injury) (Table 28.1).

Patients need to be made aware of all these potential complications during the preoperative discussion. Increasingly surgeons are expected to

Table 28.1 Late complications after total thyroidectomy for Graves' disease

Complication	Mechanism	Incidence	Treatment	Prognosis
Hypocalcaemia—hypoparathyroidism	Injury to parathyroid glands (e.g. compromising their vascular supply) or their inadvertent removal. Patients with severe thyrotoxicosis develop hungry bone syndrome and become hypocalcaemic even though their PTH is normal/high.	1:50 Incidence after surgery for Graves' disease is higher (up to 10%) compared with multinodular goitre.	Calcium supplements (e.g. calcichew ii tds) and/or vitamin D replacement (e.g. calcitriol 1 μg od)	Likely to settle within 6–12 months if PTH becomes measurable.
Subtle voice changes (loss of high pitch, loss of projection)	Injury to superior laryngeal nerve	1:10	Possibly the use of voice exercises might be beneficial but it remains unproven.	Likely to improve/settle with 3–6 months
Severe voice changes (hoarse voice)	Injury to recurrent laryngeal nerve (transection, traction, heat injury)	1:100	Voice therapy for those with associated swallowing difficulties is likely to mitigate the difficulties. If symptoms persist over 6–12 months, the paralysed cord could be injected to encourage a more medial position and possible better voice outcome. A clinical trial of reinnervation using ansa cervicalis is being under way.	

Box 28.12 Specialist Nurse Recommendations: Thyroid Surgery
Explanation:

- Surgery indications for Graves' or nodular goitre
- Equip with information leaflets and BTF: website address or local hospital policy and guidelines
- Importance of thyroid hormone control preoperatively with anti-thyroid drug (ATD) or alternative
- Graves' hyperthyroidism usually requiring total thyroidectomy and lifelong Thyroxine replacement
- Toxic nodular goitre often requiring either partial or total thyroidectomy
- Explain rare risks such as vocal cord, laryngeal nerve damage, and transient or permanent calcium deficiency and how these can be managed
- Arrange formal assessment with thyroid surgeon for suitability for surgery and confirmation of surgical date

Preoperative preparation of patient:

- Aim for euthyroidism with ATD or alternative
- Thyroid function test (TFT) 4–6 weekly until euthyroid, then 8 weekly–3 monthly (or as per hospital protocol) when euthyroid until surgery

Post-thyroidectomy monitoring:

- TFTs monitoring 4–6 weekly until euthyroidism achieved either on or off Thyroxine.
- Check surgical site for healing.
- BioOil recommended to be gently massaged over surgical site only when completely healed to minimise scar effects.
- Explain the need for 'lifelong' Thyroxine replacement in Graves' hyperthyroidism and in cases of toxic nodular goitre where replacement is required.
- When euthyroidism is achieved either on or off Thyroxine replacement, discharge from secondary care back to healthcare provider.

Discharge instruction from secondary care and long-term follow-up:

- Patient will require 'lifelong' Thyroxine replacement.
- TFT monitoring 6 monthly for the first year, if stable then annually thereafter or earlier should symptoms of thyroid dysfunction return.
- Access to websites for further information: BTF http://www.btf-thyroid.org & those with TED: http://tedct.org.uk/

(ATA 2016; BTF 2015a, b; BTA 2006; National Institute for Health and Care Excellence-NICE 2016; Thyroid eye disease committee 2018)

quote the incidence of these complications in their own practice rather than using figures published in large series from centres with large practice.

Summary of recommendations for the management of hyperthyroidism and thyroid surgery (Box 28.12).

28.4 Conclusions

Hyperthyroidism is represented by the presence of supressed thyroid stimulating hormone with increased levels of circulating thyroid hormones, fT4 (thyroxine), and fT3 (triidothyronine).

The most common hyperthyroid condition seen in endocrine clinical practice is firstly Graves' disease, followed by toxic nodular goitre (single adenoma or multinodular) and thyroiditis (subacute).

Pregnancy cases require a prompt obstetrics referral for close specialist monitoring, and

patients with signs of thyroid eye disease necessitates a timely ophthalmology referral for monitoring and follow-up.

A number of investigations can be undertaken to diagnose hyperthyroidism and include TFTs, TSHR, TPO antibodies thyroid uptake scan and CT scan. These can be tailored to diagnose Graves' disease, toxic nodular goitre, and thyroiditis. Relevant knowledge and understanding of hyperthyroidisms is therefore paramount to ensure a swift diagnosis can be made without delay so that the appropriate treatment is selected.

The treatment options include anti-thyroid drugs (Carbimazole, Propylthiouracil), B blockers (Propranolol), radioiodine, or thyroid surgery (thyroidectomy).

A multidisciplinary approach is crucial to manage hyperthyroidism appropriately and effectively. This provides an enhanced delivery of efficient, effective and, safe, patient care that ultimately provides optimal outcomes.

Useful Resources

Endocrine Surgery Oxford. SCOOP: how to open the neck quickly and safely to relieve airway pressure in acute post op haemorrhage after thyroid or parathyroid surgery-acute management of post op haemorrhage in thyroid and parathyroid surgery. 2018. Available at: https://www.youtube.com/watch?v=uCM9FuutGbY. Accessed 3 Nov 2018.

References

Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Primary Review Group-Cochrane. 2010. Available at: http://www.cochrane.org/CD003420/ENDOC_antithyroid-drug-regimen-for-treating-graves-hyperthyroidism. Accessed 22 Oct 2017.

Akamizu T, Amino N. Hashimoto's thyroiditis. Endotext. 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK285557/. Accessed 22 Jan 2018.

American Thyroid Association – ATA. Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. ATA. 2016. Available at: https://www.thyroid.org/professionals/ata-professional-guidelines/. Accessed 24 July 2017.

Amino N, Kubota S. Thyroid disease after pregnancy-3.4.5. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Barrio R, López-Capapé M, Martinez-Badás I. Graves' disease in children and adolescents: response to long-term treatment. Acta Paediatr. 2005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16303698. Accessed 20 Oct 2017.

Bartelena. Treatment of hyperthyroidism: block and replace versus titration. Endocrine abstracts. Endocr Connect. 2008. Available at: http://www.endocrine-abstracts.org/ea/0016/ea0016s1.1.htm. Accessed 11 Oct 2017.

Bath S. Food facts-Iodine. The Association of UK Dieticians-BDA; 2016. Available at: https://www.bda.uk.com/foodfacts/Iodine.pdf. Accessed 23 Dec 2017.

Benker G, Reinwein D, Kahaly G, Tegler L, Alexander WD, Fassbinder J, Hirche H. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. Clin Endocrinol. 1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=benker+1998+remission+in+graves. Accessed 22 Dec 2017.

Benner P. From novice to expert: excellence and power in clinical nursing practice. London: Addison-Wesley; 1984.

Berghout A, Wiersinga WM, Smits NJ, Touber JL. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. Am J Med. 1990. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2239979. Accessed 29 July 2017.

Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, Da Costa BR, Wirth CD, Peeters RP, Asvold BO, Den Elzen WP, Luben RN, Imaizumi M, Bremner AP, Gogakos A, Eastell R, Kearney PM, Strotmeyer ES, Wallace ER, Hoff M, Ceresini G, Rivadeneira F, Uitterlinden AG, Stott DJ, Westendorp RG, Khaw KT, Langhammer A, Ferrucci L, Gussekloo J, Williams GR, Walsh JP, Juni P, Aujesky D, Rodondi N. Thyroid Studies Collaboration: subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA. 2015. Available at: https://jamanetwork.com/journals/jama/fullarticle/2297170. Accessed 22 Jan 2018.

Boettlin R. Uber zahnentwickelung in dermoid cysten des ovariums. 1889. In: Yoo SC, Chang KH, Lyu MO, Chang SJ, Ryu HS, Kim HS. Clinical characteristics of struma ovarii. J Gynaecol Oncol. 2008. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676458/. Accessed 22 July 2017.

Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. 2010. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879398/. Accessed 28 July 2017.

Bondi B, Bartalena L, Cooper DS, Hededus L, Laurberg J, Kahaly GJ. European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. Eur Thyroid J. 2015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26558232. Accessed 22 July 2017.

Bowman P, Osborne NJ, Sturley R, Viadya B. Carbimazole embryopathy: implications for the choice of antithyroid drugs in pregnancy. QJM. 2012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=bowman+2012+pregnancy+antithyroid. Accessed 23 July 2017.

British National Formulary. Propranolol hydrochloride/carbimazole/propylthiouracil/thyroxine. BNF-NICE. 2018a. Available at: https://bnf.nice.org.uk/drug/propranolol-hydrochloride.html#medicinalForms. Accessed 22 July 2017.

British National Formulary. Non-steroidal anti-inflammatory drugs/Paracetamol: therapeutic effects. NICE. 2018b. Available at: https://bnf.nice.org.uk/treatment-summary/non-steroidal-anti- inflammatory-drugs.html. Accessed 22 Jan 2018.

British National Formulary. BNF. 2018c. Available: https://www.bnf.org/products/bnf-online/. Accessed 23 May 2017.

British Thyroid Association-BTA. UK guidelines for the use of thyroid function tests: thyrotoxicosis. BTA. 2006. Available at: http://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf. Accessed 22 July 2017.

British Thyroid Foundation. Thyroid surgery/radioiodine. BTF. 2015a. Available at: http://www.btf-thyroid.org/information/leaflets/31-thyroid-surgery-guide, http://www.btf-thyroid.org/information/quick-guides/101-hyperthyroidism-radioactive-iodine. Accessed 22 July 2017.

British Thyroid Foundation. Antithyroid drug therapy to treat hyperthyroidism. BTF. 2015b. Available: http://www.btf-thyroid.org/information/leaflets/40-antithyroid-drug-therapy-guide. Accessed 29 June 2017.

Bülow Pedersen I, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Laurberg P. Large differences in incidences of overt hyper- and hypothyroidism asso.ciated with a small difference in iodine intake- a prospective comparative register-based population survey. J Clin Endocrinol Metab. 2002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12364419. Accessed 23 Oct 2017.

Burch HB, Cooper DS. Management of Graves disease a review. Network-J Am Med Assoc. 2015. Available at: https://jamanetwork.com/journals/jama/article-abstract/2475467. Accessed 10 Jan 2018.

Burman. Overview of thyroiditis. UpToDate. 2017. Available at: https://www.uptodate.com/contents/overview-of-thyroiditis#H5. Accessed 22 Feb 2018.

Callissendorf J, Falhammar H. Lugol's solution and other iodide preparations: perspectives and research directions in Graves' disease. Endocrine. Springer. 2017. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5693970/. Accessed 23 March 2018.

Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10695693. Accessed 22 Oct 2017.

Caplan RH. Thyroxine toxicosis. A common variant of hyperthyroidism. J Am Assoc. 1980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6775100. Accessed 22 May 2017.

Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006. Available: https://www.ncbi.nlm.nih.gov/pubmed/16507804. Accessed 23 Oct 2017.

Cerci C, Cerci SS, Eroglu E, Dede M, Kapucouglu N, Yildiz M, Bulbul M, et al. Thyroid cancer in toxic and non-toxic multinodular goiter. J Post Grad Med. 2007. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=17699987. Accessed 22 May 2017.

Cooper DS. Antithyroid drugs. N Engl J Med. 2005. Available at: http://www.nejm.org/doi/full/10.1056/nejmra042972. Accessed 22 Nov 2017.

Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012. Available at: https://pdfs.semanticscholar.org/49c4/c2df1a7a4470127e09e34aafbae347e4ff6c.pdf. Accessed 22 Oct 2017.

Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Diab Endocrinol Lancet. 2013. Available at: http://www.thelancet.com/journals/landia/article/PIIS2213-8587(13)70086-X/abstract. Accessed 22 Aug 2017.

Cooper DS, Rivkees SA. Putting Propylthiouracil in perspective. 2009. In Vaidya B, Pearce SHS. Diagnosis and management of thyrotoxicosis-clinical review. Br Med J. 2014. Available at: https://medicinainternaal-dia.files.wordpress.com/2014/09/tirotoxicosis.pdf. Accessed 22 Aug 2017.

Davis TF. Pretibial myxedema (thyroid dermopathy) in autoimmune thyroid disease. UpToDate. 2017. Available at: http://www.uptodate.com/contents/pretibial-myxedema-thyroid-dermopathy-in-autoimmune-thyroid-disease. Accessed 22 July 2017.

DeSimone CP, Lele SM, Modesitt SC. Malignant struma ovarii: a case report and analysis of cases reported in the literature with focus on survival and I131 therapy. Gynecol Oncol. 2003. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=12798728. Accessed 22 Oct 2017.

Dunzendorfer T, DelLas Morenas A, Kalir T, Levin RM. Struma ovarii and hyperthyroidism. Thyroid American Thyroid Association. 1999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10365682. Accessed 26 Oct 2017.

Electronic Medical Com. Potassium iodide. Elecectronic Medical Compendium. 2016. Available at: https://www.medicines.org.uk/emc/product/3019. Accessed 20 March 2018.

Engkakul P, Mahachoklertwattana P, Poomthavorn P. Eponym: De Quervain thyroiditis. 2011. Available: https://www.ncbi.nlm.nih.gov/pubmed/20886353. Accessed 23 Nov 2017.

European Thyroid Association. Guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. Eur Thyroid J. 2015. Available at: http://www.eurothyroid.com/files/download/ETJ-2015-4-149-163-GUIDELINES-SUBCLIN-HYPER-PDF-438750.pdf. Accessed 22 March 2018.

Fazal-Sanderson V, Karavitaki N, Grossman AB, Kalhan A. Abstract: Outcomes of a nurse-led thyroid clinic at

a tertiary-care endocrine centre. Endocr Connections. 2017. Available at: http://www.endocrine-abstracts.org/ea/0049/ea0049GP114.htm. Accessed 22 Oct 2017.

Franklyn JA. Subclinical hyperthyroidism:3.3.4. In: Wass JAH, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet. 2012. Available at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(11)60782-4.pdf. Accessed 28 July 2017.

Fuhrer D, Lazarus JH. Management of toxic multinodular goitre and toxic adenoma-3.3.11. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Goichot B, Caron P, Landron F, Bouée S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin Endocrinol. 2015. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/cen.12816. Accessed 10 Oct 2017.

Harvey CB, O'Shea PJ, Scott AJ, Robson H, Siebler T, Shalet SM, Samarut J, Chassande O, Williams GR. Molecular mechanisms of thyroid hormone effects on bone growth and function. Mol Genet Metab. 2002. Available at: http://www.mgmjournal.com/article/S1096-7192(01)93268-8/pdf. Accessed 22 Oct 2017.

Hedley AJ, Young RE, Jones SJ, Alexander WD, Bewsher PD. Antithyroid drugs in the treatment of hyperthyroidism of Graves' disease: long-term follow-up of 434 patients. Scottish Automated Follow-Up Register Group. Clin Endocrinol – Oxf. 1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Hedley+1989+antithyroid. Accessed 22 Dec 2017.

Hennessey JV. Subacute thyroiditis. In DeGroot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Kock C, Korbonitis M, McLachian R, New M, Pumeli J, Rebar R, Singer F, Vinik A, editors. ENDOTEXT. 2015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25905310, https://www.ncbi.nlm.nih.gov/books/NBK279084/. Accessed 23 Oct 2017.

Hiromatsu Y, Satoh H, Amino N. Hashimoto's thyroiditis: history and future outlook. Hormones (Athens). 2013. In: Tidy C. Hashimoto's thyroiditis. Patient UK. 2015. Available at: https://patient.info/doctor/hashimotos-thyroiditis. Accessed 22 Nov 2017.

Hogan-Quigley B, Palm ML, Bickley L. Bates' Nursing Guide To Physical Examination And History Taking. London: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

Kaplan B, Pearce EN, Farewell AP. Thyroiditis. 3.2.7. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Kondi-Parfit A, Mavrigigiannaki P, Grigoriadis CH, Kontogianni-Katsarou K, Mellou A, Kleanthis CK, Liapis A. Monodermal teratomas (struma ovarii). Clinicopathological characteristics of 11 cases and literature review. Eur J Gynaecol Oncol. 2011. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=22335029. Accessed 22 Oct 2017.

Kraemer B, Girschke EM, Staebler A, Hirides P, Rothmund R. Laparoscopic excision of malignant struma ovarii and 1 year follow-up without fur further treatment. Fertil Steril. 2011. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=21269611. Accessed 22 Oct 2017.

Latrofa F, Vitti P, Pinchera A. Causes and laboratory investigations of thyrotoxicosis-3.3.5. In: Wass JAH, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Laurberg P. Remission of Graves' disease during antithyroid drug therapy. Time to reconsider the mechanism? Eur J Endocrinol. 2006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17132745. Accessed 12 June 2017.

Laurberg P, Vestergaard H, Neilson S, Christensen SE, Seefeldt, Hellberg K, Pederson KM. Sources of circulating 3,5,3′-triiodothyronine in hyperthyroidism estimated after blocking of type 1 and type 2 iodothyronine deiodinases. 2007. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=17389703. Accessed 22 May 2017.

Leger J, Gelwane G, Kaguelidou F. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: National Long-Term Cohort Study. J Clin Endocrinol Metab. 2012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22031519. Accessed 20 Dec 2017.

Makani S, Kim W, Gaba AR. Struma Ovarii with a focus of papillary thyroid cancer: a case report and review of the literature. Gynecol Oncol. 2004. Available at: http://www.gynecologiconcology-online.net/article/S0090-8258(04)00414-7/pdf. Accessed 22 Dec 2017.

Marcocci C, Cetani F, Pinchera A. Clinical assessment and systemic manifestations of thyrotoxicosis-3.3.1. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Marqusee E, Haden ST, Utiger RD. Subclinical thyrotoxicosis. Endocrinol Metab Clin N Am. 1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9534026. Accessed 22 Oct 2017.

McGregor AM, Petersen MM, McLachlan SM, Rooke P, Smith BR, Hall R. Carbimazole and the autoimmune response in Graves' disease. N Engl J Med. 1980. Available at: http://www.nejm.org/doi/full/10.1056/NEJM198008073030603. Accessed 23 June 2018.

Mui MP, Tam KF, Tam FK, Ngan HY. Coexistence of struma ovarii with marked ascites and elevated CA-125 levels: case report and literature review. Arch Gynecol Obstet. 2009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Mui+MP%2C+2009. Accessed 22 Dec 2017.

National Institute for Health and Care Excellence-NICE. Hyperthyroidism. NICE. 2016. Available at: https://cks.nice.org.uk/hyperthyroidism#!management. Accessed 22 Aug 2017.

Organzi, Bournard. Management of graves' hyperthyroidism-3.3.9. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Paul T, Meyers B, Witorsch RJ, Pino S, Chipkin S, Ingbar SH, Braverman LE. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism. 1988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3340004. Accessed 24 May 2017.

Pearce EN, Farwell AP, Braverman LE. Thyroiditis-3.2.7. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2003.

Perros P, Dayan CM, Dickinson AJ, et al. Management of patients with Graves' orbitopathy: initial assessment, management outside specialised centres and referral pathways. Clin Med. British Thyroid Foundation. 2015. Available at: http://www.clinmed.rcpjournal.org/content/15/2/173.full.pdf+html. Accessed 03 Aug 2017.

Plummer HS. The value of iodine in exopthalmic goiter. J Iowa Med Soc 1924;14:66–73. In: Calissendorff J, Falhammar H. Rescue pre-operative treatment with Lugol's solution in uncontrolled Graves' disease. Endocr Connect. 2017. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5434745/#bib3. Accessed 22 Nov 2017.

Ross D. Treatment of toxic adenoma and toxic multinodular goiter. Up-To-Date. 2016. Available at: https://www.uptodate.com/contents/treatment-of-toxic-adenoma-and-toxic-multinodular-goiter?source=search_result&search=toxic+adenoma&selectedTitle=1%7E150. Accessed 22 May 2016.

Ross DS. Diagnosis of hyperthyroidism. Up-To-Date. 2017a. Available at: https://www.uptodate.com/contents/diagnosis-of-hyperthyroidism. Accessed 22 June 2017.

Ross DS. Clinical presentation and evaluation of goiter in adults. UpToDate. 2017b. Available at: https://www.uptodate.com/contents/clinical-presentation-and-evaluation-of-goiter-in-adults#H1. Accessed 22 June 2017.

Ross DS. Iodine treatment of hyperthyroidism. UpToDate. 2017c. Available at: https://www.uptodate.com/contents/iodine-in-the-treatment-of-hyperthyroidism. Accessed 30 March 2018.

Sanderson V, Alberts B, Grossman AB, Karavitaki, N. Outcome of patients with Graves' disease after long-term follow-up: data from a Nurse-led Clinic. Endocrine Abstracts - Endocr Connect. 2012. Available at: http://www.endocrine-abstracts.org/ea/0028/ea0028P157.htm. Accessed 22 Aug 2017.

Schwartz KM, Fatourechi V, Ahmed DDF, Pond GR. Dermopathy of Graves' disease (Pretibial myxedema): long-term outcome. J Clin Endocrinol Metab. 2002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=schwartz+2002+graves%27+dermopathy. Accessed 22 Oct 2018.

Shreshtha RT, Hennessey J. Acute and subacute thyroiditis. ENDOTEXT. 2015. Available at: http://www.thyroidmanager.org/chapter/acute-and-subacuteand-riedels-thyroiditis/#_ENREF_32. Accessed 24 July 2017.

Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G, Greenspan FS, McDougall IR, Nikolai TF. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. JAMA. 1995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7532241. Accessed 22 Oct 2017.

Smith P. Milestone in European thyroidology-Robert James Graves'. European Thyroid Association; 2018. Available at: http://www.eurothyroid.com/about/met/graves.html. Accessed 22 Jan 2018.

Stagnaro-Green. Postpartum thyroiditis. J Clin Endocrinol Metab. Oxford Academic. 2002. Available at: https://academic.oup.com/jcem/article/87/9/4042/2846380. Accessed 22 Dec 2017.

Szyfelbein WM, Young RH, Scully RE. Cystic struma ovarii: a frequently unrecognized tumor. A report of 20 cases. Am J Surg Pathol. 1994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8037292. Accessed 22 Dec 2017.

Takasu N, Yamashiro K, Komiya I, Ochi Y, Nagata A. Remission of Graves' hyperthyroidism predicted by smooth decreases of thyroid-stimulating antibody and thyrotropin-binding inhibitor immunoglobulin during antithyroid drug treatment. 2000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11081255. Accessed 22 Nov 2017.

Thyroid Eye Disease Committee Team. Patient information. TEDct. 2018. Available at: http://tedct.org.uk/. Accessed 22 Dec 2017.

Tidy C. Antithyroid medication. Patient UK. 2014. Available at: https://patient.info/health/overactive-thyroid-gland-hyperthyroidism/antithyroid-medicines. Accessed 22 Nov 2017.

Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N. TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Syst Rev Meta-Analysis. 2012. Available: https://www.ncbi.nlm.nih.gov/pubmed/22776786. Accessed 28 July 2017.

Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Grimley Evens J, Young E, Bird T, Smith PA. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol. 1977. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2265.1977.tb01340.x. Accessed 22 Sept 2017.

Vaidya B, Pearce SHS. Clinical review: diagnosis & management of thyrotoxicosis. Br Med J. 2014. Available at: https://medicinainternaaldia.files.wordpress.com/2014/09/tirotoxicosis.pdf. Accessed 27 July 2017.

Vanderpump. The epidemiology of thyroid disease. Br Med J-Oxford Academic. 2011. Available at: https://academic.oup.com/bmb/article/99/1/39/298307. Accessed 22 Dec 17.

Vicente N, Cardoso L, Barros L, Carrilho F. Antithyroid drug-induced agranulocytosis: state of the art on

diagnosis and management. 2017. Available at: https://www.ncbi.nlm.nih.gov/m/pubmed/28105610/. Accessed 22 Dec 2017.
Vickery AL, Hamlin E. Struma lymphomatosa (Hasimoto's thyroiditis): observations on repeated biopsies in 16 patients. N Engl J Med. 1961. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJM196102022640505. Accessed 22 Dec 2017.
Visser, TJ. (2011) Biosynthesis, transport, metabolism, and actions of thyroid hormones. In, Wass, JAH., Stewart, PM., Amiel, SA. & Davis, MJ. Oxford textbook of endocrinology, diabetes and metabolism (2). Oxford: Oxford University Press.
Volpe R, Sawin C. The history of iconography relating to the thyroid gland-3.1.1. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.
Wass JAH, Owen K. Chapter 1. Thyroid. In: Turner HE, editor. Oxford handbook of endocrinology and diabetes. 3rd ed., Advisory Ed. Oxford: Oxford University Press; 2014.
Weetman AP. The thyroid gland and disorders of thyroid function. In: Warrell DA, Cox TM, Firth JD, editors. Oxford textbook of medicine. Oxford: Oxford University Press; 2010.
Weetman AP. Investigating low thyroid stimulating hormone (TSH) level. BMJ. 2013. Available at: http://www.bmj.com/content/347/bmj.f6842. Accessed 22 Nov 2017.
Weiner JD, DeVries AA. On the natural history of Plummer's disease. Clin Nucl Med. 1979. Available at: https://www.ncbi.nlm.nih.gov/pubmed/582300. Accessed 22 July 2017.
Wirth CD, Blum MR, Da Costa BR, Baumgartner C, Collet TH, Medici M, Peeters RP, Aujesky D, Bauer DC, Rodondi N. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. Annu Intern Med. 2014. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25089863. Accessed 23 Oct 2017.
Yassa L, Sadow P, Marquesee E. Malignant struma ovarii. Nature clinical practice. Endocrinol Metab. 2008. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=18560398. Accessed 22 Oct 2017.
Yoo SC, Chang KH, Lyu MO, Chang SJ, Ryu HS, Kim HS. Clinical characteristics of struma ovarii. J Gynaecol Oncol. 2008. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676458/. Accessed 22 July 2017.
Young RH. New and unusual aspects of ovarian germ cell tumors. 1993. Available at: https://www.ncbi.nlm.nih.gov/pubmed?term=7694512. Accessed 24 Aug 2017.
Zimmerman MB. Iodine and Iodine deficiency disorders. Wiley Online library. 2012. Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1002/9781119946045.ch36. Accessed 22 Oct 2017.

Key Reading

1. British Thyroid Association-BTA. UK guidelines for the use of thyroid function tests: thyrotoxicosis. BTA. 2006. Available at: http://www.british-thyroid association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf. Accessed 22 July 2017.
2. American Thyroid Association – ATA. Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. ATA. 2016. Available at: https://www.thyroid.org/professionals/ata-professional-guidelines/. Accessed 24 July 2017.
3. European Thyroid Association. Guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. Eur Thyroid J. 2015. Available at: http://www.eurothyroid.com/files/download/ETJ-2015-4-149-163-GUIDELINES-SUBCLIN-HYPER-PDF-438750.pdf. Accessed 22 March 2018.
4. Stagnaro-Green A. Post-partum thyroiditis. J Clin Endocrinol Metab. Oxford Academic; 2002. Available at: https://academic.oup.com/jcem/article/87/9/4042/2846380. Accessed 22 Nov 2017.
5. Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2016. Available at: https://pdfs.semanticscholar.org/fbbd/c83f6b89a-ca96059519b33bbc15a10aae5d5.pdf. Accessed at: 10 Jan 2018.
6. Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet. 2012. Available at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(11)60782-4.pdf. Accessed at: 28 July 2017.
7. Vaidya B, Pearce SHS. Clinical review: diagnosis & management of thyrotoxicosis. Br Med J. 2014 Available at: https://medicinainternaaldia.files.wordpress.com/2014/09/tirotoxicosis.pdf. Accessed at: 27 July 2017.
8. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016. Available at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)00278-6.pdf. Accessed 22 Dec 2017.
9. Thyroid Eye Disease (committee team). Available at: http://tedct.org.uk/. Accessed 22 Feb 2018.
10. British Thyroid Foundation. Available at: http://www.btf-thyroid.org/. Accessed 22 March 2018.
11. UpToDate: hyperthyroidism. Available at: https://www.uptodate.com/contents/search?search=hyperthyroidism. Accessed 22 March 2018.
12. PubMed: Hyperthyroidism. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014602/. Accessed 22 March 2018.
13. Endotext. Thyroid disease. 2017. Available at: http://www.endotext.org/.
14. Thyroid Disease. Available at: www.thyroidmanager.org. Accessed 22 March 2018.

Thyroid Cancer

29

Ingrid Haupt-Schott, Geraldine Hamilton, and Petros Perros

Contents

29.1 **Introduction** 559
29.1.1 Epidemiology 559
29.1.2 Risk Factors 560
29.1.3 Overview of the Different Types of Thyroid Cancer 560

29.2 **Differentiated Thyroid Cancer** 561
29.2.1 Diagnostic Investigations and Staging 561
29.2.2 Surgery 563
29.2.3 Radioiodine Ablation 565
29.2.4 Thyroid Stimulating Hormone (TSH) Suppression, Biochemical Monitoring and Dynamic Risk Stratification 568
29.2.5 Metastatic, Recurrent and Radioiodine Refractory DTC 570

29.3 **Medullary Thyroid Cancer** 571
29.3.1 Symptoms/Presentation 571
29.3.2 Diagnostic Investigations and Staging 571
29.3.3 Treatment 572
29.3.4 Prognosis 572
29.3.5 Follow-Up and Monitoring 572
29.3.6 Additional Treatment Options in Advanced MTC 573

29.4 **Anaplastic Thyroid Cancer** 573
29.4.1 Symptoms/Presentation 573
29.4.2 Diagnostic Investigations and Staging 573

I. Haupt-Schott (✉)
Velindre NHS Trust, Velindre Cancer Centre, Cardiff, UK
e-mail: Ingrid.Haupt-schott@wales.nhs.uk

G. Hamilton
Macmillan Support Line, Macmillan Cancer Support, Glasgow, UK
e-mail: ghamilton@macmillan.org.uk

P. Perros
Newcastle upon Tyne Hospitals NHS Foundation Trust and Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK
e-mail: petros.perros@ncl.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_29

29.4.3 Treatment ... 573
29.4.4 Outcome ... 574
29.5 **Genetics** ... 574
29.6 **Living with Thyroid Cancer** ... 574
29.6.1 Voice Problems ... 575
29.6.2 Weight Gain ... 575
29.6.3 Fatigue ... 575
29.6.4 Lifelong Monitoring ... 575
29.7 **Future Developments in the Management of Thyroid Cancer** ... 575
29.7.1 Encapsulated Non-invasive Follicular Variant PTC ... 575
29.7.2 Role of Radioiodine Ablation in Low-Risk Well-Differentiated Thyroid Cancer ... 576
29.7.3 Radioiodine Refractory Disease ... 576
29.7.4 Tissue Bank for Anaplastic Thyroid Cancer ... 576
29.8 **The Role of the Specialist Nurse** ... 576
29.9 **Conclusions** ... 577
References ... 577

Abstract

Thyroid cancer is rare and accounts for less than 1% of all cancers, but represents the most common endocrine malignancy. Incidence rates have increased in the past decade in most countries. This is mainly due to an increased use of imaging and subsequent incidental detection of thyroid cancers, but other unidentified factors may also contribute.

The natural history of thyroid cancer, its management and its long-term prognosis are very different to most other solid cancers and therefore warrant specialist support.

The last decade has seen a shift in the management of thyroid cancer with a tendency for less aggressive treatments for the more indolent types and a focus on a more personalised approach to decision-making and management.

The following chapter describes the various types of thyroid cancer, their current management protocols and some developments into future treatments.

Keywords

Thyroid cancer · Papillary · Follicular Medullary · Anaplastic · Radioiodine treatment · Thyroid surgery

Abbreviations

ATC	Anaplastic thyroid cancer
CT	Computed tomography
DTC	Differentiated thyroid cancer
FNA	Fine needle aspiration
FTC	Follicular thyroid caner
LN	Lymph node
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
PET	Positron emission tomography
PTC	Papillary thyroid cancer
RAI	Radioactive iodine
RLN	Recurrent laryngeal nerve
Tg	Thyroglobulin
TgAbs	Thyroglobulin antibodies
TKI	Tyrosine kinase inhibitors
US	Ultrasound scan
VC	Vocal cords

Key Terms

- **TNM Staging:** Malignant thyroid tumours are sorted into categories based on size, extension and spread which estimate prognosis.
- **Radioiodine Ablation:** Radioactive iodine is administered orally in order to destroy remnant thyroid tissue and cancer cells.

- **Radioiodine Refractory Disease:** Residual tumour and/or metastatic disease that does not take up radioiodine anymore and therefore cannot be treated with radioiodine any further.
- **Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP):** An encapsulated follicular variant of papillary thyroid cancer with a very low risk of an adverse outcome.

Key Points

- The number of thyroid cancer diagnoses is increasing, primarily due to incidental detection of small, biologically indolent tumours.
- The prognosis for most patients with thyroid cancer is good.
- The approach to treatment should be personalised.
- Psychological factors are vital to be considered as patients will remain on monitoring and may experience lifelong physical and emotional consequences.
- An important objective for healthcare professionals managing people with thyroid cancer is remembering to treat the person, not just the disease.

29.1 Introduction

29.1.1 Epidemiology

Thyroid cancers are rare and account for less than 1% of all cancers. They represent however the most common endocrine malignancy. In most countries, thyroid cancer incidence rates have increased in the past decade (Vigneri et al. 2015). In 2012, the global figure for new cases of thyroid cancer was 230,000 and 40,000 deaths (Vecchia et al. 2015). In the UK, there were 3241 cases diagnosed in 2013 (Cancer Research UK n.d.).

In the UK, the increase of incidence amounted to 71% over the last decade (Cancer Research UK n.d.). Incidental detection of small (<1 cm) thyroid cancers due to the widespread use of imaging techniques and pathology reporting of thyroidectomy specimens resected for benign disease is thought to explain most of this increase, but it does not account for all the rises we are seeing. Other factors are thought to be at play such as changes in prevalence of risk factors including obesity, exposure to radiation, dietary iodine levels and hormonal factors (Vigneri et al. 2015). Presently we have very little evidence to back these theories.

While the incidence of thyroid cancers may be on the rise, cure rates are still very high and death rates are declining (Vecchia et al. 2015). Eighty-five to over 95% of people with differentiated thyroid cancer (papillary and follicular) can expect to have a normal life span after treatment.

Thyroid cancer can affect people of all ages from children to the elderly. Of the over 3000 newly diagnosed patients in the UK in 2013, 27% were men and 73% were women (Cancer Research UK n.d.). Incidence in men is strongly related to age, with the highest incidence being in older men. In females, the rates are highest in younger and middle-aged women (Fig. 29.1).

Thyroid cancer is a disease of paradoxes. Most small papillary thyroid cancers (PTCs) are indolent and overdiagnosed in the Western world and potential harm to patients from overtreatment has been highlighted (Brito et al. 2013). The prognosis in young adults (the majority of cases) with differentiated thyroid cancer (DTC) is excellent and the presence of lymph node (LN) metastases in the neck does not appear to influence long-term survival. Unlike many cancers however, late recurrences (sometimes decades after diagnosis) are not uncommon. Some DTCs behave aggressively and are associated with premature death (Reiners 2014; Roman and Sosa 2013). DTC is one among few solid cancers that can be cured even when there are distant metastases (Pawelczak et al. 2010). Many patients with recurrent thyroid cancer still survive for several years. Uncertainty is a companion to many patients with thyroid cancer and although survival overall is very favourable, quality of life is frequently chronically impaired (Sawka et al. 2014; Duan et al. 2015; Banach et al. 2013). Around 10% of patients have refractory disease.

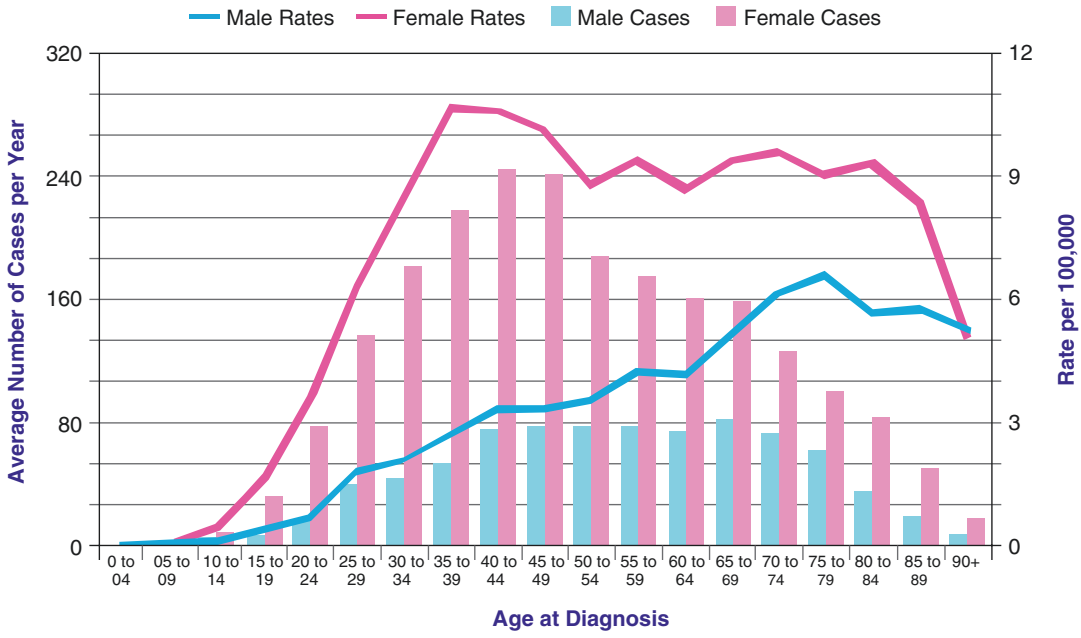


Fig. 29.1 Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,00 Population, UK (2011–2013) (Cancer Research UK n.d.). Content supplied with permission by the world's largest charitable funder of cancer research, © Cancer Research UK [2002] All rights reserved http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence#heading-One

There are therefore numerous challenges for patients, carers and healthcare professionals associated with the diagnosis of thyroid cancer. The last decade has seen a shift in the management of thyroid cancer with a tendency for less aggressive treatments for the more indolent types and a focus on a more personalised approach to treatment (Perros et al. 2014).

In most cases the cause of thyroid cancer is unknown; however, there are a number of risk factors.

29.1.2 Risk Factors

- **Ionising radiation**: This is known to be the biggest risk factor for thyroid cancer. Studies in childhood cancer survivors have shown an increased risk of thyroid cancer after radiotherapy (Sklar et al. 2012; Veiga et al. 2000). The cancer may not develop until 10–40 years after treatment. Although this risk is highest in children treated with radiotherapy, there is a slightly increased risk for anyone who has had external beam radiotherapy (Schonfeld et al. 2011).

  Thyroid cancer is also more common in survivors of atomic explosions or accidents. After the Chernobyl nuclear reactor accident the number of cases in the Ukraine rose in people exposed to radiation, particularly as children or adolescents. Thyroid cancer cases also increased in the USA after nuclear testing in Utah.
- **Familial adenomatous polyposis** (FAP)—a genetic disorder (Triggiani et al. 2012).
- **Family history** of thyroid cancer (Metzger and Milas 2014).
- **Weak associations** (insufficient to justify screening) have been observed with obesity (Pappa and Alevizaki 2014), acromegaly (Wolinski et al. 2014) and diabetes (Schmid et al. 2013).

29.1.3 Overview of the Different Types of Thyroid Cancer

There are four main types of thyroid cancer.

Papillary thyroid cancer is the most common and accounts for around 65–80% of all thyroid cancers. It is a slow growing cancer originating in the follicular cells of the thyroid gland. It is usually well

differentiated, may be multifocal and has a good prognosis for most patients. LN spread to the neck is present in up to 60% of papillary tumours (Mazzaferri et al. 2006), but these are often small foci of doubtful significance. LN involvement at diagnosis is associated with a higher risk of recurrence but not a higher mortality. Distant metastases are not common even in patients with neck node involvement. This is an important message for patients as the prospect of a cancer spreading can cause extreme stress. PTC is diagnosed in younger people and the female to male ratio is 2:1. Subtypes and variants of classic PTC include tall cell, columnar, diffuse sclerosing and poorly differentiated PTC (Kazaure et al. 2012). Certain oncogenic mutations are associated with more aggressive clinical behaviour (Xing et al. 2014). These variants generally have a propensity to recur and metastasise, but even then progression can be slow and patients can live for many years with relatively inactive metastases. Noninvasive encapsulated follicular variant PTC (NEFVPTC) has a very low risk of adverse outcome and the classification as 'non-invasive follicular thyroid neoplasms with papillary-like nuclear features '(NITFP) has now been introduced (Lloyd et al. 2017).

Follicular thyroid cancer (FTC) is the second most common type of thyroid cancer and accounts for around 15% of all thyroid cancers. It mostly presents as a solitary, slow growing tumour that is usually well differentiated. It generally has a good prognosis; however, vascular invasion is associated with worse outcomes (Mazzaferri et al. 2006). If more advanced at diagnosis, FTC can metastasise more readily. It has a peak onset between 40 and 60 years of age. People over 55 years often tend to have a more aggressive form of the disease.

There is a distinct subgroup of FTC called Hürthle cell thyroid cancer. One of its characteristics is that it has limited ability to concentrate iodine. It has the highest incidence of metastases among the DTCs with lungs, bones and central nervous system being the most common sites. LNs can also be affected.

Medullary thyroid cancer originates in the C cells of the thyroid gland and accounts for 3–10% of all thyroid cancers. Around 75% are sporadic with the other 25% being familial due to genetic predisposition. It requires genetic testing to establish the specific type.

Families of patients with MTC who carry genetic mutations are offered genetic screening and, if appropriate, assessment and treatment. Disease progression is usually slow and for this reason patients diagnosed with metastases that have spread to LNs or to distant sites can live for many years, but overall prognosis is less favourable than that of DTCs.

Anaplastic thyroid cancer is the rarest form of thyroid cancer and accounts for 1–3% of all thyroid cancers. Its prognosis is poor and its aggressive growth pattern often leads to death within a few months of diagnosis. Anaplastic elements can be found in well-differentiated tumours at diagnosis or at a later stage affecting the progression of these tumour types.

Lymphomas of the thyroid gland such as non-Hodgkin lymphoma are rare and treated as other haematological malignancies.

29.2 Differentiated Thyroid Cancer

29.2.1 Diagnostic Investigations and Staging

The suspicion of a thyroid cancer is raised in several ways and may include one or more of the symptoms listed in Table 29.1.

Increasingly thyroid nodules are found incidentally when imaging of the neck is performed for other clinical reasons. Occasionally patients present with metastases.

29.2.1.1 Pre-operative Investigations and Classification

Thyroid ultrasound (US) with fine needle aspiration (FNA) biopsy: Thyroid ultrasound in expert hands is a valuable investigation and can separate benign nodules (that do not require further investi-

Table 29.1 Clinical presentation (adapted from Hanna et al. (2015))

• Lump in the thyroid area
• Dysphonia (hoarse voice)
• Dysphagia (difficulty in swallowing)
• Stridor or impaired breathing
• Sense of fullness in the neck

gations) and suspicious lesions that merit further assessment with FNA biopsy. This is current advice from the British Thyroid Association (Perros et al. 2014) as performing a FNA of a lump by palpitation might not identify and assess the most suspicious nodules and not yield a reliable diagnostic result.

CT/MRI scan: If there is suspicion of locally advanced disease, a CT or MRI should be performed pre-operatively to facilitate surgical planning. A time interval of 2 months between CT and radioactive iodine (RAI) ablation is required as the CT contrast medium contains iodine and may interfere with the uptake of RAI. Unlike other cancers, extensive pre-operative staging with imaging (e.g. CT, MRI, PET CT) is unnecessary in most cases, as in low-risk patients disease outside the neck is highly unlikely, while in intermediate or high risk cases whole-body radioiodine imaging 1–2 weeks after radioiodine ablation provides adequate staging information and the potential presence of metastases will not affect the extent and timing of surgery.

LN involvement is common in PTC, but much less so in FTC. A number of US features are associated with benign or malignant nodules. LN levels are as per Fig. 29.2.

The British Thyroid Association guidelines (Perros et al. 2014) recommend the classification below which will guide the clinician in planning further investigations and treatment (Table 29.2).

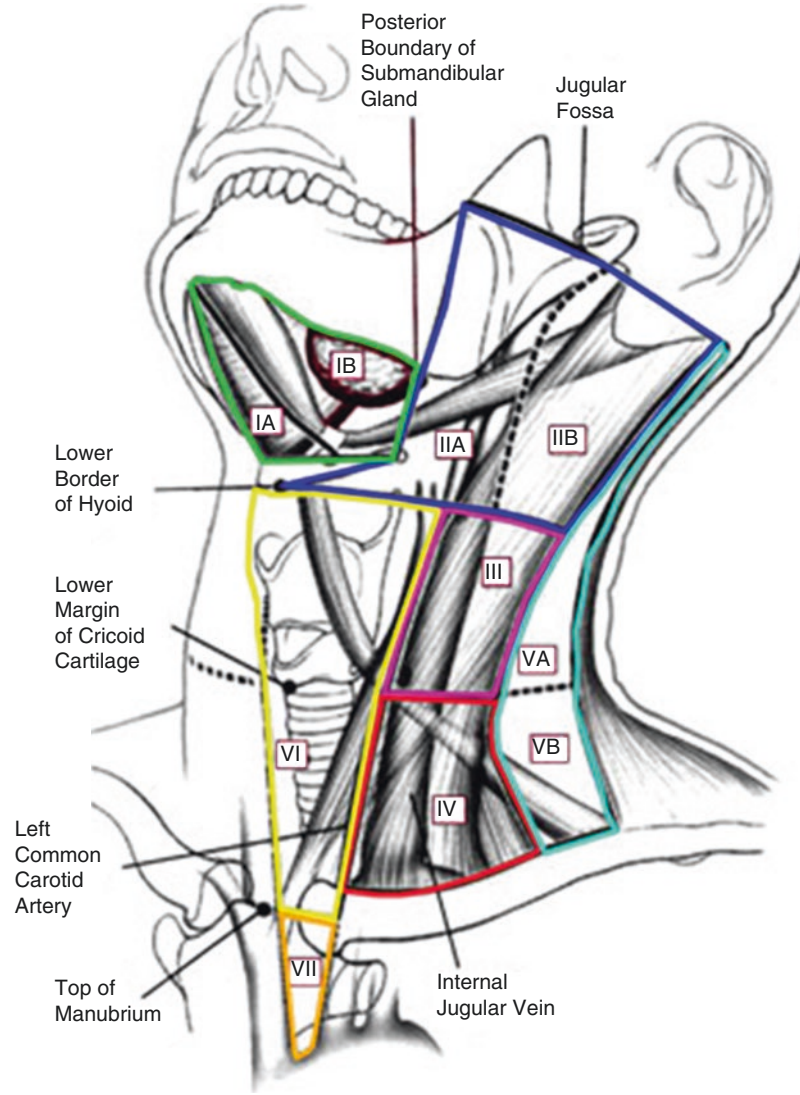


Fig. 29.2 The neck and upper mediastinum LN levels, based on surgical compartments. Used with permission from Author/website owner, accessed via http://www.endocrinesurgery.net.au/lymph-node-management/

Table 29.2 Thyroid nodules—USS classifications (adapted from Perros et al. (2014))

• U1. Normal
• U2. Benign changes (e.g. cystic changes)
• U3. Indeterminate
• U4. Suspicious (e.g. hypo-echoic area)
• U5. Malignant (solid hypo-echoic nodule, micro-calcification, taller than wide cells)

Table 29.3 Diagnostic classifications of FNA cytology (adapted from Cross et al. (2016))

• THY1—non-diagnostic (e.g. due to poor sampling or only poorly preserved cells)
• THY1c—cystic fluid
• THY2—non-neoplastic (normal thyroid tissue)
• THY2c—non-neoplastic cystic lesion
• THY3—neoplasm possible
– THY3a—atypical features present, but not enough to categorise
– THY3f—possible follicular adenoma or carcinoma
• THY4—suspicious of malignancy (usually suspected papillary carcinoma in about 70% of patients)
• THY5—malignant

A U3–U5 finding would be followed by a FNA biopsy to obtain more information about the nature of the nodule. The classification recommended by the Royal College of Pathologists based on the Bethesda system for reporting thyroid cytopathology (www.rcpath.org) is shown below (Table 29.3).

Pre-operatively a vocal cord (VC) check is required to ascertain function. The recurrent laryngeal nerves (RLNs) which innervate the VCs lie very close to the thyroid gland. Any handling of the RLN during surgery can affect VC function (usually temporarily). The incidence of permanent VC damage through surgery in expert surgical hands is low at <1% (Mazzaferri et al. 2006).

29.2.1.2 Thyroid Cancer Staging

Malignant tumours are staged into categories which will allow for treatment planning and risk assessment (Table 29.4). The TNM classification (Tuttle et al. 2017) identifies the tumour size—T, the presence and location of nodules—N and the presence of metastases—M. It is generally used for staging of thyroid cancers.

If the staging categories 1–4 are being used, patients <55 years are either stage 1 (if no metastases) or stage 2 (if metastatic disease present) regardless of TN status. This is because patients <55 years have a slightly better prognosis, so staging is stratified to match outcomes.

For patients ≥55 years Stage 1 equals a T1/2N0/XM0 category and Stage 2 a T1/2N1M0 and a T3N0/1/XM0 category. Stage 3 is defined as T4aN0/1/XM0. Stage IVA disease is T4bN0/1/XM0 and Stage IVb anyT, anyN and M1.

Table 29.4 TNM classification (adapted from Bychkov (2018)) (8th edition)

• T1—Tumour size ≤2 cm in greatest dimension and limited to the thyroid gland
– T1a—Tumour ≤1 cm in greatest dimension, limited to the thyroid gland
– T1b—Tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid gland
• T2—Tumour size >2 cm but ≤4 cm in greatest dimension, limited to the thyroid gland
• T3—Tumour size >4 cm, limited to the thyroid gland or gross extrathyroidal extension invading only strap muscles
– T3a—tumour >4 cm limited to the thyroid gland
– T3b—tumour of any size with gross extrathyroidal extension invading only strap muscles
• T4a—Tumour of any size with gross extrathyroidal extension into subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve
• T4b—Tumour of any size invading prevertebral fascia or encasing carotid artery or mediastinal vessels
• N0a—one or more cytologic or histologically confirmed benign lymph nodes
• N0b—no clinical or radiological evidence of locoregional lymph node metastases
• N1a—metastasis to level VI or VII lymph nodes (unilateral or bilateral)
• N1b—metastasis to level I, II, III, IV or V (unilateral, bilateral or contralateral) or retropharyngeal lymph nodes
• M0—no distant metastasis
• M1—distant metastasis

29.2.2 Surgery

Surgery is the most important initial treatment for well-differentiated and medullary thyroid cancer (MTC).

Guidelines recommend that thyroid cancer surgery is performed by experienced surgeons who perform high volumes of thyroid operations (National Cancer Peer Review—National Cancer Action Team n.d.).

The table below lists the types of surgery performed for thyroid cancer (Table 29.5).

A hemithyroidectomy is often performed if the diagnosis is unclear; however, if cancer is confirmed it may be followed by completion thyroidectomy. A hemithyroidectomy is considered adequate treatment for small tumours without adverse factors such as no adverse histological features, no extrathyroidal extension, no multifocal disease, no vascular invasion, no LN involvement, and no distant metastases.

A total thyroidectomy reduces the risk of local recurrence and distant metastases, allows for RAI ablation and facilitates long-term follow-up with serum thyroglobulin (Tg) monitoring.

If there is an underlying symptomatic thyroid disease (like Graves' disease or multinodular goitre), a total thyroidectomy is usually undertaken.

There are two notable recent trends in surgical management of thyroid cancer. Increasingly evidence suggests that hemithyroidectomy is associated with equally good outcomes as total thyroidectomy in carefully selected patients with DTCs up to 4 cm in diameter that are deemed low risk based on well-defined criteria (Kuba et al. 2014). Evidence mainly from Japan suggests that patients with a diagnosis of papillary thyroid microcarcinoma can be followed up safely with US without surgery, with excellent long-term outcomes (Ito et al. 2016).

One of the many paradoxes of PTC is that if sought intensively by pathologists, micrometastases in cervical LNs are found with high frequency, even in patients with microcarcinomas (Qubain et al. 2002). Yet, whether these are resected surgically or not does not seem to make a difference on survival (Randolph et al. 2012). The role of prophylactic neck dissection (i.e. surgery to remove LNs in the neck that are not obviously involved based on palpation and US) is controversial in patients with DTC as such surgery increases the risk of VC palsy and permanent hypoparathyroidism. Therefore prophylactic central LN dissection should only be considered if there are adverse risk factors (age >55 years, tumour size >4 cm, extrathyroidal extension, adverse histological subtype) and be a personalised decision. Equally prophylactic lateral LN dissection should be planned on an individual basis if the central LNs are involved. Radical neck dissection is a mutilating operation, which generally has no role in the surgical management of thyroid cancer. Therapeutic LN removal is indicated if LN involvement is evident pre- or intraoperatively.

Table 29.5 Types of thyroid cancer surgery

• Hemithyroidectomy
• Total thyroidectomy
• Completion thyroidectomy
• Selective neck dissection
• Isthmusectomy

29.2.2.1 Surgical Complications

Damage to the RLN can lead to a hoarse/whispery/weak/breathy voice due to compromise or loss of function of one or both of the VCs. Incidental cutting of the RLN or its removal to achieve the best outcome if it is infiltrated by thyroid tumour leads to corresponding VC palsy.

Damage to the superior laryngeal nerve will affect the voice quality, resulting in a lowered voice tone, early voice fatigue and loss of high pitches of the singing voice. This is a more frequent complication than a whispery voice.

The VCs might recover spontaneously during the first few months; therefore active voice rehabilitation is usually commenced only at least 6 months after surgery.

Damage to the hypoglossal nerve will affect the movement of the tongue and eating might be more difficult.

The accessory nerve innervates the sternocleidomastoid and the trapezius muscle and so facilitates the head, arm and shoulder movement. Damage to this nerve during surgery will make it difficult to lift the corresponding shoulder and raise the arm high, and results in neck stiffness. This can in most cases be treated successfully with physiotherapy.

Smaller sensory nerves of the skin can easily be cut during surgery. This can lead to numbness of the skin. For men it is noticeable e.g. during shaving. While sensation can return when nerves grow back together again, it can be lost permanently in certain areas of the face or neck.

Lymphoedema might occur when there is extensive LN removal or surgical removal of the internal jugular vein in neck dissections which will

impair the normal lymph drainage. This can occur either immediately or months and even years later.

A chyle leak can occur through damage to the thoracic duct, resulting in leakage of lymphatic fluid (called chyle). It will be seen as a collection under the skin or in the wound drain after the patient has eaten. A strict fat free diet for 2–3 weeks is required until the leak has healed.

Hypocalcaemia results from damage to or removal of one or more of the parathyroid glands. Temporarily reduced functionality of the parathyroid glands due to manipulation during surgery is quite common initially. Permanent damage or loss of all parathyroid function occurs in a minority and requires long-term calcium and vitamin D analogue supplementation supplementation (see 29.2.4.4).

29.2.3 Radioiodine Ablation

29.2.3.1 Indications

Radioiodine ablation has been used in PTC and FTC after total thyroidectomy especially for those patients with an intermediate or high risk of recurrence or death. The potential benefits and problems associated with radioiodine ablation are outlined below (Tables 29.6 and 29.7). The BTA guidelines recommend an individualised approach to RAI ablation as shown in Tables 29.8.

Table 29.6 Benefits of RAI ablation (adapted from Perros et al. (2014))

• Prolonged survival
• Reduced risk of local and distant tumour recurrence
• Potential detection of distant metastases at diagnosis
• Easier long-term monitoring with undetectable Tg
• Easier detection of possible recurrence or metastases
• Reassurance for patients

Table 29.7 Problems associated with RAI ablation (adapted from Perros et al. (2014) and Hanna et al. (2015))

• Admission to stay in isolation for 1–4 days
• Post RAI ablation contact restrictions
• Having to avoid pregnancy or fathering a child for 6 or 4 months, respectively
• Slight increased risk of miscarriage within the first year
• Effect on salivary glands—sialadenitis (inflammation of the salivary glands) and xerostomia (dry mouth)—short term and possibly long term, even though this is rare
• Second malignancy (low risk)

Table 29.8 RAI Ablation Guidelines for Thyroid Cancer (adapted from Perros et al. (2014))

RAI Ablation Guidelines for Thyroid Cancer	
Definitive indications for RAI ablation	
• Tumour >4 cm	
• Gross extrathyroidal extension	
• Distant metastases at diagnosis	
Indications against RAI ablation	
• Tumour is ≤ 1 cm (unifocal or multifocal) in	– Classical PTC
	– Follicular variant PTC
	– FTC without vascular invasion or extrathyroidal extension

In all other situations, certain risk factors need to be weighed as they might indicate a higher risk of recurrence. These include unfavourable cell type (tall cell, columnar, diffuse sclerosing PTC, poorly differentiated elements), large tumour size, extrathyroidal extension, widespread invasion (capsular and/or vascular invasion), multiple LN involvement, large LN size, high ratio of positive vs negative nodes and/or extracapsular nodal involvement (Table 29.8).

29.2.3.2 Preparation

Withdrawal of thyroid hormones: For optimal iodine transport into thyroid cells TSH levels need to be high (above 30 mU/L). This can be achieved by thyroid hormone withdrawal (2 weeks of withdrawal of liothyronine tablets or—if taking levothyroxine—a change to liothyronine 4 weeks prior to RAI for 2 weeks and then stopping it). However, the symptoms of the occurring hypothyroidism can be debilitating, so in psychiatric conditions, severe ischaemic heart disease or pituitary underfunction this might not be well tolerated or exacerbate comorbidities (adapted from Hanna et al. 2015).

Use of recombinant TSH: The alternative is injecting recombinant TSH 24 h and 48 h prior to RAI administration and continuation of levothyroxine administration. This is currently recommended by the BTA (Perros et al. 2014) for

patients with the following characteristics—T1–3, N0/X/1, and M0 and R0 (i.e. no residual disease). It gives a much better quality of life and patient experience during this time (Hanna et al. 2015). It also leads to more rapid elimination of the RAI, thus reducing the whole-body retention, the exposure of healthy tissue to radiation and possibly the length of the hospital stay while giving very similar ablation results.

Reduction of dietary iodine: Patients are advised to reduce their dietary iodine intake for 1 or 2 weeks prior to RAI ablation to encourage optimum uptake of RAI (Perros et al. 2014).

Iodinated contrast medium: An interval of at least 2 months following scans with iodinated contrast is required to ensure optimal uptake of RAI.

When to discontinue breastfeeding: Breastfeeding must be stopped 8 weeks prior to RAI ablation in order to minimise the radiation uptake into breast tissue and to reduce any future risk of breast cancer (Perros et al. 2014).

29.2.3.3 Dosage and Scans

Usual doses are between 1.1 GigaBecquerel (GBq) and 3.7 GBq for ablation (Perros et al. 2014). If RAI administration is repeated for therapeutic purposes, a dose of 3.7 or 5.5 GBq is given as there is no scientific evidence of the optimal dose in persistent or metastatic disease.

A trend in recent years is to use RAI ablation less often and in lower doses.

In low-risk DTC, 1.1 GBq is as effective in ablating thyroid remnant tissue as 3.7 GBq. The lower dose is recommended (Lamartina et al. 2015; Mallick et al. 2012a). Current clinical trials are exploring the option of not ablating the remnant thyroid tissue with radioiodine in patients with low-risk thyroid cancer (Mallick et al. 2012b).

Whole-body radioiodine scans are performed a few days after RAI administration. This shows the uptake of RAI into the body. Physiological uptake is often seen in the thyroid bed, the salivary glands, the digestive tract and in the bladder (Fig. 29.3). A single-photon emission computed tomography (SPECT-CT) improves the information obtained through the post-ablation iodine scan for locating cervical lymph node and any distant metastases.

29.2.3.4 Potential Side Effects of RAI Ablation

Patients can experience a number of side effects following RAI ablation (Table 29.9).

Prophylactic steroid cover is recommended in metastatic disease in the central nervous system, lung and bones (Hanna et al. 2015). Apart from a slightly increased risk of miscarriage in the first year after RAI ablation, female fertility has not been shown to be affected. Male fertility can be affected if several high doses need to be given. In such cases, sperm banking should be discussed.

If repeated doses are required, the long-term risk of sialadenitis (inflammation of the salivary glands) and xerostomia (dry mouth) is increased. The risk of a second cancer is low, but increases with high cumulative doses (>18.5 GBq as total dose) and is probably negligible for doses <3.7 GBq (Clement et al. 2015).

High fluid intake as well as frequent voiding of bladder and bowels will minimise the exposure of the associated organs to radiation. Frequent showering and high fluid intake will help reduce the radiation levels and expedite discharge.

29.2.3.5 RAI Restrictions

The patient will usually need to stay in isolation until the radioactivity measures less than 800 MBq. Visiting is restricted to designated areas close by and to non-pregnant adults only (Hanna et al. 2015).

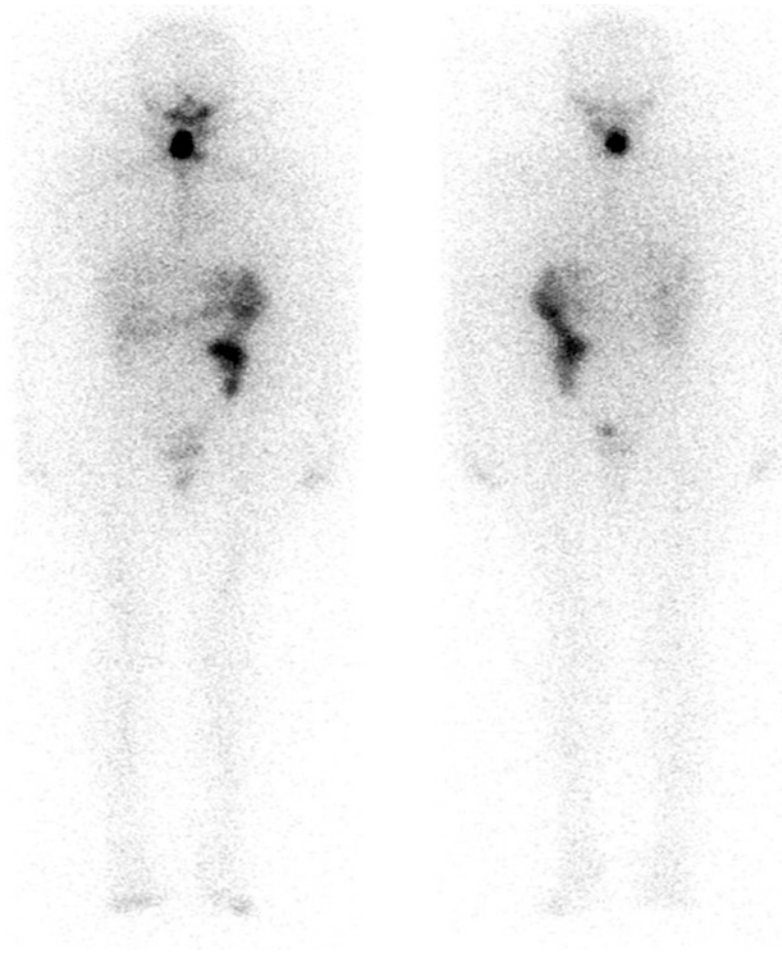


Fig. 29.3 Post-radioiodine ablation scan showing physiological uptake in thyroid remnant, nose and salivary glands, colon and bladder. Image from the Author's (Dr. Petros Perros) personal collection

Table 29.9 RAI ablation side effects (adapted from Perros et al. (2014))

• Sensation of tightness in the neck
• Mild nausea
• Inflammation of the salivary glands
• Dry mouth
• Taste changes (usually a week after RAI administration and lasting for 1–2 weeks)
• Radiation cystitis
• Gastritis
• Bleeding/oedema in metastatic disease

After discharge, the patient needs to avoid close and prolonged contact with other people for several days to minimise unnecessary exposure to radiation for others. This restriction period is longer for children and pregnant women due to the higher susceptibility to radiation damage to fast developing cells. Restrictions include sleeping alone for a few days and avoidance of any other close and prolonged contact, including potentially time off work depending on the type of employment. The length of each of these restrictions is decided individually depending on the rate of radiation clearance of the individual patient (Perros et al. 2014). Any personal belongings from the isolation room must either be checked for radiation exposure, left behind or kept separately, e.g. clothes should be washed separately at home on discharge.

Box 29.1 A Letter from Doctor to a GP and a 'Patient's Poem'

Doctor's letter to the GP	A Poem
Multifocal papillary thyroid cancer, 32 mm, encapsulated follicular variant of papillary thyroid cancer with capsular invasion but no vascular invasion, completely excised, left lobe of thyroid, pT2 pNx R0. Single incidental papillary thyroid micro carcinoma, 9 mm, predominantly tall cell variant (TCV) with infiltrative growth, desmoplastic stroma and lymphovascular invasion, minimal extra thyroidal extension, almost reaching the specimen margin, pT3 (on ETE) pNx Rx. Background of Hashimoto's thyroiditis. Left diagnostic hemithyroidectomy followed by completion thyroidectomy and right level 6 dissection (no evidence of malignancy). Background of florid focally fibrotic Hashimoto's thyroiditis's. The MDT recommendation for radioiodine ablation was communicated. She has signed the consent form and I have arranged for her to receive radioiodine	I've had 5 months of tests, of prods and pokes, and probes. Chats about tumours, nodules and nodes. Tubes down my throat, tubes up my nose. Been cut stitched and sliced. Twice! Stapled and diced. Twice! Talked to and talked at, stripped naked and stared at. Handshakes, phone calls, incorrect roll calls, Miss B, Mrs. B, Miss B, Miss B, Who I am doesn't matter. I'm now T3, ETE, PNx, TCV. Papillary, follicular. **I USED TO BE ME.** Uniforms, uniforms, blue, purple and green, stop eating fish, no more iodine. Give up cappucino, change the life I know. So I look really well? So my scar's really great? I'll offer you one, It's not up for debate. I'll hand you my life, do you know what it's worth? Do you know how much impact I have on this earth? Pass my life to the people I've known for no time, relinquish control, you're going to be fine. Drink poison to order, be ill to request. Bleed to be better. To prolong, for how long? Just prolong. For how long?

The text on the left was written by a doctor in a letter to the GP, at the same time as that on the right by the patient in the radioiodine suite who had just received ^{131}I ablation. (*Used with consent from Patient and Dr. Petros Perros*)

29.2.3.6 RAI Refractory Disease

RAI refractory thyroid cancer is defined as any one of the categories listed in Table 29.10.

In metastatic disease thyroid cancer tissue can become completely or partially radioiodine refractory. If there is a partial response to RAI ablation (as evidenced by reduction in serum Tg levels), further treatments might be considered. However, if there is no response, treatment options are limited to conventional palliative measures or tyrosine kinase inhibitors (TKIs) (see under 29.2.5).

Table 29.10 RAI refractory disease (adapted from Schlumberger et al. (2014))

1.	Patients with metastatic disease that does not take up RAI at the time of initial treatment
2.	Patients whose tumours lose the ability to take up RAI after previous evidence of uptake
3.	Patients with RAI uptake retained in some lesions but not in others
4.	Patients with metastatic disease that progresses despite significant uptake of RAI in the metastases and following a course of adequate radioiodine treatment

29.2.3.7 Follow-Up Assessment

The success of RAI ablation is assessed after 9–12 months with an US of the neck, a stimulated Tg test (if Tg and Thyroglobulin Antibodies (TgAbs) are undetectable), and in some cases iodine scans (Perros et al. 2014). In persistent metastatic or recurrent disease, further RAI treatment can be given.

29.2.4 Thyroid Stimulating Hormone (TSH) Suppression, Biochemical Monitoring and Dynamic Risk Stratification

29.2.4.1 TSH Suppression

After surgery and RAI ablation, all patients will require thyroid hormone replacement medication

in the form of levothyroxine (T4). Patients should have a dose big enough to prevent hypothyroidism and to suppress their blood level of TSH below 0.1 mU/L as this is associated with a reduction in the risk of recurrence of the thyroid cancer in selected cases (Biondi and Cooper 2010). This is called TSH suppression. The level to which each patient will need their TSH suppressed in the long term will be individualised to each patient, and is usually based on their risk of recurrence. Risk of recurrence is generally assessed at two points during treatment. The first point is right after surgery, where people fall into three groups:

- Low risk of recurrence
- Intermediate risk of recurrence
- High risk of recurrence

This is based on histology, tumour size, extent and spread of disease, and extent of surgical resection.

Patients in the high and intermediate categories who go on to have RAI ablation post surgery should have their TSH suppressed to <0.1 mU/L until they are restaged, usually 9–12 months later (Perros et al. 2014).

From this point on TSH suppression will depend on the response to RAI ablation, and patients are stratified according to their risk of recurrence (see under 29.2.4.3).

29.2.4.2 Blood Tests and Thyroid Hormones

The main blood tests done for patients during follow-up are TSH, Free Thyroxine (FT4), Tg and TgAbs.

Tg is a protein secreted by both normal and cancerous thyroid cells. Post total thyroidectomy and RAI ablation, Tg would be expected to be undetectable; however, it can take several months for the levels to reduce.

A persistently raised or rising Tg while on a suppressive dose of T4 is suggestive of persistent or recurrent disease, that warrants further investigation (Evans et al. 2015). Low levels of detectable Tg may be present in patients treated with hemithyroidectomy or total thyroidectomy without RAI ablation.

Around 25–30% of people with thyroid cancer will test positive for the presence of TgAbs, and these antibodies can interfere with the measurement of serum Tg giving misleading results (Hanna et al. 2015). It is essential that patients have blood tests done by the same biochemistry laboratory, as different methods can lead to a variation in results and give misleading interpretation.

A number of assay types are used to measure Tg. Radioimmunoassay (RIA) and Immunometric assay (IMA) are two that are most regularly used. RIA has been used since the 1970s, but in many laboratories it has been superseded by the IMA test which was introduced in the 1990s.

The IMA test is easier to automate, giving quicker results, and is particularly good at picking up very low levels of Tg. Unfortunately, it is more prone to interference from thyroid antibodies than the older RIA test, and therefore the IMA can give falsely low values of Tg. On the other hand, the RIA test can sometimes give falsely raised levels of Tg. Serum Tg results have to be interpreted in the context of the serum TSH concentration, which stimulates secretion of Tg.

Measurement of serum Tg with mass spectrometry was initially reported to be very accurate for detecting Tg in the presence of antibodies; however, investigations have not yet confirmed this (Hoofnagle and Rogh 2013). Its use in the future may be promising, but there is no consensus on its use at present and it is not routinely available.

29.2.4.3 Dynamic Risk Stratification

The follow-up assessment (see above) allows for restaging according to response to RAI and future risk of recurrence—this is called dynamic risk stratification (Table 29.11).

TSH suppression is associated with a risk of atrial fibrillation, cardiovascular disease and osteoporosis and therefore not indicated in low-risk patients whose prognosis is probably unaffected by TSH suppression.

Annual monitoring of serum Tg and thyroid function tests (TFTs) will continue lifelong as thyroid cancer is slow growing and recurrences can occur decades after initial treatment. This monitoring can provide reassurance for patients.

However for some it is an annual reminder of their cancer diagnosis and may provoke anxiety.

If there are detectable or rising Tg and/or TgAbs levels, further investigations are required. As the commonest sites of recurrence are cervical LNs and the thyroid bed, a neck US is the initial recommended imaging test. Neck recurrences are best treated surgically.

29.2.4.4 Hypoparathyroidism and Calcium Supplements

The four parathyroid glands are usually attached to or sit behind the thyroid gland, and are normally no bigger than a grain of rice. The parathyroid glands produce parathyroid hormone (PTH), which helps control calcium levels in the body.

The parathyroid glands can sometimes be removed accidentally or damaged during surgery. An estimated 30% of cases will develop temporary symptoms of low calcium following thyroid surgery, requiring vitamin D analogues and calcium supplements. For most patients this is transient in that it rights itself very quickly, but for others it can take months. If the parathyroid glands fail to function normally within 6 months post-operatively, the damage is usually permanent. Attempts should therefore be made to gradually wean patients off vitamin D analogues and calcium supplements and to assess whether parathyroid function is restored. The incidence of permanent hypoparathyroidism depends among other factors on the expertise of the surgeon, and in centres where high volume of thyroidectomies are performed by experienced surgeons, the expected rate of permanent hypoparathyroidism is less than 5%. Vitamin D deficiency is common among the general population and it is good practice to screen patients for vitamin D deficiency and correct it pre-operatively.

Table 29.11 Dynamic risk stratification (adapted from Perros et al. (2014))

An excellent response – all of these:
• Suppressed and stimulated Tg of <1 μg/L
• Negative imaging (USS and/or other imaging if performed)
The strict suppression of TSH in this low-risk situation can be lifted to a TSH level in the lower half of normal (0.3–2 mU/L)
In an intermediate response – any of these:
• Suppressed Tg of <1 μg/L and stimulated Tg between ≥1 and <10 μg/L
• Imaging (USS and/or other imaging if performed) with nonspecific changes or stable LNs <1 cm on USS
TSH suppression is recommended for 5–10 years followed by reassessment
Incomplete response – any of these:
• Suppressed Tg of ≥1 μg/L or stimulated Tg of ≥10 μg/L
• Rising Tg levels
• Evidence of disease (newly identified or known) on nuclear medicine and/or other imaging
As thyroid cancer is still present (as evidenced by elevated or rising Tg/TgAbs levels and on imaging), additional treatment may be required and the serum TSH will have to be suppressed lifelong to reduce growth and spread of the disease

29.2.5 Metastatic, Recurrent and Radioiodine Refractory DTC

Most patients with DTC have good disease-specific outcomes. However, around 30% of patients are reported to experience persistent or recurrence of disease. Many recurrences occur in the neck while a smaller number of patients can metastasise to the lungs and bones. There are several approaches to recurrent disease (Table 29.12).

Surgery with curative intent is usually the treatment of choice for recurrent disease confined to the thyroid bed or to cervical LNs. However, low volume disease in the neck which is asymptomatic and not progressing may also be managed by active surveillance.

If there is either a rising Tg with an undetectable location of disease, multiple lung metastases or soft tissue metastases that are still responsive to RAI, repeated radioiodine therapy

Table 29.12 Approaches to recurrent disease (Perros et al. 2014)

• Observation
• Surgery
• RAI
• External beam Radiotherapy (EBRT)
• TKIs

can be considered to increase the possibility of long-term survival. Residual microscopic disease in the neck following surgery for recurrent disease may also be treated with RAI.

Progressive disease in the neck not amenable to surgery with compressive symptoms and/or not responsive to RAI should be considered for other palliative treatments such as external beam radiotherapy. Bone metastases are generally not curable; however, solitary bone metastases may be amenable to EBRT or surgical resection if they are symptomatic.

Recent increasing knowledge about the biology of DTC has led to the use of TKIs (also known as targeted therapies). Targeted therapies are not curative treatment, but studies have demonstrated improved progression free survival for patients.

Sorafenib and lenvatinib are currently licensed for RAI refractory DTC—they have shown a significant increase in progression free survival in trials. They are principally indicated for progressive symptomatic disease; however, access and availability of the drugs differ in various countries. The most problematic side effects of sorafenib include hand and foot skin reaction (palmar plantar), hypertension, diarrhoea and fatigue. Lenvatinib has a similar side effect profile with hypertension being the most common and significant side effect. Side effects of these drugs can be serious and drug-related deaths can occur. The biggest challenge for many clinicians is deciding when to initiate TKI therapy and how to maintain a balance between side effects and benefits for the patient. If side effects are troublesome and both clinical and biochemical benefit are achieved, a dose reduction or 'drug holiday' can be considered. Treatment continues until side effects become intolerable or disease progression occurs. This is an evolving area in thyroid cancer treatment and ongoing studies continue to evaluate new agents.

29.3 Medullary Thyroid Cancer

MTC is the third most common type of thyroid cancer and makes up about 5–10% of all thyroid malignancies. MTCs arise from the calcitonin-secreting para-follicular C cells which are clustered in the upper two-thirds of the thyroid lobes.

Around 75% are known as sporadic MTCs and mostly occur between 50 and 70 years of age.

The incidence rate is 1.5 fold higher in women than in men. Approximately 25% are familial and can present either without any involvement of other glands (in about 55% of patients) or as part of multiple endocrine neoplasia (MEN) type 2 syndromes that comprise a more complex disease pattern such as tumours of the adrenal glands (phaeochromocytomas) and the parathyroid glands as well as other features.

29.3.1 Symptoms/Presentation

The patient with MTC can present with a number of troublesome symptoms including wheezing (Table 29.13). LN involvement at diagnosis is common. About 20% of patients present with locally advanced disease beyond LN involvement. Symptoms indicating metastatic disease include diarrhoea or flushes of the face due to hormone overproduction in large-volume MTC.

29.3.2 Diagnostic Investigations and Staging

Diagnostic procedures in MTC are similar to those for well DTCs (USS and FNA). Serum calcitonin (CTN) and carcinoembryonic antigen (CEA) are useful serum markers. Once the diagnosis of MTC is made, it is important to exclude phaeochromocytoma before surgery. The serum calcium should also be measured as this may be elevated due to hyperparathyroidism in patients with MEN2A. CT scans of the neck, chest, abdomen and pelvis are all part of the pre-operative staging.

Table 29.13 MTC: symptoms and presentation (Hanna et al. 2015)

• A thyroid lump
• Lymphadenopathy
• Diarrhoea and/or flushing

A detailed family history is imperative. All patients with a diagnosis of MTC are offered genetic screening.

The physiological role of calcitonin is unclear. However, in MTC it is a useful tumour marker. A substantial elevation indicates a MTC, possibly with spread to LNs and to distant areas.

The TNM classification is used for staging (Tuttle et al. 2017) (see Table 29.4); however, T4 is described as follows:

- **T4a**: Moderately advanced disease with gross extrathyroidal extension (including into subcutaneous soft tissue, the recurrent laryngeal nerve, larynx, trachea and/or oesophagus), any tumour size
- **T4b**: Very advanced disease which invades the prevertebral fascia, extends towards the spine and/or encases the mediastinal vessels or the carotid artery any tumour size (Bychkov 2018)

If staging I-IV is used, T1N0M0 is a stage I, T2/3N0M0 is stage II and T1-3 N1aM0 is stage III. All other TNM classifications are stage IV.

29.3.3 Treatment

Total thyroidectomy and prophylactic central neck dissection are the standard of care for MTC.

Therapeutic neck dissection in the lateral compartments is also indicated if there is evidence of cervical lymph node involvement. A prophylactic central neck dissection reduces the risk of central LN recurrence (which is common, but difficult to detect with an USS) and the need for repeat surgery.

A prophylactic total thyroidectomy is usually performed in asymptomatic carriers of familial MTC genes, identified by genetic screening. This has revolutionised the outcome and the timing of prophylactic thyroidectomy is dictated largely by the genotype (Wells Jr et al. 2015).

Spread occurs via the lymphatic system and blood circulation. Distant metastases arise commonly in the liver, lung and bones. If they are slow growing and asymptomatic, surveillance may be appropriate. Solitary distant metastases may justify further surgery with curative intent. Palliative surgery to symptomatic resectable metastases may also have a role in some patients.

Palliative radiotherapy may be appropriate for painful bone metastases, impending fracture of a weight bearing bone, airway compromise or lesions causing neurological and functional symptoms (e.g. spinal cord compression).

A MTC is not radioiodine sensitive, so radioiodine ablation is not indicated.

MTC is not TSH dependent, and TSH suppression will not reduce recurrence or improve survival in contrast to PTC and FTC. Therefore thyroid hormone therapy should aim for replacement with a normal TSH level.

29.3.4 Prognosis

Adverse prognostic features include older age at diagnosis, extent of primary tumour, nodal disease and distant metastases.

Patients with distant metastases are viewed as incurable. However, as mentioned above, progression rate is often slow and quality of life maintained for many years. A 10 year survival rate even for Stage III MTC is 71% (Hanna et al. 2015).

The CTN doubling time has prognostic implications with a calcitonin doubling time of <2 years indicating a poor prognosis.

29.3.5 Follow-Up and Monitoring

If surgery can completely remove any cancer and post-operative CTN is undetectable, a biochemical cure has been achieved (with a very good prognosis for the patient).

A rising calcitonin is highly suggestive of recurrent or progressive disease and usually is an indication for restaging.

Asymptomatic patients with known unresectable disease and stable or only slowly rising CTN may be managed with watchful monitoring.

29.3.6 Additional Treatment Options in Advanced MTC

A number of treatments have been reported to be effective in advanced MTC, but have not been evaluated in randomised studies and their role is unclear. They include somatostatin analogues and radiolabelled therapies with MIBG or lutetium.

Targeted therapies with TKIs are increasingly used in the treatment of progressive, metastatic or locally advanced disease. Currently vandetanib and cabozantinib are licensed for use in MTC.

They have a significant side effect profile (hypertension, palmar plantar, skin rashes, diarrhoea, electrolyte disturbances, bleeding, poor wound healing, fatigue, hair loss and loss of appetite). Vandetanib can also cause QT elongation and significant light sensitivity.

Targeted therapies are not curative, but may slow down the progression of the disease and improve quality of life (Dadu et al. 2015). The treatment can be continued until there is no clinical benefit or the side effects become intolerable.

29.4 Anaplastic Thyroid Cancer

The fourth thyroid malignancy is the anaplastic tumour, a rare and aggressive cancer. It accounts for 2–5% of all thyroid tumours. The mean life expectancy at diagnosis is estimated to 6 months or so. Seventy five percent of patients are over the age of 60 at diagnosis and it affects women more so than men.

It can develop spontaneously, but in 20–30% of cases it develops on the background of DTC.

29.4.1 Symptoms/Presentation

ATC presents with a rapidly enlarging tumour, and in some patients growth increase can be seen daily. Symptoms are included in Table 29.14. Most patients have metastatic spread into cervical and mediastinal LNs as well as into the surrounding tissue such as muscles, larynx, trachea, oesophagus, blood vessels, sternum or spinal column. Distant metastases are present at diagnosis in 15–50% of patients (mainly in the lung).

Table 29.14 ATC: symptoms and presentation (Perros et al. 2014; Mazzaferri et al. 2006)

• Goitre or a rapidly enlarging nodule
• Dyspnoea
• Dysphagia
• Hoarseness
• Cough
• Neck pain
• Less common: haemoptysis, chest pain, bone pain, headache, confusion, abdominal pain
• Weight loss, fatigue, fever of unknown origin

29.4.2 Diagnostic Investigations and Staging

The diagnosis is established with a FNA or core biopsy in combination with clinical features. CT or MRI scans are important in staging the disease.

For anaplastic thyroid cancer, the TNM classification is the same as for differentiated thyroid cancer (see Table 29.4). If using staging, intrathyroidal disease is stage IVA, gross extrathyroidal extension or cervical lymph node involvement is stage IVB. If distant metastases are present, the disease is staged as IVC.

29.4.3 Treatment

Aggressive management in selected cases seems to be beneficial. Surgery should only be considered when complete macroscopic resection is feasible. However, this is rare and for most patients the disease is too advanced for surgical intervention at diagnosis. Subtotal resection is rarely justified.

Chemotherapy and radiotherapy are also options to slow down progression, aiming to reduce size and any compressive symptoms. However, the side effects of both treatments can be self-limiting (Hanna et al. 2015).

Palliation of symptoms is usually the main treatment for these patients.

29.4.4 Outcome

Very few patients with ATC survive longer than a year.

Death occurs in 50–60% of patients from upper airway obstruction. In these patients, a tracheostomy may be difficult to justify because of poor survival. Palliative care is considered as a better option.

If a major blood vessel is affected for example through a tumour that invades the wall of a carotid artery, death might come through a catastrophic bleed.

29.5 Genetics

Most people born with inherited faulty genes that can cause MEN2A and MEN2B syndromes develop MTC. Seventy five percent cases of MTC are sporadic (not due to inherited genetic changes), the other 25% are hereditary and caused by genetic changes passed on from parent to child.

For most sporadic non-medullary thyroid cancers, a genetic predisposition has been postulated via multiple low- to moderate-penetrance genes interacting with each other and with the environment, determining individual susceptibility (Landa and Robledo 2011). A number of somatic mutations (changes in genes that are not hereditary) have been identified, which are probably causally related. These are presumed to be acquired as random events and lead to neoplasia (abnormal growth of tissue). Many of these genes are involved in signalling pathways controlling thyroid cell growth. BRAF is a protein produced by the BRAF gene, and is a key player in a number of signalling pathways and a major player in papillary thyroid carcinogenesis. If it has a fault (or a mutation), it can send the gene into overdrive and uncontrolled growth.

We know that somatic mutations are implicated in most cases of DTC. However it is only in the past decade that we have started to understand the role of these molecular drivers, and how they may affect the behaviour of certain cancers. Some studies for example have shown that PTCs with a mutation in the BRAF gene have a higher risk of recurrence. NRAS mutations have been reported in follicular variant thyroid cancers that are more likely to spread.

The clinical behaviour of some thyroid cancers correlates with specific molecular markers (Pak et al. 2015), therefore knowing what mutations are present in a small, otherwise low-risk tumour may change the plan of treatment at the outset. It may also help with the development of new drugs that block these pathways.

Newer biological therapies are treatments that interfere with the signalling pathways. One group of biological therapies (i.e. TKIs) are already being used in the treatment of thyroid cancer.

Molecular profiling of thyroid nodules using FNA material is also being used to diagnose or rule out thyroid cancer in patients with thyroid nodules (Yip 2014).

There is no doubt that genetic profiling is advancing our understanding of the behaviour of thyroid cancers, and opens the possibility of further subclassification of the disease. This gives hope that the future of potential genetic testing will further personalise the management of thyroid cancer.

29.6 Living with Thyroid Cancer

A diagnosis of cancer can be a life-changing experience and can affect all aspects of a patient's life. Focusing on thyroid cancer's excellent survival rate eclipses some of the hardships patients go through in their treatment and lifelong maintenance of the disease. Thyroid cancer is rare, so it is not in the spotlight like other cancers, and the exposure it does get often overlooks some of the other issues that go along with this cancer.

Some of the physical side effects include

- Adverse effects of long-term TSH suppression—possibly atrial fibrillation, cardiovascular disease and osteoporosis
- Long-term voice problems
- Weight gain
- Fatigue

29.6.1 Voice Problems

Permanent VC damage occurs in less than 5% of cases (Perros et al. 2014). Voice quality that is significantly affected can be improved with either a collagen injection (improves the voice quality for a few months) or a thyroplasty for a more permanent outcome (insertion of a small plastic implant that pushes the paralysed fold more centrally, allowing the cords to touch and produce a stronger voice).

Early voice fatigue is a long-standing symptom of VC paralysis. The pitch range or quality of the singing voice may never fully recover to the pre-surgical state.

29.6.2 Weight Gain

A 2014 longitudinal study (Rotondi et al. 2014) has confirmed that thyroidectomy is associated with significant weight gain in many patients, including patients with TSH suppressed to below normal. Underlying mechanisms are not yet fully understood; however, acknowledgment of this combined with healthy eating advice and positive lifestyle changes may help patients to tackle this.

29.6.3 Fatigue

Fatigue is a common problem among different groups of cancer survivors. As expected with a rare cancer, there is very limited data that show studies related to fatigue in thyroid cancer. Some of these patients will experience problems with concentration and memory despite having optimal thyroid hormone dosage. Supportive care is imperative and most oncology teams have allied health professionals who have expertise in providing support and information in managing fatigue.

Patients managed for thyroid cancer can have a number of emotional issues relating to coping with the physical side effects and to coping with lifelong follow-up.

29.6.4 Lifelong Monitoring

Recurrences in thyroid cancer occur in around 10–30% of people (Mazzaferri and Kloos 2001). This can happen decades after the original diagnosis and highlights the importance of lifelong follow-up. This is unlike other survivable or curable cancers, where patients are often discharged after some years. Some patients find this yearly follow-up reassuring, but for many this means living with some uncertainty about the future.

29.7 Future Developments in the Management of Thyroid Cancer

29.7.1 Encapsulated Non-invasive Follicular Variant PTC

A recent review by an international group of pathologists and clinicians focused on redefining encapsulated non-invasive follicular variant of PTC as a neoplasm rather than a carcinoma (Nikiforov et al. 2016).

The classification of PTC is primarily based on characteristic histological nuclear features (Ohori 2015). This variant is known to behave in a non-aggressive manner where when completely excised, neither vascular nor capsular invasion is present. Evidence for showing this is in cases of lobectomy that excludes RAI ablation (Nikiforov et al. 2016). However, rare cases of distant metastases from encapsulated follicular variant PTC have been reported (Baloch et al. 2000 and Rivera et al. 2009 as cited in Ohori (2015)). Suggestions have been made to reclassify this subgroup to a ‘non-invasive

follicular thyroid neoplasm with papillary nuclear features' rather than to classify it as a cancer due to its benign nature. Specific diagnostic criteria for this subgroup include no tumour necrosis, a clear demarcation of the nodule (or encapsulation), no psammoma bodies and no PTC variant like tall cell or diffuse sclerosing (Nikiforov et al. 2016; Johnson et al. 2016).

While treatment for this subtype is less radical due to the recognition of its low-risk behaviour (e.g. lobectomy), 're-naming' is thought to have emotional benefits for patients as it will reduce anxiety associated with a cancer diagnosis. The change in classification was undergoing discussion among thyroid professionals due to the potential benefits for patients and healthcare providers such as reducing the implications both on finance and insurance issues in the follow-up care of patients at low risk of metastases. It has now been given recognition as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in the latest edition of the WHO classification (Lloyd et al. 2017).

29.7.2 Role of Radioiodine Ablation in Low-Risk Well-Differentiated Thyroid Cancer

Whether benefits of radioiodine ablation outweigh potential harm is unknown in this patient group of thyroid cancer. Two large randomised controlled trials are underway in the UK and France to address this important question (Mallick et al. 2012b).

29.7.3 Radioiodine Refractory Disease

Selumetinib is another TKI which is currently being investigated for its ability to re-sensitise radioiodine refractory disease. Early phase studies have demonstrated increased iodine uptake in previously radioiodine refractory patients (Ho et al. 2013). Further trials are underway to add to this body of research and to establish whether successful retreatment with RAI might become feasible for some patients in the future.

29.7.4 Tissue Bank for Anaplastic Thyroid Cancer

Due to the aggressive nature of ATC, very little research is available. An international tissue bank has been established to facilitate future studies through the availability of tissue for research purposes (interNational Anaplastic Thyroid Cancer Tissue Bank—iNATT: http://www.inatt.org/).

29.8 The Role of the Specialist Nurse

The pathway of patients with suspected or confirmed thyroid cancer can be complex and also at risk of being disjointed due to the involvement of the multi-disciplinary professionals involved at various stages (radiologists, pathologists, head and neck surgeons, endocrine surgeons, endocrinologists, oncologists, nuclear medicine physicians). This can be confusing and disorientating for patients. Specialist nurses play a key role and are placed in an ideal position to provide continuity of care, valuable and reliable information and support to patients and their families at all stages of the disease process (Table 29.15).

Table 29.15 Essential roles of the specialist cancer nurse

• Explanation of investigations for a thyroid nodule
• Support during and after breaking bad news
• Continuous information and communication about planned treatments, investigations and results
• Coordinating and communicating throughout the treatment process
• Support for personalised therapeutic decision-making (e.g. merits and risks of radioiodine ablation)
• Explanation and implications of the outcomes of dynamic risk stratification
• Support for managing temporary and long-term side effects of treatment
• Education and management of thyroid hormone therapy
• Weaning off vitamin D analogues and calcium supplements
• Support for living with and managing chronic symptoms (like fatigue etc.)

29.9 Conclusions

The number of patients with thyroid cancer diagnoses is increasing globally, primarily due to incidental detection of small, biologically indolent tumours. Despite this concerning trend, the prognosis for most patients with thyroid cancer is good. The approach to treatment should be personalised aiming to match the aggressiveness of treatment to the biological nature of the cancer. The psychological impact in the aftermath of diagnosis and treatment of thyroid cancer is significant, and patients may experience lifelong physical and emotional consequences. An important objective for healthcare professionals managing people with thyroid cancer is remembering to treat the person, not just the disease.

References

Baloch et al 2000 and Rivera et al 2009 as cited in Ohori, P. FNA cytopathology and molecular test characteristics in the changing landscape of papillary thyroid carcinoma. J Basic Clin Med. 2015;4(2):103–9.

Banach R, Bartès B, Farnell K, Rimmele H, Shey J, Singer S, Verburg FA, Luster M. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosocial/informational support needs, treatment side effects and international differences in care. Hormones (Athens). 2013;12:428–38.

Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid. 2010;20:135–46.

Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ. 2013;347:f4706.

Bychkov A. Thyroid gland. Miscellaneous AJCC/TNM staging. 2018. PathologyOutlines.com. http://www.pathologyoutlines.com/topic/thyroidstaging.html. Accessed 16 Apr 2018.

Cancer Research UK. Thyroid cancer incidence by age. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence#heading-One. Accessed Apr 2016.

Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJ, van Rijn RR, van der Pal HJ, Neggers SJ, Kremer LC, van Eck-Smit BL, van Santen HM. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma—a systematic review. Cancer Treat Rev. 2015;41:925–34.

Cross P, Chandra A, Giles T, Johnson S, Kocjan G, Poller D, Stephenson T. Guidance on the reporting of thyroid cytology specimens. Royal College of Pathologists. 2016. http://ukeps.com/docs/thyroidfna.pdf. Accessed 22 March 2018.

Dadu R, Hu MN, Grubbs EG, Gagel RF. Use of tyrosine kinase inhibitors for treatment of medullary thyroid carcinoma. Recent Results Cancer Res. 2015;204:227–49.

Duan H, Gamper E, Becherer A, Hoffmann M. Quality of life aspects in the management of thyroid cancer. Oral Oncol. 2015;51:S1–5.

Evans C, Tennant S, Perros P. Thyroglobulin in differentiated thyroid cancer. Clin Chim Acta. 2015;444:310–7.

Hanna L, Crosby T, Macbeth F, editors. Practical clinical oncology. 2nd ed. Cambridge: Cambridge University Press; 2015.

Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, Ghossein RA, Ricarte-Filho JC, Domínguez JM, Shen R, Michael Tuttle R, Larson SM, Fagin JA. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013;368(7):623–32.

Hoofnagle AN, Rogh MY. Improving the measurement of serum thyroglobulin with mass spectrometry. J Clin Endocrinol Metab. 2013;98:1343–52.

Ito Y, Oda H, Miyauchi A. Insights and clinical questions about the active surveillance of low-risk papillary thyroid microcarcinomas. Endocr J. 2016;63:323–8.

Johnson SJ, Stephenson TJ, Poller DN. NIFTP addendum to the RCPath Dataset for thyroid cancer histopathology reports. London, UK: The Royal College of Pathologists; 2016.

Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Ann Surg Oncol. 2012;19:1874–80.

Kuba S, Yamanouchi K, Sakimura C, Kawakami F, Minami S, Fujita F, Takatsuki M, Kobayashi K, Kanetaka K, Kuroki T, Eguchi S. Total versus hemithyroidectomy for well differentiated thyroid cancer. Ann Oncol. 2014;25(suppl 4):iv355.

Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. Clin Endocrinol Metab. 2015;100:1748–61.

Landa I, Robledo M. Association studies in thyroid cancer susceptibility: are we on the right track? J Mol Endocrinol. 2011;47:R43–58.

Lloyd RV, Osamura RY, Klöppel G, Rosai J. WHO organisation of tumours of endocrine organs. 4th ed. Geneva: WHO; 2017.

Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerrard G, Abdel-Hamid A, Hardman J, Macias E, Roques T, Whitaker S, Vijayan R, Alvarez P, Beare S, Forsyth S, Kadalayil L, Hackshaw A. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med. 2012a;366(18):1674–85.

Mallick U, Harmer C, Hackshaw A, Moss L, IoN Trial Management Group. Iodine or Not (IoN) for low-risk differentiated thyroid cancer: the next UK National

Cancer Research Network randomised trial following HiLo. Clin Oncol (R Coll Radiol). 2012b;24:159–61.
Mazzaferri EL, Kloos RT. Current approaches to primary therapy of papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86:1447–63.
Mazzaferri E, Harmer C, Mallick U, Kendall-Taylor P, editors. Practical management of thyroid cancer. London: Springer; 2006.
Metzger R, Milas M. Inherited cancer syndromes and the thyroid: an update. Curr Opin Oncol. 2014;26:51–61.
National Cancer Peer Review—National Cancer Action Team. Manual for Cancer Services: Head and Neck Measures Version 3.0. n.d. http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_April2013.pdf (as cited in BTA 2014).
Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, Barletta JA, Wenig BM, Al Ghuzlan A, Kakudo K, Giordano TJ, Alves VA, Khanafshar E, Asa SL, El-Naggar AK, Gooding WE, Hodak SP, Lloyd RV, Maytal G, Mete O, Nikiforova MN, Nosé V, Papotti M, Poller DN, Sadow PM, Tischler AS, Tuttle RM, Wall KB, LiVolsi VA, Randolph GW, Ghossein RA. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol. 2016;2(8):1023–9. https://doi.org/10.1001/jamaoncol.2016.0386. [Epub ahead of print].
Ohori P. FNA Cytopathology and Molecular Test Characteristics in the changing Landscape of Papillary Thyroid Carcinoma. J Basic Clin Med. 2015;4(2):103–9.
Pak K, Suh S, Kim SJ, Kim IJ. Prognostic value of genetic mutations in thyroid cancer: a meta-analysis. Thyroid. 2015;25:63–70.
Pappa T, Alevizaki M. Obesity and thyroid cancer: a clinical update. Thyroid. 2014;24:190–9.
Pawelczak M, David R, Franklin B, Kessler M, Lam L, Shah B. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review. Thyroid. 2010;20:1095–101.
Perros P, Colley S, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR. Guidelines for the management of thyroid cancer, third edition. Clin Endocrinol. 2014;81(Suppl 1):1–122.
Qubain SW, Nakano S, Baba M, Takao S, Aikou T. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery. 2002;131:249–56.
Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, Tufano RP, Tuttle, for the American Thyroid Association Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery RM. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22:1144–52.
Reiners C. Thyroid cancer in 2013: Advances in our understanding of differentiated thyroid cancer. Nat Rev Endocrinol. 2014;10:69–70.
Roman S, Sosa JA. Aggressive variants of papillary thyroid cancer. Curr Opin Oncol. 2013;25:33–8.
Rotondi M, Croce L, et al. Body weight changes in a large cohort of patients subjected to thyroidectomy for a wide spectrum of thyroid diseases. Endocr Pract. 2014;20(11):1151–15.
Sawka AM, Naeem A, Jones J, Lowe J, Segal P, Goguen J, Gilbert J, Zahedi A, Kelly C, Ezzat S. Persistent posttreatment fatigue in thyroid cancer survivors: a scoping review. Endocrinol Metab Clin N Am. 2014;43:475–94.
Schlumberger M, Brose M, Elisei R, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol. 2014;2:356–8.
Schmid D, Behrens G, Jochem C, Keimling M, Leitzmann M. Physical activity, diabetes, and risk of thyroid cancer: a systematic review and meta-analysis. Eur J Epidemiol. 2013;28:945–58.
Schonfeld SJ, Lee C, Berrington de González A. Medical exposure to radiation and thyroid cancer. Clin Oncol (R Coll Radiol). 2011;23:244–50.
Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. Radiat Res. 2012;178(4):365–76.
Triggiani V, Angelo Giagulli V, Tafaro A, Resta F, Sabba C, Licchelli B, Guastamacchia E. Differentiated thyroid carcinoma and intestinal polyposis syndromes. Endocr Metab Immune Disord Drug Targets. 2012;12:377–81.
Tuttle M, Morris LF, Haugen B, Shah J, Sosa JA, Rohren E, Subramaniam RM, Hunt JL, Perrier ND. Thyroid-differentiated and anaplastic carcinoma (Chapter 73). In: Amin MB, Edge SB, Greene F, Byrd D, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley J, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, editors. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, Negri E. Thyroid cancer mortality and incidence: a global overview. Int J Cancer. 2015;136:2187–95.
Veiga LH, Lubin JH, Anderson H, de Vathaire F, Tucker M, Bhatti P, Schneider A, Johansson R, Inskip P, Kleinerman R, Shore R, Pottern L, Holmberg E, Hawkins MM, Adams MJ, Sadetzki S, Lundell M, Sakata R, Damber L, Neta G, Ron E. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. J Clin Endocrinol Metab. 2000;85(9):3227.

Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing? Curr Opin Oncol. 2015;27:1–7.

Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG, American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25:567–610.

Wolinski K, Czarnywojtek A, Ruchala M. Risk of thyroid nodular disease and thyroid cancer in patients with acromegaly—meta-analysis and systematic review. PLoS One. 2014;9:e88787.

Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, Pai S, Bishop J. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol. 2014;32(25):2718–26.

Yip L. Molecular diagnostic testing and the indeterminate thyroid nodule. Curr Opin Oncol. 2014;26:8–13.

30 Diagnosis and Management of Hypothyroidism in Adults

Raluca-Alexandra Trifanescu and Catalina Poiana

Contents

30.1 **Introduction** 583

30.2 **Definition and Classification** 583
30.2.1 Primary Hypothyroidism 583
30.2.2 Central Hypothyroidism 584

30.3 **Epidemiology** 584

30.4 **Causes of Hypothyroidism** 584
30.4.1 Primary Hypothyroidism with Goiter 584
30.4.2 Primary Hypothyroidism Without Goiter 585
30.4.3 Central (Secondary and Tertiary) Hypothyoidism: Without Goiter 585
30.4.4 "Peripheral" (Extrathyroidal) Hypothyroidism 585

30.5 **Clinical Manifestations of Hypothyroidism** 585
30.5.1 Symptoms 585
30.5.2 Signs 585

30.6 **Patient's Approach** 586
30.6.1 Blood Tests 586
30.6.2 Resting ECG (Standard 12-Lead Resting Electrocardiogram) 586
30.6.3 Thyroid Ultrasound 587
30.6.4 Other Tests 587

30.7 **Biochemical Assessment** 587
30.7.1 Diagnosis 587
30.7.2 Algorithm for Hypothyroidism Diagnosis 587

R.-A. Trifanescu (✉)
Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Department of Pituitary and Neuroendocrine Diseases, "C.I.Parhon" National Institute of Endocrinology, Bucharest, Romania
e-mail: raluca.trifanescu@umfcd.ro

C. Poiana
Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Department of Pituitary and Neuroendocrine Diseases, "C.I.Parhon" National Institute of Endocrinology, Bucharest, Romania
e-mail: catalina.poiana@umfcd.ro

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_30

30.7.3 Indications for Screening Patients with Symptoms and Risk Factors for Hypothyroidism 587
30.8 **Complications** 588
30.9 **Treatment** 588
30.9.1 Initiation of Therapy Including Doses, Route, and Time of Administration 588
30.9.2 Monitoring 589
30.9.3 Potential Side Effects of Treatment 590
30.9.4 Dose Adjustments 590
30.9.5 Association with Other Comorbidities (for Example: Ischemic Heart Disease) 590
30.10 **Conclusions** 591
References 591

Abstract

Hypothyroidism is one of the most common endocrine disorders, defined as deficient production of thyroid hormones. In primary hypothyroidism, there is a thyroidal defect in the thyroid gland and decrease in thyroid hormones leads to an increased TSH secretion; in central hypothyroidism, there is either an insufficient thyroid stimulation by TSH (secondary hypothyroidism = pituitary causes) or an insufficient hypothalamic TRH release (tertiary hypothyroidism = hypothalamic causes). The disease is more frequent in women than in men; it affects all ages, but is more frequent in middle-age patients. Incidence varies between 0.6/1000/year in men and up to 4.1/1000/year in women. Primary hypothyroidism is the most frequent, caused by chronic autoimmune thyroiditis, thyroid surgery and radioiodine (^{131}I) ablation, external radiotherapy, thyroid dysgenesis, defects in thyroid hormones biosynthesis, release and action, and drugs. Symptoms include: fatigue, cold intolerance, weight gain, dry skin, constipation, muscle weakness, impaired memory, etc. Signs include: dry skin, carotenemia, puffy facies and loss of eyebrows, edema, bradycardia, diastolic hypertension, bradylalia, bradykinesia, etc. For diagnosis, TSH and free thyroxine (FT_4) are mandatory. TSH is the screening and first-line diagnostic test for primary hypothyroidism; FT_4 is necessary for diagnosis of central hypothyroidism and for diagnosis of overt *versus* subclinical primary hypothyroidism. Treatment consists in administration of levothyroxine (LT_4), orally, once daily, aiming to normalize serum TSH, to restore patients' physical and psychological well-being, and to avoid overtreatment. In first-term pregnant women, TSH should be kept <2.5 mIU/L; in second and third trimesters of pregnancy, TSH should be <3 mIU/L.

Keywords

Adult hypothyroidism · Autoimmune thyroiditis · TSH · Levothyroxine

Abbreviations

^{131}I	Radioiodine
ATA	American Thyroid Association
BTA	British Thyroid Association
CK MB	Isoenzyme MB of the enzyme phosphocreatine kinase
ECG	Electrocardiogram
ETA	European Thyroid Association
FT_4	Free thyroxine
LDL cholesterol	Low-density lipoprotein (LDL) cholesterol
LT_3	Liothyronine
LT_4	Levothyroxine
MCT8	Monocarboxylate transporter 8
MRI	Magnetic resonance imaging
SECISBP2	Selenocystein insertion sequence (SECIS) binding protein 2
T_3	Triiodothyronine
T_4	Thyroxine

TPO	Thyroid peroxidase (thyroperoxidase)
TR	Thyroid hormone receptor
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

Key Terms

- **Overt hypothyroidism:** Elevated serum thyroid-stimulating hormone concentration
- **Primary hypothyroidism:** related to thyroid gland failure
- **Central hypothyroidism:** Secondary to hypothalamic or pituitary dysfunction or causes other than primary thyroid gland failure.
- **Overtreatment:** suppression of TSH due to inappropriately high replacement dose of thyroid

Key Points

- Hypothyroidism is insufficient thyroid hormone production due to thyroid or central (pituitary or hypothalamic) causes.
- Clinical picture includes fatigue, cold intolerance, weight gain, dry skin, carotenenia, puffy face and loss of eyebrows, constipation, muscle weakness, impaired memory, edema, bfrsdycardia, diastolic hypertension, bradycardia, and bradykinesia.
- Diagnosis is made with TFTs showing, increased TSH, low/normal FT4 in primary hypothyroidism; low-normal/low FT4 with low/inappropriately normal/slightly increased TSH in central hypothyroidism.
- Treatment requires Levothyroxine orally, once daily; in primary hypothyroidism, target TSH in young people is 1–2.5 mIU/L; in the elderly and in patients with ischemic heart disease, target TSH is the upper normal (according to age-specific reference range) and the initial Levothyroxine dose should be low (12.5–25 μg daily) and increase gradually; in pregnancy during first-term, the target TSH is <2.5 mIU/L. In the second and third trimester of pregnancy, the target TSH should be <3 mIU/L.
- In central hypothyroidism, the target FT4 is the upper half of the normal range for young patients, and in the lower half of the normal reference range in the elderly patients.

30.1 Introduction

Hypothyroidism is one of the most frequent endocrine diseases. It is very important to be recognized as early as possible, because overt hypothyroidism could be associated with several complications.

30.2 Definition and Classification

Hypothyroidism is a pathological condition due to insufficient thyroid hormones production.

Myxedema is severe hypothyroidism in adults, characterized by nonpitting edema due to accumulation of glycozaminoglycans in subcutaneous tissue and interstitial tissues.

30.2.1 Primary Hypothyroidism

Primary hypothyroidism refers to deficient thyroid hormones production due to thyroid causes and can result in overt or subclinical hypothyroidism.

Overt hypothyroidism: This happens when the serum thyroid-stimulating hormone concentration is elevated, (for example, TSH > 10 mIU/L) and serum-free thyroxine (FT_4) concentration is low.

In pregnancy, overt hypothyroidism can comprise of a serum TSH > 2.5 mIU/L with decreased FT_4 concentrations during the first trimester of pregnancy or serum TSH > 3 mIU/L with decreased FT_4 concentrations during the second and third trimester of pregnancy (Negro and Stagnaro-Green 2014; Stagnaro-Green et al. 2011). However, recent studies suggest only a modest downward shift (0.5–1 mIU/L) in the first trimester upper normal limit of TSH, typically in weeks 7–12, with significant differences depending on BMI, ethnicity, geography and iodine sta-

Table 30.1 Classification of subclinical hypothyroidism according to TSH levels in different categories of patients (adapted from Biondi and Wartofsky (2014))

Classification of subclinical hypothyroidism	TSH (mIU/L)	FT_4
Mild subclinical hypothyroidism	4.5–9.9	Normal
Mild subclinical hypothyroidism in elderly	>7	Normal
Severe subclinical hypothyroidism	≥10	Normal
Subclinical hypothyroidism in pregnancy	2.5–10	Normal

tus, and TPO antibodies positivity. So, overt hypothyroidism will be defined as both elevated TSH and decreased FT_4 concentration during gestation as compared with pregnancy trimester-specific reference range values. If pregnancy-specific TSH reference range is not available, upper reference range for TSH should be considered 4 mIU/L (Alexander et al. 2017). Furthermore, overt hypothyroidism can occur in pregnancy, when the serum TSH > 10 mIU/L, irrespective of FT_4 concentrations (Negro and Stagnaro-Green 2014; Stagnaro-Green et al. 2011; Alexander et al. 2017).

Subclinical hypothyroidism: refers to a high serum TSH concentration and a normal serum-free thyroxine (FT_4) concentration (Cooper and Biondi 2012; Biondi and Wartofsky 2014) (Table 30.1).

30.2.2 Central Hypothyroidism

Central hypothyroidism: also known as secondary hypothyroidism, is referred to deficient thyroid hormone production due to pituitary or hypothalamic causes and characterized by a low serum FT_4 concentration and a serum TSH concentration that is not appropriately elevated.

- Secondary hypothyroidism: due to pituitary causes
- Tertiary hypothyroidism: due to hypothalamic causes (Ross and Cooper 2017; Wiersinga 2014)

Hypothyroidism may be persistent or transient. Transient primary hypothyroidism occurs after subacute, painless, or postpartum thyroiditis, antithyroid drugs, and toxic injury of the thyroid.

30.3 Epidemiology

In the UK, the prevalence of spontaneous overt hypothyroidism is 1–2%, and it is more common in older women and ten times more common in women than in men (Vanderpump 2011; Vanderpump et al. 1995).

The prevalence of subclinical hypothyroidism is higher (5–10%); it is also more frequent in women and its prevalence increases with age (Biondi and Cooper 2008). Factors associated with increased risk of progression from subclinical to overt hypothyroidism are high iodine intake, higher TSH (>10 mU/L), positive thyroid antibodies, low-normal FT_4 levels, and adult age (Walsh et al. 2010).

Primary hypothyroidism represents 95–99% of cases, while central hypothyroidism 1–5% (Biondi and Wartofsky 2014).

30.4 Causes of Hypothyroidism

30.4.1 Primary Hypothyroidism with Goiter

- Goitrous chronic autoimmune thyroiditis—the most common etiology in iodine sufficient areas (Tunbridge et al. 1977)

Box 30.1 Case Example 1: Drug-Induced Hypothyroidism

A, 63 year ♂, resident in an iodine deficiency area, treated with Sunitinib for metastatic renal carcinoma, presented with myxedema:

TSH = 75 mIU/L (high)
FT4 = 3.8 pmol/L (low)
Antithyroglobulin antibodies = 11 IU/mL
TPO antibodies = 10 IU/ml
Serum 8 a.m. cortisol = normal

Treatment with Levothyroxine normalized both TSH and FT4.

- Silent and postpartum thyroiditis
- Cytokine-induced thyroiditis
- Iodine deficiency
- Iodine overload (e.g., Amiodarone)
- Drugs: thionamides, lithium carbonate, amiodarone, interferon α, perchlorate, tyrosine kinase inhibitors—sunitinib, sorafenib
- Infiltrative disorders of the thyroid gland (amyloidosis, hemochromatosis, sarcoidosis, Riedl's thyroiditis)
- subacute thyroiditis
- defects in thyroid hormones synthesis

30.4.2 Primary Hypothyroidism Without Goiter

- Atrophic chronic autoimmune thyroiditis
- Iatrogenic: thyroidectomy, radioiodine ablation, external beam radiation therapy for malignant tumors of head and neck (Hodgkin's lymphoma, leukemia, bone marrow transplantation, etc.)
- Congenital thyroid agenesis, dysgenesis.

30.4.3 Central (Secondary and Tertiary) Hypothyoidism: Without Goiter

- Hypopituitarism (pituitary tumors, pituitary surgery or radiotherapy, infiltrative diseases—sarcoidosis, amyloidosis, hemochromatosis), pituitary apoplexy-Sheehan's syndrome, traumatic, genetic, lymphocytic hypophysitis, infectious disorders (tuberculosis), metastases
- Isolated TSH deficiency
- Congenital hypopituitarism (multiple pituitary hormone deficiencies)
- Treatment with somatostatin analogues (octreotide, lanreotide), bexarotene

  Hypothalamic diseases: tumors (craniopharyngioma, germinoma, glioma, meningioma), trauma, infiltrative diseases (sarcoidosis, hemochromatosis, cell hystiocytosis, Langerhans' cell), idiopathic (birth defects)

30.4.4 "Peripheral" (Extrathyroidal) Hypothyroidism

- Mutations in gene encoding TR β, TR α (thyroid hormone resistance), MCT8, SECISBP2
- Massive infantile hemangioma with consumptive hypothyroidism (Ross and Cooper 2017; Wiersinga 2014).

30.5 Clinical Manifestations of Hypothyroidism

Patients with hypothyroidism can present with any of the following signs and symptoms

30.5.1 Symptoms

- Fatigue
- Cold intolerance
- Weight gain
- Dry skin
- Constipation
- Hoarseness
- Muscle weakness and/or cramps, myalgia, and paresthesia
- Impaired memory, slow thinking, decreased concentration, depression, dementia (in elderly people)
- Menstrual disturbances (irregular or heavy menses), infertility, galactorrhoea
- Pleural, pericardial effusions, ascites (Ross and Cooper 2017; Wiersinga 2014).

30.5.2 Signs

- Dry skin, carotenemia
- Puffy facies and loss of eyebrows
- Edema (periorbital)
- Tongue enlargement
- Bradycardia
- Diastolic hypertension
- Slow speech (bradylalia), slow movements (bradykinesia)
- Goiter/thyroid atrophy

- Delayed relaxation phase of the deep tendon reflexes, ataxia
- Loss of hair
- Constipation
- Hypothermia (Ross and Cooper 2017; Wiersinga 2014).

30.6 Patient's Approach

30.6.1 Blood Tests

TSH is the screening and first-line diagnostic test for primary hypothyroidism; third generations assays have detection limit of 0.01 mIU/L and up to 99% sensitivity and specificity. Normal TSH range is usually 0.4–4 mIU/L (Association of Clinical Biochemistry, British Thyroid Association, and British Thyroid Foundation 2006). Note that upper normal limit of TSH range is higher in older people: 97.5th percentile of the upper normal limit of TSH was reported to be: 4.5 mIU/L in people 50–59 years, 5.9 mIU/L in elderly subjects 70–79 years old, and 7.5 mIU/L in those at 80 years and older (Surks and Hollowell 2007). Some studies suggested a much lower cut-off for the upper normal limit of TSH (2–2.5 mIU/L), but there is presently insufficient justification to lower the upper normal limit of TSH (Brabant et al. 2006).

Free T_4–FT_4 is necessary for diagnosis of central hypothyroidism and for diagnosis of overt *versus* subclinical primary hypothyroidism.

Antithyroglobulin antibodies and TPO antibodies are positive in 50–70% and 90–95%, respectively, of cases of hypothyroidism due to autoimmune thyroiditis. They confirm autoimmune etiology and may predict the evolution towards overt hypothyroidism in patients with subclinical hypothyroidism, pregnant women, and in patients treated with amiodarone, lithium, interferon α.

Additional Tests

- Lipids: hypothyroidism is associated with mixed dyslipidemia, for example, increased total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, lipoprotein (a), and triglycerides. Lipid changes are reversible with levothyroxine (LT_4) treatment;
- blood count: anemia (due to blood loss/coexistence of vitamin B_{12} deficiency—pernicious anemia/folic acid deficiency);
- Urea and electrolytes and liver function tests: Hyponatremia (due to hemodilution);
- Increased creatine phosphokinase (CK) or other muscle and liver enzymes;
- prolactin: Hyperprolactinemia: severe, long-standing primary hypothyroidism leads to increased TRH and to hyperprolactinemia (Ross and Cooper 2017; Wiersinga 2014).

Box 30.2 Case Example 2: Increased Creatine Phosphokinase in Severe Hypothyroidism

66 year, ♀ resident in an iodine-sufficient area, presented with asthenia, constipation, and depression. Biochemical data showed severe hypothyroidism:

TSH = 71.4 mIU/L (high)
FT4 = 3.9 pmol/L (low)
Positive TPO antibodies = 107 IU/mL
Serum 8 a.m. cortisol = normal

Patient-associated anemia, and increased creatinine kinase = 1385 IU/L with the upper normal CKMB (28 IU/L)

After 3 months of Levothyroxine treatment, there was significant clinical and biochemical improvement (TSH = 11 mIU/L and creatinine kinase normalized).

30.6.2 Resting ECG (Standard 12-Lead Resting Electrocardiogram)

Sinus bradycardia, low-voltage QRS complexes, flattening or inversion of the T wave, QT prolongation, and increased dispersion of the QT interval may be present. Sometimes, there is prolonged PR interval (first-degree atrioventricular block) or interventricular conduction delays. Premature ventricular beats can also be present. Sustained or non-sustained attacks of ventricular tachycardia

and torsades de pointes are seldom reported (Ross and Cooper 2017; Wiersinga 2014).

30.6.3 Thyroid Ultrasound

A thyroid ultrasound is very useful in the diagnostic evaluation of thyroid nodules and can show any of the following features;

- Focal or diffuse thyroid enlargement/thyroid atrophy
- Hypoechogenicity of the thyroid gland in autoimmune thyroiditis (even in 10% patients with negative thyroid antibodies)
- Hypoechoic micronodules (1–6 mm)
- Fine echogenic fibrous septae generating a pseudolobulated pattern
- Doppler colour: increased/decreased/normal vascularization
- Perithyroidal lymph nodes, especially the "Delphian" node may be enlarged (Chaudhary and Bano 2013)

Note: due to higher risk for papillary thyroid carcinoma and thyroid lymphoma, suspected nodules should be referred for fine needle biopsy according to guidelines (British Thyroid Association guidelines for nodules).

30.6.4 Other Tests

Doppler echocardiography: this should be undertaken in patients with severe hypothyroidism.

Chest X rays: in patients with cardiomegaly, pericardial, and/or pleural effusion.

Pituitary MRI: Pituitary enlargement (in primary myxedema, due to thyrotroph and lactotroph hyperplasia (Ross and Cooper 2017; Wiersinga 2014)).

30.7 Biochemical Assessment

30.7.1 Diagnosis

Relies on measurement of thyroid function tests (TFTs): TSH and FT_4 for blood (BTA Guidelines-Table 30.2)

Differential diagnosis of raised TSH: resistance to TSH, TSH-secreting pituitary adenoma, recovery from nonthyroidal illness, presence of heterophilic antibodies against mouse proteins—falsely raise serum TSH.

30.7.2 Algorithm for Hypothyroidism Diagnosis

In the presence of either clinical suspicion or biochemical suspicion (dyslipidemia, hyperprolactinemia, hyponatremia, anemia, and/or elevated creatine phosphokinase), TSH and FT_4 should be measured.

30.7.3 Indications for Screening Patients with Symptoms and Risk Factors for Hypothyroidism

These can include any from the list below:

- Goiter
- Autoimmune diseases (such as type 1 diabetes mellitus, adrenal insufficiency, premature ovarian failure, lymphocytic hypophysitis, vitiligo, celiac disease, pernicious anemia, multiple sclerosis, Sjogren syndrome, primary pulmonary hypertension, etc.)
- Previous history of Graves' disease (with or without radioiodine therapy), subacute thyroiditis, painless thyroiditis
- Head and/or neck irradiation

Table 30.2 Biochemical diagnosis of hypothyroidism (adapted from Cooper and Biondi (2012), Ross and Cooper (2017), Wiersinga (2014), and Association of Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation (2006))

	Serum TSH	Serum FT_4
Overt Primary Hypothyroidism	Increased	Low
Subclinical Primary Hypothyroidism	Increased	Normal
Central hypothyroidism	Low/inappropriately normal/slightly increased	Low-normal/low

- Family history of autoimmune thyroid diseases
- Turner's syndrome
- Down's syndrome

Hypothalamic diseases: tumors, radiotherapy, surgery, infiltrative diseases (sarcoidosis, hemochromatosis, Langerhans' cell histiocytosis)

Pituitary disease: tumors, radiotherapy, surgery, apoplexy (Sheehan's syndrome), metastatic cancer

Pregnant women: from area with iodine deficiency, those who have symptoms of hypothyroidism, a family or personal history of thyroid disease (such as personal history of hemithyroidectomy and/or treatment with radioactive iodine) who are positive for TPO antinodies and antithyroglobulin antibodies, who have type 1 diabetes, head and neck radiation, recurrent miscarriage, morbid obesity, or infertility

On treatment with drugs interfering with thyroid function: lithium carbonate, amiodarone, interferon α, tyrosine kinase inhibitors—sunitinib, sorafenib.

Laboratory test: radiological abnormalities such as: hypercholesterolemia, hyponatremia, hyperprolactinemia, elevated creatine phosphokinase, anemia, hyperhomocysteinemia, pleural and pericardial effusions, pituitary enlargement (Ross and Cooper 2017; Wiersinga 2014)

30.8 Complications

Complications of hypothyroidism can include any of the listed below.

- Dyslipidemia and atherosclerosis
- Coronary heart disease (Rodondi et al. 2010) (especially in patients with TSH > 10 mIU/L)
- Pleural and pericardial effusion
- Heart failure (especially in patients with TSH > 7–10 mIU/L)

30.9 Treatment

30.9.1 Initiation of Therapy Including Doses, Route, and Time of Administration

The aim of treatment is to normalize serum TSH, to restore patients' physical and psychological well-being and to avoid overtreatment, especially in old people (Okosieme et al. 2016).

The exception to this is in the first-term of pregnancy in women where the TSH should be kept <2.5 mIU/L; in second and third trimesters of pregnancy, TSH should be <3 mIU/L (Negro and Stagnaro-Green 2014; Stagnaro-Green et al. 2011).

Methods: Levothyroxine (LT_4) as monotherapy, orally, once daily.

Doses:

- 1.6–1.8 μg/kg/day levothyroxine (lean body weight or ideal body weight) in young and middle-age patients for replacement therapy in primary hypothyroidism
- 1.3 μg/kg/day levothyroxine in central hypothyroidism
- 2–2.4 μg/kg/day levothyroxine in pregnant women with overt hypothyroidism
- 2–2.5 μg/kg/day levothyroxine for suppressive therapy

LT_4 requirements are higher in young patients than in the elderly, in overt hypothyroidism than in subclinical hypothyroidism, premenopausal women than in postmenopausal, in men, pregnancy (Biondi and Wartofsky 2014) (30–50%), severely obese people—due to increased plasma volume, delayed gastrointestinal absorption, and those with altered T_4 to T_3 conversion (Michalaki et al. 2011).

Five to ten percent of hypothyroid patients treated with levothyroxine have persistent symptoms, despite TSH normalization. Guidelines recommend against the routine use of combination treatment with LT_4 and LT_3 (ATA), because of insufficient evidence from randomized controlled trials. However, ETA and ATA guidelines sug-

gested considering combined LT_4 and LT_3 therapy as an experimental approach in compliant patients treated with LT_4, who have persistent symptoms despite serum TSH normalization. Combined LT_4 and LT_3 are not recommended in pregnancy or in patients with cardiac arrhythmias. If there is no improvement in patient's condition after 3 months, the combined $LT_4 + LT_3$ therapy should be stopped (Okosieme et al. 2016).

Oral intake of levothyroxine: this should be taken on fasting in the morning, 30–60 min before breakfast. Some studies suggest some benefits of levothyroxine administration 2 h after the evening meal (Bolk et al. 2007).

Specific situations: *it should be noted that all recommended treatments should adhere to local hospital policy and guidelines*

Subclinical hypothyroidism and indications for treatment:

- Symptomatic patients, depression, goiter, cardiovascular risk factors (high blood pressure, dyslipidemia, diabetes/insulin resistance)
- Patients with positive thyroid antibodies and rising TSH
- Smaller levothyroxine doses are needed compared to patients with overt hypothyroidism.

Suggested levothyroxine starting doses in subclinical hypothyroidism (Teixeira et al. 2008).

- 25 μg LT_4 for TSH = 4–8 mIU/L,
- 50 μg LT_4 for TSH = 8–12 mIU/L
- 75 μg LT_4 for TSH > 12 mIU/L

30.9.1.1 Associated Adrenal Insufficiency (Central or Autoimmune)

Start with hydrocortisone treatment, because full-dose levothyroxine replacement may be associated with exacerbation of adrenal insufficiency (Biondi and Wartofsky 2014).

30.9.1.2 Pregnancy

Both hypothyroidism and maternal hypothyroxinemia are associated with fetal and maternal negative outcomes (miscarriages, preterm delivery, neurodevelopmental delay, autistic symptoms in the offspring); levothyroxine treatment improves these outcomes in some studies. In hypothyroid women, thyroid hormones requirement increases during pregnancy (Negro and Stagnaro-Green 2014; Stagnaro-Green et al. 2011; Alexander et al. 2017; Biondi and Wartofsky 2014). LT_4 dose should, therefore, be increased around 4–6 weeks of pregnancy by 25–30% (Alexander et al. 2017). Oral levothyroxine is the recommended treatment for maternal hypothyroidism.

Overt hypothyroidism diagnosed during pregnancy should be treated with full replacement dose of 2–2.4 μg/kg/day levothyroxine, in order to restore euthyroidism as soon as possible. For women with subclinical hypothyroidism (TSH greater than the pregnancy-specific reference range with positive TPO antibodies and TSH greater than 10 mIU/L with negative TPO antibodies, respectively), a dose of 50 μg levothyroxine/day is usually required (Alexander et al. 2017). Levothyroxine therapy may be also considered in pregnant women with TSH higher than 2.5 mIU/L and below the upper limit of the pregnancy-specific reference range with positive TPO antibodies and in women with TSH levels higher than the upper pregnancy-specific reference range and below 10 mIU/L with negative TPO antibodies (Alexander et al. 2017). T_3 or desiccated thyroid should not be used during pregnancy. Targeted TSH during pregnancy is in the lower half of the trimester-specific reference range (when this is not available <2.5 mIU/L). After delivery, LT_4 should be reduced to the preconception dose and TSH assessed in about 6 weeks (Alexander et al. 2017).

30.9.1.3 Central Hypothyroidism

The target FT_4 should be in the upper half of the normal range for young patients and in the lower half of reference range in older patients.

30.9.2 Monitoring

Serum TSH and FT_4: The target TSH in young hypothyroid patients should be 1–2.5 mIU/L (Biondi and Wartofsky 2014)

- 8 weeks after starting levothyroxine
- Every 4–8 weeks after levothyroxine dose adjustment/drug changes (manufacturer)
- Every 6–12 months after establishing the correct dose

Thyroid ultrasound: Recommended annually

ECG, Doppler echocardiography monthly in patients with ischemic heart disease, arrhythmias, and pericardial effusion (Biondi and Wartofsky 2014).

30.9.3 Potential Side Effects of Treatment

Overtreated patients (with suppressed TSH, especially those with TSH < 0.1 mIU/L) are frequent in up to 30–50%. The risks associated with overtreatment include:

- Tachycardia, arrhythmias (atrial fibrillation), increased left ventricular mass, diastolic dysfunction, heart failure
- Loss of bone mass (osteoporosis) and fractures (especially postmenopausal women), and therefore, thyroid hormone excess should be avoided, especially in elderly people and postmenopausal women (Biondi and Wartofsky 2014).

Table 30.3 Drugs interfering with levothyroxine absorption and metabolism (Ross and Cooper 2017; Wiersinga 2014)

Mechanism	Drug
Decrease levothyroxine (LT_4) absorption	Cholestyramine, Colestipol
	Sucralfate
	Aluminum hydroxide
	Ferrous sulfate
	Antiacids, sucralfate, proton pump inhibitors, H2 receptor antagonists
	Laxatives
	Calcium carbonate (allow at least 3–4 h between LT_4 and calcium tablets)
	Food: Soy protein supplements, coffee, grapefruit juice, dietary fibers
Increase metabolic (nondeiodinative) levothyroxine clearance	Rifampicin
	Carbamazepine, Phenobarbital
	± Phenytoin
Block T_4 to T_3 conversion	Amiodarone
	Glucocorticoids
	β blockers
	Selenium deficiency
Increased need for levothyroxine	Estrogens
Precise mechanism unknown	Sertraline, Chloroquine
	Tyrosine kinase inhibitors: Imatinib, Motesanib, Sorafenib

30.9.4 Dose Adjustments

Persistent increased TSH despite levothyroxine treatment should be further investigated. Possible causes are:

- Incorrect LT_4 dose/administration
- Poor patients compliance; for differential diagnosis between poor patient compliance and malabsorption, 1000 μg LT_4 (weekly dose: 1.6 × body weight (kg) × 7) are administered fasting, in the morning, in liquid or tablet form; FT_4 is measured 0, 30, 45, 60 min, 2, 4, 6 h after ingestion; FT_4 above 25 pmol/L or an increment of 20 pmol/L for FT_4 at 2 h suggest poor compliance (Ain et al. 1991).
- Malabsorption (celiac disease, autoimmune gastritis, after gastrointestinal surgery, short bowel syndrome, lactose intolerance, Helicobacter Pylori infection, cirrhosis, pancreatic diseases)
- Drugs or food that interfere with levothyroxine absorption or thyroid axis (Table 30.3).

30.9.5 Association with Other Comorbidities (for Example: Ischemic Heart Disease)

- Elderly people with or without evidence of cardiac disease: it is advisable to start with low doses, because full-dose levothyroxine replacement is associated with angina, myocardial infarction, and arrhythmias.
- Elderly people (>50–60 years) without evidence of cardiac disease: the starting dose is

usually 25–50 μg/day, increasing the dose with 25–50 μg/day every 3–4 weeks
- Elderly patients over the age of 60 years: the starting dose is lower: 12.5–25 μg/day, increasing the dose with 12.5–25 μg/day every 3–4 weeks
- Patients with ischemic heart disease: the starting dose: 12.5 μg/day, increasing the dose with 12.5 μg/day every 3–4 weeks; in severe ischemic heart disease, increasing dose with 12.5 μg/day every 4–6 weeks
- Coronary revascularization can be necessary in some cases to tolerate levothyroxine treatment (Biondi and Wartofsky 2014).

30.10 Conclusions

Hypothyroidism is one of the most frequent thyroid disorders, of which primary hypothyroidism prevails over secondary hypothyroidism. The causes of primary hypothyroidism include chronic autoimmune thyroiditis (Hashimoto), subacute, silent and postpartum thyroiditis, cytokine-induced thyroiditis, iodine deficiency or iodine overload, drugs-induced hypothyroidism, infiltrative disorders of the thyroid, defects in thyroid hormones synthesis, thyroidectomy, radioiodine ablation, external beam radiation therapy for malignant tumors of head and neck, congenital thyroid agenesis, or dysgenesis.

Central (secondary and tertiary) hypothyoidism is caused by acquired or congenital hypopituitarism, pituitary apoplexy (Sheehan's syndrome), traumatic, genetic, lymphocytic hypophysitis, infectious disorders (tuberculosis), metastases, isolated TSH deficiency, treatment with somatostatin analogues, and hypothalamic disorders. Causes of peripheral hypothyroidism are rare (mutations in gene encoding TR β, TR α—thyroid hormone resistance, MCT8, SECISBP2, massive infantile hemangioma). The screening tools are serum TSH and freeT4. An increased TSH and low FT4 are found in primary overt hypothyroidism. Increased TSH and normal FT4 are found in primary subclinical hypothyroidism. Low-normal/low FT4 with low/inappropriately normal/slightly increased TSH are found in central hypothyroidism. Complementary abnormal tests can include mixed dyslipidemia, anemia, hyponatremia, increased creatine phosphokinase (CK) or other muscle and liver enzymes, hyperprolactinemia, ECG (sinus bradycardia, low-voltage QRS complexes, etc.), and chest X rays (cardiomegaly, pericardial, and/or pleural effusion).

The treatment for hypothyroidism is Levothyroxine and is prescribed as monotherapy, orally, once daily (usually in the morning, 30–60 min before breakfast). The dose of levothyroxine in young and middle-age patients for replacement therapy in primary hypothyroidism is 1.6–1.8 mg/kg/day, with lower requirements (1.3 mg/kg/day) in central hypothyroidism and higher doses in pregnancy.

References

Ain KB, Refetoff S, Fein HG, et al. Pseudomalabsorption of levothyroxine. JAMA. 1991;266:2118–20.

Alexander EK, Pearce N, Brent GA, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89.

Association of Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation. UK guidelines for the use of thyroid function tests. 2006. www.british-thyroid-association.org.

Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76–131.

Biondi B, Wartofsky L. Treatment with thyroid hormone. Endocr Rev. 2014;35(3):433–512. https://doi.org/10.1210/er.2013-1083.

Bolk N, Visser TJ, Kalsbeek A, et al. Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. Clin Endocrinol. 2007;66:43–8.

Brabant G, Beck-Peccoz P, Jarzab B, et al. Is there a need to redefine the upper normal limit of TSH? Eur J Endocrinol. 2006;154(5):633–7.

Chaudhary V, Bano S. Thyroid ultrasound. Indian J Endocrinol Metab. 2013;17(2):219–27. https://doi.org/10.4103/2230-8210.109667.

Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54. https://doi.org/10.1016/S0140-6736(11)60276-6.

Michalaki MA, Gkotsina MI, Mamali I, et al. Impaired pharmacokinetics of levothyroxine in severely obese volunteers. Thyroid. 2011;21(5):477–81. https://doi.org/10.1089/thy.2010.0149.

Negro R, Stagnaro-Green A. Diagnosis and management of subclinical hypothyroidism in pregnancy. BMJ. 2014;349:g4929. https://doi.org/10.1136/bmj.g4929.

Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol. 2016;84(6):799–808. https://doi.org/10.1111/cen.12824.

Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304(12):1365–74. https://doi.org/10.1001/jama.2010.1361.

Ross DS, Cooper DS. Hypothyroidism. UpToDate. 2017. http://www.uptodate.com.

Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyoid. 2011;21(10):1081–25. https://doi.org/10.1089/thy.2011.0087.

Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007;92(12):4575–82.

Teixeira PF, Reuters VS, Ferreira MM, et al. Treatment of subclinical hypothyroidism reduces atherogenic lipid levels in a placebo-controlled double-blind clinical trial. Horm Metab Res. 2008;40(1):50–5.

Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in the community: the Whickham survey. Clin Endocrinol. 1977;7:481–93.

Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39–51. https://doi.org/10.1093/bmb/ldr030.

Vanderpump MPJ, Tunbridge WMG, French JM, et al. The incidence of thyroid disorders in the community; a twenty-year follow up of the Whickham survey. Clin Endocrinol. 1995;43:55–68.

Walsh JP, Bremner AP, Feddema P, et al. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab. 2010;95(3):1095–104. https://doi.org/10.1210/jc.2009-1977.

Wiersinga WM. Adult hypothyroidism. Thyroid manager. 2014. http://www.thyroidmanager.org/chapter/adult-hypothyroidism.

Key Reading

1. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54. https://doi.org/10.1016/S0140-6736(11)60276-6.
2. Ross DS, Cooper DS. Hypothyroidism. UpToDate. 2017. http://www.uptodate.com.
3. Wiersinga WM. Adult hypothyroidism. Thyroid manager. 2014. http://www.thyroidmanager.org/chapter/adult-hypothyroidism.
4. Association of Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation. UK guidelines for the use of thyroid function tests. 2006. www.british-thyroid-association.org.
5. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf). 2016;84(6):799–808. https://doi.org/10.1111/cen.12824.

Thyroid Eye Disease

31

Rebecca Ford and Violet Fazal-Sanderson

Contents

31.1 **Introduction** 596
31.1.1 Overview of the Eye Anatomy 596
31.1.2 The main Structures of the Eye 597
31.1.3 Extraocular Muscles 598

31.2 **What Is Thyroid Eye Disease?** 598

31.3 **Aetiology of Thyroid Eye Disease** 598

31.4 **Risk Factors for Thyroid Eye Disease** 598
31.4.1 Thyroid Dysfunction 598
31.4.2 Demographics and Genetics 599
31.4.3 Environment 599

31.5 **Natural History of Thyroid Eye Disease** 599

31.6 **Symptoms and Signs of Thyroid Eye Disease** 599
31.6.1 Ocular Surface Signs and Symptoms 601
31.6.2 Eyelid Signs and Symptoms 601
31.6.3 Ocular Motility Signs and Symptoms 601
31.6.4 Orbital Signs and Symptoms 601
31.6.5 Visual Dysfunction in Thyroid Eye Disease 602

31.7 **Grading Thyroid Eye Disease** 602

31.8 **Investigation of Thyroid Eye Disease** 602

31.9 **Treatment of Thyroid Eye Disease** 603
31.9.1 Early and Supportive Treatment 603
31.9.2 Management of Hyperthyroidism 603

R. Ford
Bristol Eye Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
e-mail: Rebecca.ford@uhbristol.nhs.uk

V. Fazal-Sanderson (✉)
Department of Endocrinology, Centre for Diabetes and Endocrinology, Royal Berkshire Hospital NHS Foundation Trust, Reading, UK
e-mail: violet.sanderson@royalberkshire.nhs.uk; Violetsanderson@royalberkshire.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_31

31.9.3 Medical Treatment 604
31.9.4 Surgical Treatment 605
31.10 **Multidisciplinary Management of TED** 606
31.11 **Psychological Aspects of Thyroid Eye Disease** 607
31.12 **The Future of Thyroid Eye Disease** 607
31.13 **Conclusions** 608
References 608

Abstract

Thyroid eye disease (TED) is an autoimmune condition usually associated with thyroid dysfunction and characterised by inflammatory and fibrotic changes in the periocular tissues. It is most commonly associated with hyperthyroidism, but patients with TED may also be hypothyroid or euthyroid, and it does not always present at the same time as the thyroid dysfunction. Patients may present with inflamed eyes, ocular surface discomfort, double vision, and proptosis and may even progress to optic nerve compression and visual loss.

Risk factors include smoking and radioiodine treatment. Early recognition is important since treatment in the active phase with steroids, immunomodulatory agents, and sometimes radiotherapy can prevent persistent disability and disfigurement. Once the disease is inactive, treatment is focused more on surgical rehabilitation, with orbital decompression, strabismus surgery, and lid surgery. Urgent orbital decompression may be needed if the optic nerve is compressed. People with TED may have significant psychological distress related to hormonal changes, vision problems, changing appearance, and medication side effects, and the psychological care of these patients is often neglected. Future developments may offer the possibility of earlier diagnosis, biologic treatments tailored to the disease to stop its activity, and effective less invasive surgical rehabilitation.

It is imperative that clinical practitioners are familiar with the clinical features of Graves' ophthalmopathy. Furthermore, the thyroid endocrine nurse must be equipped with the relevant knowledge and understanding of eye anatomy and how thyroid eye disease (TED) presents. In this way, any eye signs and symptoms can be identified early, and managed more effectively, potentially reversing GO if referred promptly to an 'endocrine' ophthalmologist who specialises in thyroid eye disease.

Keywords

Graves' ophthalmopathy · Eye anatomy
Signs and symptoms · Extraocular muscles
Proptosis · Management

Abbreviations

CD20 marker	CD20, a transmembrane protein expressed on the surface of pre-B and mature B lymphocytes
CN	Cranial nerve
CT	Computerised tomography
EUGOGO	European Group on Graves' Orbitopathy
FT3	Free total triiodothyronine
fT4	Free thyroid hormone or thyroxine
GP	General practitioner
IGF-IR inhibitor	Insulin-like growth factor-I receptor (inhibits targets of signaling pathways)
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NOSPECS	Mnemonic often is used as a scoring system for severity of eye change
RAI	Radioactive iodine
STIR	Short Tau Inversion Recovery (used with MRI)

TED	Thyroid eye disease
TPO antibodies	Thyroid peroxidase antibodies
TSH receptor	Thyroid-stimulating hormone receptor
TSH	Thyroid stimulation hormone
UK	United Kingdom
USA	United States of America
VISA	vision, Inflammation, strabismus, and appearance

Key Terms

- **Proptosis or exophthalmos**: Forward protrusion of the eyeball that can result in failure of the upper and lower eyelids to fully oppose, for example, when patient is asked to close the eyelids the iris or sclera may be visible. This can cause risk of developing corneal ulceration.
- **Keratitis**: Inflammation or infection of the cornea, e.g. due to bacterial, viral, or fungal infection, or associated with autoimmune disease, and can result in blurred vision, eye pain, tearing, photosensitivity, red eyes, or eye discharge.
- **Gritty eyes**: Feeling of sand or grit in the eyes. Occurs in patients with hyperthyroidism as a result of corneal exposure or dry eyes.
- **Excessive tearing of eyes**: Results from impaired tear drainage or excess tear production. In TED, increased tear production can be due to conjunctival inflammation, corneal drying, or corneal exposure due to proptosis.
- **Conjunctiva injection and Chemosis**: Inflammation of the conjunctiva is known as conjunctival injection. It appears similar to the 'pink eye' caused by viral or bacterial infection of the conjunctiva (conjunctivitis). Chemosis is conjunctival oedema- fluid build-up between the inflamed conjunctival layer and the sclera, giving a puffy or gelatinous appearance.
- **Lid retraction**: Visible sclera above the iris when patient looks straight ahead and may be due to stimulation of the levator (lid-lifting) muscle by hyperthyroidism, or direct involvement of the muscle by TED.
- **Lid lag**: When the patient looks down, the eyelid movement lags behind that of the eye. This is a symptom of hyperthyroidism rather than of TED itself.
- **Diplopia**: Also known as double vision. In TED, this is usually 'binocular', i.e. it is due to the two eyes being misaligned and will disappear if one eye is covered. The two images seen may be horizontally or vertically separated, or both. Examination of eye movements is one key way of checking for significant thyroid eye disease.
- **Stare**: The eyes may appear to 'stare' in TED due to proptosis or due to lid retraction.
- **Periorbital oedema**: Puffy upper and lower eyelids and can occur in hypothyroidism myxoedema, but is more often a sign of TED.
- **Corneal ulceration**: Can occur in TED as a result of proptosis or lagophthalmos (incomplete closure of eye) causing exposure of the cornea. Ulcers appear as raw patches on the cornea, which may go densely white if infected. They are usually accompanied by symptoms of pain and red eye.
- **Pain**: Pain in TED may be due to corneal exposure or ulceration; the corneal nerves are very sensitive and corneal pain may be intense. TED patients may also experience a deep-seated orbital pain if there is raised pressure within the orbit, or pain on eye movements if eye muscles are inflamed.
- **Photophobia**: This is painful light sensitivity and usually occurs when the cornea is dry or damaged.

Key Points

- Thyroid eye disease can be bilateral and unilateral. It can occur before, during, or after thyroid dysfunction.
- Knowledge of eye anatomy is paramount to understanding how thyroid eye disease can spotted promptly and managed effectively.
- Smoking is a strong risk factor for TED.
- The active phase of TED lasts 18–24 months on average. Patients may experience red eyes, double vision, proptosis, and visual dysfunction.
- Radioiodine treatment may trigger TED in some patients.
- Stabilising thyroid function may help TED symptoms, but does not in itself treat the condition.

- Early referral to a specialist ophthalmologist enables early treatment and may prevent disabling and disfiguring eye changes. Treatment may involve steroids, radiotherapy, and immunomodulatory drugs.
- Once inactive, patients may need rehabilitative orbital decompression, strabismus, and/or lid surgery.

31.1 Introduction

31.1.1 Overview of the Eye Anatomy

To better understand thyroid eye disease, knowledge of eye anatomy (Fig. 31.1) and physiology is essential.

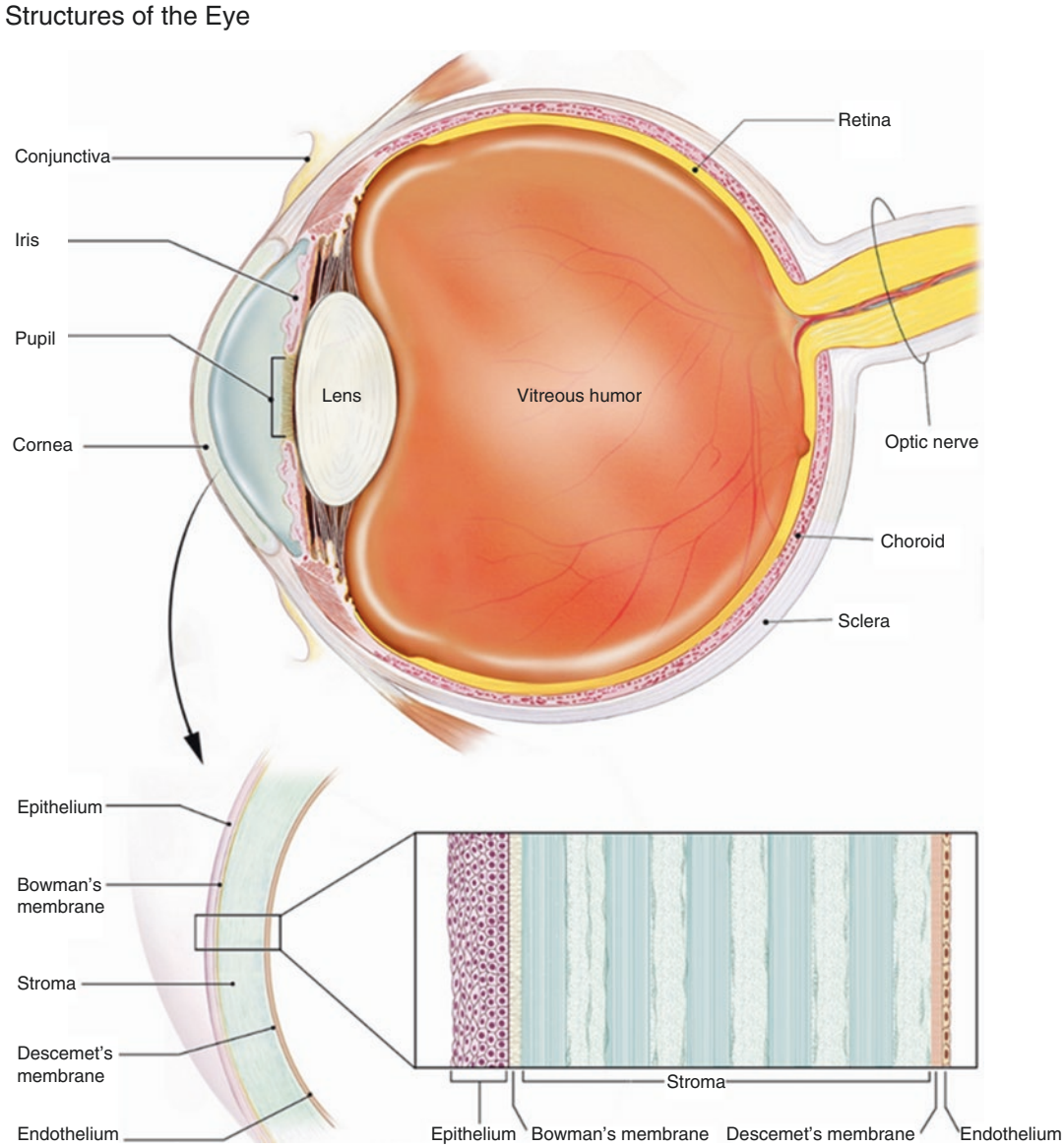


Fig. 31.1 Eye anatomy (accessed via NIH NEI, National Eye Institute, free Images Catalogue- https://nei.nih.gov/photo)

31.1.2 The main Structures of the Eye

Anterior and posterior chambers: The anterior chamber is located behind the cornea, and in front of the iris and lens. It contains clear fluid supplied by the cillary body and provides not only nutrition to local tissue, but also removes any metabolic waste.

The posterior chamber lies behind the iris and in front of the lens. This is filled with a clear gel called vitreous containing small fibres and water. Unlike aqueous fluid, vitreous gel has no consistent formation or drainage process.

Conjunctiva: This is a thin transparent protective membrane that covers the exposed part of the eye (protected by a film of tear fluid) and is continuous to line the under surface of the eye lid.

Cornea: A transparent slightly convex structure located at the anterior of the eye is the cornea. It refracts light as it enters the eye through the pupil. The light is further focussed by the lens as it passes through the vitreous gel, forming an inverted image onto the retina.

The cornea has no blood supply and is composed of three layers

1. The outer epithelial cell layer, continuous with the conjunctiva
2. The central fibrous layer called the stroma.
3. The inner endothelial cell layer, a membrane that lines the anterior chamber of the eye ball

Lens: A transparent biconcave disc located posteriorly to the pupil is the lens surrounded by the ciliary body. The lens helps to refract light passing through the eye to focus an image on the retina. It also changes shape (known as accommodation) to enable the eye to focus on near and distant objects.

Pupil: The circular hole within the iris muscle is the pupil. The size of the pupil depends on the amount of light entering the eyes, controlled by the pupillary muscles of the iris and supplied by the sympathetic and parasympathetic autonomic nervous activity running with the third cranial nerve.

Iris: The coloured part of the eye located in the anterior chamber immediately in front of the lens is the iris. It comprises a ring of muscle at the margins of the iris that controls the size of the pupil, for example, in the presence of bright light the muscles of the iris contract via parasympathetic activity, reducing the size of pupil, whist sympathetic activity in the presence of dim light causes the iris muscles to relax, enlarging the pupils.

Sclera: The outer layer of the eye is composed of tough white fibrous tissue called the sclera and is continuous with the cornea in front of the iris and the pupil.

Choroid: The middle layer of the eye comprises vascular tissue (a dark pigmentation) and is continuous with the ciliary body and the iris. It supplies nourishment to the retina.

Retina: This is located at the inner/ posterior aspect of eye. The retinal vessels have large paired veins and arteries that are usually brighter, red, and narrow compared to veins.

The inner surface retina contains a layer of photosensitive cells on the inner surface of the retina known as cones and rods.

1. **Cones**: There are three types that respond to different parts of the light spectrum and enable colour vision. Cone cells are packed close together in the fovea at the centre of the retina and are also responsible for fine visual detail.
2. **Rods**: these predominate in the peripheral retina enabling vision in dim light and detecting motion.

The images focussed onto the retina are detected by the photoreceptors that pass on information to layers of nerve cells that further process and relay this to the optic nerve and the brain.

Optic disc: this is composed of nerve fibres that converge to form the optic nerve.

The main characteristics of the optic disc

1. Creamy or pinkish in colour
2. Round or oval in shape
3. Sharp demarcated margins mainly at the temporal region
4. A small circular area inside the disc where blood vessels enter and exit giving a cup shape appearance via an ophthalmoscope

Macula and Fovea: the central area of the retina is the macula and fovea that contain cone cells responsible for colour vision and fine detail.

Vitreous humour: this comprises a clear gel that fills the area behind the lens and the retina.

Optic nerve: the optic nerve enters the eyeball posteriorly together with the retinal vessels. It transfers visual information from the retina to the visual area of the brain.

31.1.3 Extraocular Muscles

Six muscles are involved in eye movement and supplied by three different cranial nerves (CN) (Fig. 31.3):

- Superior rectus muscle: CN III (oculomotor)- elevates eye (looks up)
- Inferior oblique muscle: CN III- extorts (outwardly rotates) eye
- Lateral rectus muscle: CN VI (abducens)- abducts eye (moves it laterally)
- Medial rectus muscle: CN III- adducts eye (moves it medially)
- Inferior rectus muscle: CN III- depresses eye (looks down)
- Superior oblique muscle: CN IV (trochlear)- intorts (inwardly rotates) eye

31.2 What Is Thyroid Eye Disease?

Thyroid eye disease (TED) is an autoimmune condition affecting the tissues around the eyes, causing a spectrum of problems from dry, sore, puffy eyes to double vision, proptosis, and even visual loss. It usually occurs in patients with thyroid disorders, most commonly Graves' disease. It is usually self-limiting, but can lead to significant functional impairment, disfigurement, or even loss of vision in severe cases.

31.3 Aetiology of Thyroid Eye Disease

The pathogenesis of thyroid eye disease is far from fully understood. It is an autoimmune disease, and most patients will have detectable autoantibodies against thyroid antigens such as the TSH receptor (typical in Graves' disease) or thyroid peroxidase at some stage in their disease process. Tests for these antibodies may be helpful in diagnosis of TED, especially in patients with unusual presentations or those without a known history of thyroid dysfunction. However, no single antibody test is diagnostic of the disease and the antibody levels do not correlate well with disease activity.

Autoimmune-activated T lymphocytes circulate into the orbit, where they cause inflammation, stimulate fibroblasts to proliferate and produce more glycosaminoglycans (inter-cellular matrix substances), and trigger adipocytes (fat cells) to mature. This stiffens and enlarges the extraocular muscles and expands the fat in the orbit, leading to congestion and proptosis (bulging eyes).

31.4 Risk Factors for Thyroid Eye Disease

31.4.1 Thyroid Dysfunction

Most people who develop thyroid eye disease have a history of Graves' disease (autoimmune hyperthyroidism), although it may occur in other conditions including Hashimoto's thyroiditis, thyroid cancer, and primary hypothyroidism. About 25% of people with Graves' disease experience some eye symptoms, but only around 2% develop sight-threatening disease. The eye disease does not necessarily start at the same time as the hyperthyroidism—while this is often the case, some patients will develop eye problems years before or after the thyroid disorder. TED disease activity is not directly proportional to thyroid function, which can be a difficult concept for patients and their clinicians to comprehend. While in general controlling the thyroid function is beneficial for eye symptoms, the eye disease may flare or remain active even after thyroid function normalises. Rapid swings from hyperthyroidism to hypothyroidism can risk worsening eye disease, and some treatments of hyperthyroidism carry more risk than others for the eye condition (see later).

31.4.2 Demographics and Genetics

Thyroid eye disease can occur at any age, but is most common in the fifth decade. It is very rare in children but has been reported, and in elderly people, it can take an insidious course with little apparent inflammation, making it challenging to diagnose.

Thyroid eye disease overall is about five times more common in females than males. However, this reflects the female preponderance of thyroid disorders, and when males are affected, they have a relatively higher chance of developing severe disease.

Risk factors for developing TED may be both genetic and environmental. There may be a familial tendency, but no individual genes have been identified as predisposing to TED. All races can be affected. Black Europeans and Americans may have an increased risk of TED, but this is probably not a purely genetic phenomenon; TED is rare in Africa and Korean studies show that while the prevalence of TED is relatively low in Korea, it increases in Koreans living in the USA. Hence, there appears to be an inter-play between genetic and environmental risk factors.

31.4.3 Environment

The most important environmental risk factor for TED is smoking—smokers are about five times more likely to develop TED than non-smokers and also tend to develop more severe disease and respond less well to medical treatment. We don't yet know which chemical(s) in cigarette smoke are responsible for this effect, but support with smoking cessation is critical for people with TED. It is unlikely that nicotine alone is the main driver of TED activity within cigarettes, so switching to nicotine replacement or 'e-cigarettes' is probably a viable option for patients trying to stop smoking after a diagnosis of TED.

Theories of autoimmunity suggest that exposure to pathogens may be a trigger for such disease, though no specific infectious trigger has been identified for TED. Stress also seems to be a risk factor, and research is ongoing into the role of diet and the microbiome in the condition.

31.5 Natural History of Thyroid Eye Disease

Thyroid eye disease has an active phase, in which periocular and orbital tissues are actively inflamed or changing, which on average lasts 18–24 months. Symptoms and signs typically get worse for 3–6 months, before plateauing. As activity reduces, the disease may improve somewhat until around 24 months, by which time some people's eyes will have returned to normal, but most will be left with some degree of residual discomfort, dysfunction, or altered appearance. This can be illustrated as 'Rundle's curve' (Fig. 31.2). Once the active inflammatory phase is over, the disease can be considered to be 'burned out'. The key significance of this is that anti-inflammatory treatment will only work during the active phase. We can use the 'burning house' analogy to explain this to patients and colleagues, i.e. interventions to 'put out the fire' (immunomodulatory treatments to suppress inflammation) will only work before 'the house has burned down' (the eye disease has become inactive and the damage is already done), by which time it is too late for such treatments to be effective. It is likely that the earlier in the disease the treatment is started, the less final burden of disability or disfigurement will result. Once the disease has become 'burned out', signs and symptoms should stabilize, and this is the stage when rehabilitative surgery may be safely considered.

The active phase may be longer in some patients than others; it is likely that factors such as smoking, uncontrolled or unstable thyroid function, and possibly stress can prolong the active phase.

31.6 Symptoms and Signs of Thyroid Eye Disease

It is important that clinical practitioners are familiar with the clinical features of Graves' ophthalmopathy (Fig. 31.3). Furthermore, it is advantageous for endocrine nurses to be equipped with the relevant knowledge and understanding of eye

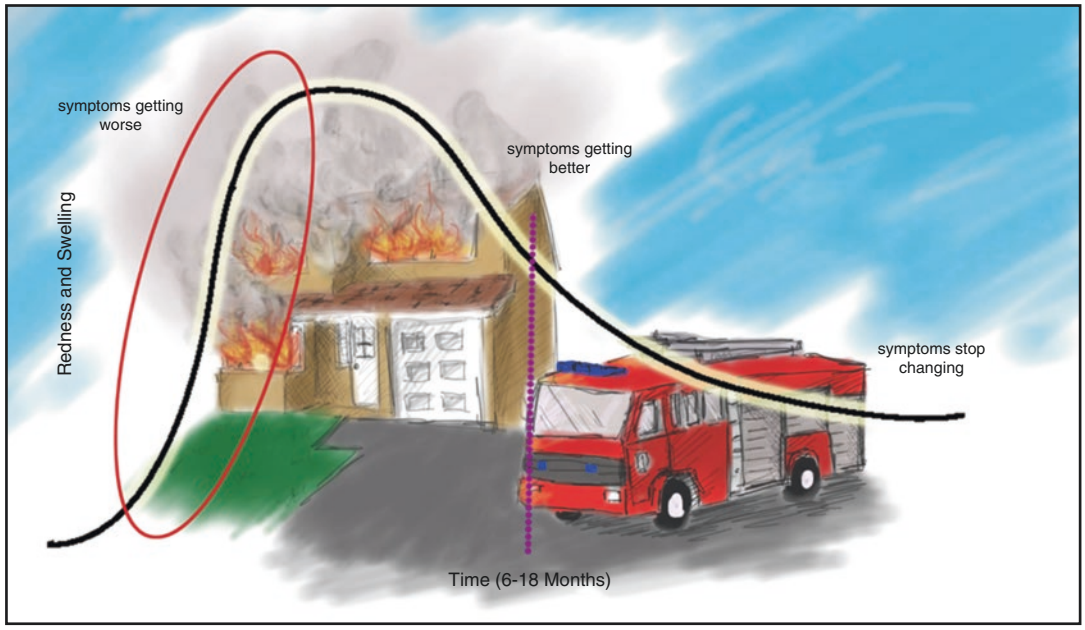


Fig. 31.2 Rundle's curve and the 'burning house' analogy. (Courtesy of Dan Morris, TEDct Newsletter, Spring 2010 edition, Pages 13–16)

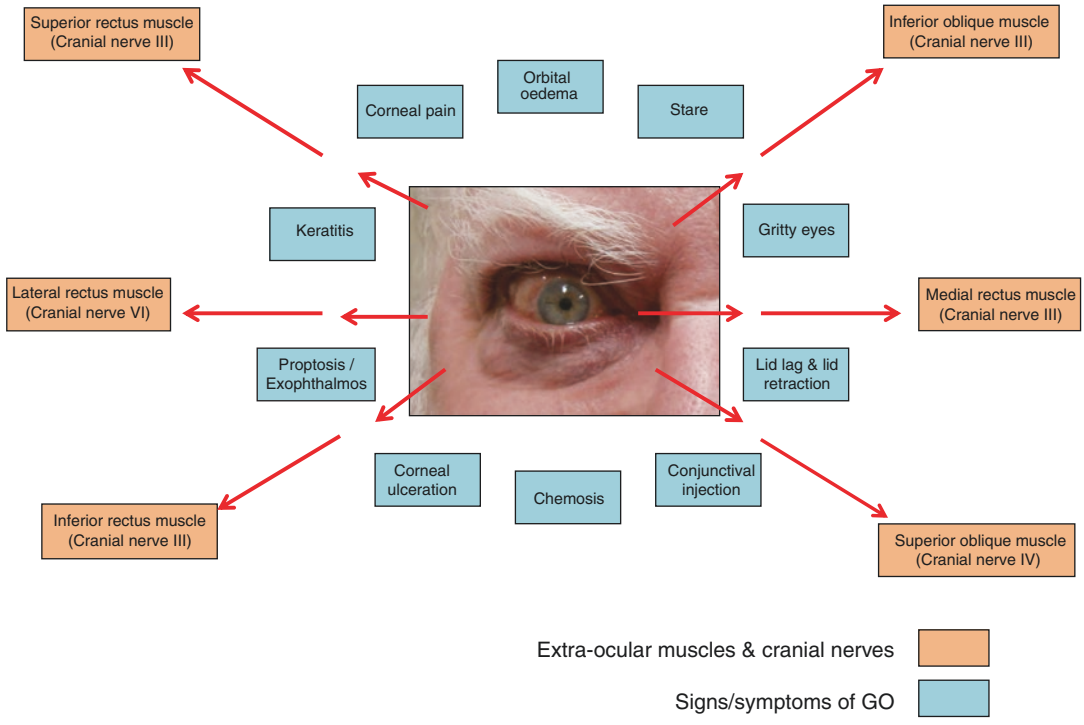


Fig. 31.3 Photo illustration of Graves' Ophthalmopathy and eye muscles at risk. Eye picture provided by Dr. R. Ford from private collection, Illustration by Violet Fazal-Sanderson

anatomy and how thyroid eye disease (TED) presents. Spotting eye signs and symptoms early enables prompt referral to an ophthalmologist who specialises in thyroid eye disease so that early treatment can help prevent the development of distressing or disabling eye problems.

Symptoms and signs of thyroid eye disease can occur in almost any order, and it is worth remembering that one eye may be affected first or more severely than the other, and up to 10% of patients may only ever develop thyroid eye disease in one eye. Those with unilateral signs need early investigation such as scans to ensure that they do not have a serious alternate diagnosis such as an orbital tumour.

31.6.1 Ocular Surface Signs and Symptoms

- **Red eyes**: this can be the earliest sign of active thyroid eye disease, and early disease is often mistaken for conjunctivitis. This is why it is especially important for endocrinologists and endocrine nurse specialists to be aware of TED, since early referral of thyroid patients with eye symptoms to an ophthalmologist can facilitate early diagnosis and treatment, potentially reducing the burden of disease on the patients. Redness in more than one quadrant and redness in the upper quadrant (under the eyelid) are particularly significant as signs of active disease.
- **Dry, sore eyes or watery eyes**: Any can occur or two of these symptoms may alternate or coexist.
- **Chemosis**: This may develop which is oedema beneath the conjunctiva leading to a puffy, jelly-like look to the white of the eye. The caruncle (the pink fleshy part at the inner corner of the eye) may become inflamed, redder, and enlarged.

31.6.2 Eyelid Signs and Symptoms

- **Red and puffy eyelids**: This often occurs in active disease. The redness should resolve with reduced disease activity, but expansion of tissue matrix can lead to permanently swollen or thickened-looking lids even once the disease has burned out.
- **Upper lid retraction**: This is usually due to overstimulation of the sympathetic nervous system when people are hyperthyroid ('fight-or-flight' type stimulation), but is often due to involvement of the levator palpebrae (eyelid-lifting) muscle in the disease process. This gives the eyes a 'starey' appearance, and patients may be unable to close their eyes (lagophthalmos), leading to sore red eyes and even reduced vision from corneal exposure.

31.6.3 Ocular Motility Signs and Symptoms

- **Double vision**: or diplopia in TED occurs as a result of the impairment of the movements of the extraocular muscles, which can become stiffened or restricted in movement.
- **Painful eye movements**: Eye movements may be painful or feel strained. Scans of the orbit often show enlarged extraocular muscles in TED. Any muscle can be affected, but the inferior rectus and medial rectus are often first to become involved, and restriction of upgaze is common in TED as fibrosis of the inferior rectus tethers the eye down when the affected individual tries to look up. However, virtually any pattern of eye movement abnormality can result from TED. Strabismus surgery may help those with underlying diplopia, though this should not be attempted until the orthoptic measurements (size and type of squint) are stable for 6 months. Those with highly variable orthoptic measurements should be tested for myasthenia gravis, an autoimmune condition of the neuro-muscular junction that may be present in up to 5% of those with TED.

31.6.4 Orbital Signs and Symptoms

- **Eyes bulging forwards**: forwards bulging of the eyes (proptosis) is a common finding in TED and occurs due to the increased volume

of tissues inside the orbit. The orbit is contained within solid bony walls, so the only direction in which tissues can move in response to pressure of expanded orbital contents is forwards. Proptosis can be measured with a device called an exophthalmometer.

- **Orbital pressure**: Tissue expansion can also lead to increased pressure within the orbit, causing pain and aching sensations often felt behind the eyes. The intraocular pressure can go up and a minority of patients can develop glaucoma if untreated.

31.6.5 Visual Dysfunction in Thyroid Eye Disease

The vision may be adversely affected in a number of ways in TED.

- **Blurring**: Intermittent blurring is usually caused by ocular surface problems from tear film insufficiency
- **Diplopia**: this can make focusing difficult.
- Proptosis and lid retraction can lead to lagophthalmos and corneal exposure, which can cause serious breakdown of the cornea with ulcers and infections that may need urgent treatment.
- **Optic nerve compression**: Pressure on the optic nerve is perhaps most serious, though fortunately rare, where the pressure within the orbit can become high enough to compress the optic nerve and its vasculature, leading to potentially irreversible visual loss if not treated urgently. Optic nerve involvement (dysthyroid optic neuropathy) may start with subtle signs such as reduced colour vision or red desaturation (red colours looking 'washed out'), so colour vision is typically tested at every eye clinic visit for thyroid eye disease patients. The pupils are also examined for a relative afferent pupillary defect and the optic disc examined for papilloedema. If you suspect dysthyroid optic neuropathy, contact an orbital specialist urgently since early treatment can save vision.

31.7 Grading Thyroid Eye Disease

There are several grading systems in current usage to assess disease activity and severity in TED. The most commonly used grading of disease activity in Europe is the Clinical Activity Score based on that of Mourits, as standardised by the European Group on Graves' Ophthalmopathy (EUGOGO) (Table 31.1).

Other scores in common use include the 'VISA' score, an activity score common in the USA, and the 'NOSPECS' grading, which assesses disease severity rather than activity.

31.8 Investigation of Thyroid Eye Disease

There is no single investigation to diagnose or monitor thyroid eye disease, and the diagnosis is often made clinically; however, the following may be included:

- **An MRI or CT scan**: of the orbits help to confirm the diagnosis by looking at the shape and size of the extraocular muscles. MRI, especially the 'STIR' sequence protocol, examines soft tissue in detail and can help to assess disease activity by revealing the water content of the muscles. CT scans assess the bone structure of the orbit and are useful in

Table 31.1 EUGOGO clinical activity score

Score 1 for each of these 10 findings	
1	Spontaneous orbital pain
2	Gaze-evoked orbital pain
3	Eyelid swelling considered to be due to active TED
4	Eyelid erythema
5	Conjunctival redness considered to be due to active TED
6	Chemosis
7	Inflammation of caruncle OR plica
8	Increase of >2 mm in proptosis
9	Decrease in uniocular ocular excursion in any one direction of >8°
10	Decrease of acuity equivalent to 1 Snellen line or more

NB: Points 1–7 can be measured at the first visit to produce an initial score out of 7; at follow-up visits, all elements can be measured to give a score out of 10

planning bony orbital decompression surgery.

- **Blood tests** such as TSH, T4, and T3 are reviewed in conjunction with the endocrinologists to monitor thyroid function.
- **Auto-antibodies** such as anti-TSH receptor and anti-TPO antibodies can help to reach a diagnosis, and some clinicians believe these may help to monitor disease progress.
- **Other blood** tests may be needed as part of planning and monitoring of immunosuppressive therapy.
- **Orthoptic testing** is essential to assess and objectively monitor ocular motility. Hess charts and field of binocular single vision testing help to quantify eye movements and diplopia.
- **Electro diagnostic tests**: visual-evoked potentials that measure conduction in the optic nerve may sometimes be useful in defining whether visual problems in TED are due to dysthyroid optic neuropathy.

31.9 Treatment of Thyroid Eye Disease

31.9.1 Early and Supportive Treatment

Smoking cessation and thyroid function: Early in the disease process, supportive treatment must include smoking cessation advice and efforts to stabilize thyroid function.

Eye lubricants: Many patients have ocular surface problems and may benefit greatly from provision of tear supplement drops, and those with nocturnal lagophthalmos will benefit particularly from thicker ointment-type lubricants at night. Some will find cold compresses helpful, and raising the head of the bed may reduce the build up of oedema overnight if puffy eyes are problematic on waking.

Selenium: There has recently been some investigation of selenium supplementation for thyroid eye disease. Some studies suggest that thyroid eye disease is more common in those with a relative deficiency of the mineral selenium, and that selenium at a dose of 100 mcg bd may help prevent early disease becoming more severe. Therefore, in the absence of contraindications, patients with early thyroid eye disease may wish to take selenium supplements for 6 months; the level of evidence that this helps is relatively low, but it is unlikely to cause any harm and so many patients and doctors consider it worth trying. Selenium is also present in nuts such as Brazil nuts for those who would prefer to avoid more pills, though this would provide a less consistent dose.

Dark glasses: Patients with photophobia (light sensitivity) may find that dark glasses help, and glasses in general may keep wind out of the eyes and reduce tearing.

Fresnel prisms: For those with double vision, particularly if it affects straight ahead gaze, it may be possible for an orthoptist to fit Fresnel prisms to a pair of spectacles. These stick-on prisms refract the light to compensate for misalignment between the two eyes.

31.9.2 Management of Hyperthyroidism

The therapy chosen to control the hyperthyroidism may have some impact on TED. Firstly, **Normalising thyroid function**: It is important to normalize thyroid function without causing a rapid dip into hypothyroidism. This has led many endocrinologists with an interest in TED to recommend 'block and replace' regimens for Graves with TED; an anti-thyroid drug such as carbimazole is used in a high enough dose to 'block' all the patient's thyroid hormone production, with levothyroxine prescribed alongside from the start to avoid hypothyroidism.

Radioiodine restriction in TED: Radioactive iodine (RAI) therapy can trigger the development or worsening of thyroid eye disease. Around 20% of those treated with RAI develop worsening eye problems compared to 5% of those treated with anti-thyroid drugs, and 7% of those treated with RAI develop severe TED. These figures seem to be higher in smokers. A course of concurrent oral prednisolone

started at the time of the RAI much reduces this risk, so a sensible precaution would be to give oral steroid cover for RAI in patients with mild eye signs and consider it in smokers, and to try to avoid RAI wherever possible in those with active or severe eye disease.

Thyroidectomy does not appear to affect thyroid eye disease much, although there is some relatively low-grade evidence that it may be beneficial in controlling TED provided patients are not allowed to become hypothyroid.

31.9.3 Medical Treatment

Medical treatment for thyroid eye disease is based on the strategies of reducing inflammation and suppressing the immune system to treat the underlying autoimmune condition. Many different drugs and regimes have been tried, and thyroid eye disease specialists are far from reaching agreement about the ideal therapy. Patients also have different comorbidities, disease patterns, and needs, so treatments must be selected on an individual basis.

31.9.3.1 Steroid Treatment

Steroid treatment is currently a mainstay of treatment in the active phase. There is some evidence that intravenous therapy is at least as effective as oral, while producing fewer serious side effects. All steroid treatments carry the following risk and require monitoring:

- blood sugar
- hypertension
- gastric ulceration
- mood disturbance
- weight gain
- induction of diabetes
- osteoporosis

Most clinicians aim to keep steroid treatment duration short for TED so that the risks are minimised. A typical protocol would be that recommended by EUGOGO, suggested for patients with active disease and no contraindications to steroid treatments, having a Clinical Activity Score of 4 or more. This regimen is as follows:

- *500 mg intravenous methylprednisolone* given once weekly for 6 weeks, followed by, *250 mg weekly for a further 6 weeks*.

This may be enough to render the disease inactive in some cases, but bearing in mind that the active phase of the disease may last around 24 months, further therapy is often needed.

31.9.3.2 Immunomodulatory Agents

These can be used to supplement or replace steroid treatment. These drugs work by suppressing the immune system, and hence, the autoimmune activity of the disease. All of these drugs have potential side effects, including increased susceptibility to some infections. However, with proper monitoring they can be safer and more effective in longer term control of inflammation and progress of TED than steroids. No single drug is totally effective for TED, and research studies are ongoing to try to establish which drugs are more effective and how they should be combined with other treatments. Drugs in current use include azathioprine, mycophenolate, ciclosporin, and methotrexate. They would generally be used only for those with more severe or active disease and are continued for a year to 18 months in most cases if tolerated. Active monitoring with blood tests is essential.

31.9.3.3 Orbital Radiotherapy

Orbital radiotherapy has been in use for TED for decades and seems to improve inflammation in some cases. It is not highly effective and is rarely used alone, but usually as a supplementary treatment with steroids or other agents. There is some evidence, though relatively weak, that it may be more effective in patients with extraocular muscle involvement. If radiotherapy is used for TED, it is usually fractionated over 10 days of treatment. Patients should expect to have an initial assessment and fitting for a mask that protects the face outside the treatment area. The treatments

themselves are very short. Side effects are usually minimal, but for some people the inflammatory signs may become temporarily worse before improving, and patients should be warned that there is a theoretical increased risk of tumours in the treated tissues in future (though this has never been demonstrated in reality in patients having the relatively low-dose radiotherapy used for TED).

31.9.3.4 New Drugs in the 'Biologic' Group Are Under Investigation in TED

Biologics are monoclonal antibodies directed against substances involved in the disease to be treated. The most prevalent biologic to be tried in TED so far has been rituximab, which is directed against the CD20 marker on lymphocytes and was originally developed for lymphoma. Use of rituximab results in a long period of B-cell depletion and immunosuppression and knock-on effects on T cell activity, which may be effective for TED if given early enough in the active phase, although studies with this agent have provided conflicting results. TED is not a common enough disease to attract large investment in research funding, so biologic therapies trialled for TED have usually been developed to treat other conditions such as arthritis rather than being designed for TED. There are a few other drugs under investigation, including teprotumumab, an IGF-IR inhibitor, which is showing promise in early studies, though none of these drugs are available in general usage yet.

31.9.4 Surgical Treatment

Surgery for TED can be broadly categorised into orbital decompression, strabismus surgery, and lid surgery. Many patients do not need any surgery, especially if treated early with appropriate medical treatment, but for those left with functional or appearance-related problems once the disease has become inactive, surgery can be a critical part of rehabilitation. Urgent orbital decompression surgery may also be needed to treat dysthyroid optic neuropathy (optic nerve compression).

One surgery can affect the next by affecting the position, pressure, or blood supply to tissues. Hence, the order of surgery is important—any orbital decompression needed should be done first, then strabismus then lid surgery, although many patients do not need all three of these steps. Some researchers are looking into whether it is possible to combine some of these steps.

Orbital Decompression Surgery: This is usually performed to correct proptosis (bulging eyes), but may also be indicated for optic nerve compression or sometimes for other symptoms of raised pressure within the orbit. Other than emergency cases, most surgeons will not recommend this operation until the disease process is inactive. In some cases, orbital congestion and persistently raised intraorbital pressure can mimic active disease (this may be termed 'hydraulic' or 'congestive' disease) and decompression may also help. The surgery aims to make more room for the important orbital structures, either by removing fat to decrease the volume of the orbital contents, or by removing bone from the walls of the orbits to make more space for the tissues, or a combination of the two. The more walls of the orbit that are removed or reduced, the more proptosis is corrected. The exact choice of surgery will depend on the patient's individual situation. Orbital decompression carries a small risk to the vision, as well as a chance of worsening double vision and numbness beneath the eye area if the orbital floor is to be removed. Most patients will stay in hospital overnight and need at least 2 weeks off work.

Strabismus (squint) surgery: is performed for double vision. Eye movement muscles are detached from the sclera of the eyeball and their position is adjusted to change the alignment of the eye. This is usually done under general anaesthetic, but most patients can go home the same day. It is usually safe surgery, with minimal risk to vision, but it is not always possible to correct all double vision in thyroid eye disease and most squint surgery is performed for those who have double vision all the time in straight ahead gaze.

Eyelid surgery: may be done to reduce swelling or excess tissue once the disease is inactive (blepharoplasty). It may also be necessary to surgically lower eyelids that have become retracted. These procedures are often done under local anaesthetic, partly so that the surgeon can check the height and appearance of the lid as the patient looks around with eyes open. They are not always successful, and some patients who have lid lowering will develop an overcorrection (ptosis or drooping of the lid) at some stage and require further surgery, but for many patients this is the final step in achieving a more normal appearance. It is important not to raise expectations too highly, as most patients with TED severe enough to require surgery will not end up looking the same as they did before the disease hit, but the aim is to achieve an acceptable appearance without obvious signs of the disease process. For UK patients in some areas, at the time of writing, lid procedures may unfortunately not be routinely funded on the NHS.

31.10 Multidisciplinary Management of TED

People with thyroid eye disease are often under the care of multiple clinicians, such as an endocrinologist, an oculoplastic surgeon, a GP, and sometimes a thyroid surgeon, an orthoptist, a strabismus specialist, and possibly a radiotherapist (for orbital radiotherapy). Input from scans may be needed from a radiologist, and some centres may have nurse specialists in various roles. It is important that all these professionals work well together, communicate well, and provide consistent information and planning for patients to prevent confusion or conflict. Evidence is growing that working in multidisciplinary teams, such as those based around joint endocrine-oculoplastic clinics, leads to better patient outcomes. Other clinicians should have a low threshold for referral of patients with signs of TED to a specialist MDT clinic, as these are now available in larger centres in most of the UK. The Endocrine Nurse plays a key role as delineated in Box 31.1 below.

Box 31.1 Nursing Recommendations for Graves' Ophthalmopathy Prior to an Ophthalmology Referral

Explanation
- Complications of eye disease
- Importance of ophthalmology referral
- Early referral for effective management of GO

Aim to stabilise thyroid function (TSH, fT4, and fT3)
- In patient with Graves' hyperthyroidism: anti-thyroid medication such as CBZ or equivalent is usually effective; eye disease is a relative contraindication to radioiodine treatment.

Gritty eye and proptosis
- Lubricant eye drops (as per local hospital policy) are useful. Hypromellose is cheap and available over the counter; it may be sufficient for mild to moderate cases. Preservative-free lubricants such as hyaluronate preparations are preferred by many patients and ophthalmologists.
- Sufficient fluids in severely hyperthyroid patients: Frequency of bowel movement and excessive flushing can cause dehydration and thus contribute to dry eyes.
- Dark glasses (sunglasses): Patients with proptosis and corneal dryness may be affected by photophobia.
- Night-time eye ointment according to local hospital policy to prevent corneal exposure
- Cold compresses and raising the head of the bed can help reduce the build up of oedema overnight if puffy eyes are problematic on waking.

Smokers to abstain from smoking

- Smokers have an increased risk for developing TED, and the disease tends to be more severe in those who smoke.
- Leaflets that explain the relevance of *STOPPING SMOKING* should be available to smokers.
- Nicotine patches and referral to smoking cessation services may be an option as per local hospital policy guidelines.

Once referred to the ophthalmologist, a formal assessment will determine the severity of GO. Treatment is aimed at protecting the cornea and relieving symptoms such as photophobia and diplopia in those with active TED (BTA 2015; BTA 2006; NICE 2016).

31.11 Psychological Aspects of Thyroid Eye Disease

A large proportion of people with thyroid eye disease will suffer with psychological distress related to the disease. This is a chronic condition, and many patients will have emotional and psychological symptoms related to hyperthyroidism or fluctuating thyroid hormone levels as they start treatment. They then have to contend with changes in eye and facial appearance that may have far-reaching effects on their self-image, confidence, and relationships with others. Added to this, treatments may have significant side effects, such as steroids causing mood swings, sleep disturbance, and weight loss. Patients may also have functional concerns, such as diplopia or blurred vision affecting driving and reading, which can be enough to stop some people from working and hence contribute to financial worries. Patients with thyroid eye disease, therefore, need attention to their psychological well-being. This is not always easy in a busy clinic setting, but nurse specialists may be particularly well-placed to gently enquire about how a person is coping with their TED. For some patients, it may be enough just to reassure them that their feelings are normal and shared by many others going through the trials of TED. People who placed a high value on their personal appearance before their illness are most at risk from psychological distress related to changes in appearance, and those whose work is affected (either by visual problems or by loss of confidence in facing other people) are another high-risk group. External help may be available for those who are worst affected, such as referral to a psychologist, and others may find benefit from things like patient support groups and meetings, online fora, and online information such as that from Thyroid Eye Disease Charitable Trust (http://www.tedct.org.uk).

31.12 The Future of Thyroid Eye Disease

Research in TED is progressing in a number of areas. The ultimate goal would be to identify the causes and triggers for TED and try to prevent its occurrence. Until that is possible, important areas for development include improving early diagnosis and specialist referral for TED, to allow all patients access to appropriate treatment as soon as possible. This may be achieved by simple methods like education of endocrinologists, general practitioners, and optometrists in how to spot early TED, development of more specialist clinics, and possibly more sophisticated methods like improved diagnostic testing enabling us to predict which patients may become severely affected. Medical therapy is improving all the time, and the aim is to find one or more drugs, possibly from the new biologics category, that can stop TED in its tracks, preventing disease progression and need for surgical interventions. For those whose disease has already left them with problems, improvements in surgical techniques are gradually making the reconstructive surgery safer and less invasive.

31.13 Conclusions

Thyroid eye disease is a complex condition, for which patients require both expert medical care and plenty of psychological and emotional support. Endocrine nurse specialists with a knowledge of thyroid eye disease can be instrumental in spotting the condition early and promoting early specialist referral, as well as being important in long-term care of patients by supplying accurate clinical information and advice, smoking cessation advice, facilitating medical treatment, and providing psychological support.

References

British Thyroid Association (BTA). UK guidelines for the use of thyroid function tests: thyrotoxicosis (online). BTA. 2006. http://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf. Accessed 22 Apr 2018.

British Thyroid Foundation. Thyroid eye disease (online). BTF. 2015. http://www.btf-thyroid.org/information/leaflets/36-thyroid-eye-disease-guide. Accessed 22 Apr 2018.

Hogan-Quigley B, Palm ML, Bickley L. Bates' Nursing guide to Physical Examination and History taking. London: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

Khong JJ, McNab AA, Ebeling PR, et al. Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. Br J Ophthalmol. 2016;100:142–50.

National Institute for Health and Care Excellence (NICE). Hyperthyroidism (online). NICE. 2016. https://cks.nice.org.uk/hyperthyroidism#!management. Accessed 22 Apr 2018.

Perros P, Dayan CM, Dickinson AJ, et al. Management of patients with Graves' orbitopathy: initial assessment, management outside specialised centres and referral pathways. Clin Med. 2015;15(2):173–8. https://doi.org/10.7861/clinmedicine.15-2-173.

Perros P, Hegedus L, Bartelena L, Weirsinga WM, et al. Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. Orphanet J Rare Dis. 2017;12:72. https://doi.org/10.1186/s13023-017-0625-1.

Thyroid Eye Disease Charitable Trust. An introduction to thyroid eye disease (online). TEDct. 2017. http://tedct.org.uk/thyroid-eye-disease. Accessed 22 Aug 2017.

Verity D, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. Eye. 2013;27:308–19.

Weiler DL. Thyroid eye disease: a review. Clin Exp Optom. 2017;100:20–5. https://doi.org/10.1111/cxo.12472.

Wiersinga WM. Graves' ophthalmopathy and dermopathy-3.3.10. In: JAH W, Stewart PM, Amiel SA, Davies MJ, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press; 2011.

Key Reading

1. Verity DH, Rose GE. Acute thyroid eye disease (TED): Principles of medical and surgical management. Eye. 2013;27:308–19.
2. Bartelena L, Baldeschi L, et al. on behalf of EUGOGO: The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9–26.

Disorders of the Thyroid in Childhood and Adolescence

32

Suma Uday, Christine Davies, and Helena Gleeson

Contents

32.1 **Introduction** 611

32.2 **Hypothyroidism** 612
32.2.1 Congenital Hypothyroidism (CHT) 612
32.2.2 Autoimmune Hypothyroidism 617
32.2.3 Secondary or Central Hypothyroidism 619

32.3 **Hyperthyroidism** 620
32.3.1 Neonatal Thyrotoxicosis 620
32.3.2 Graves' Hyperthyroidism 621

32.4 **Thyroid Nodules and Cancers** 624
32.4.1 Thyroid Nodules 624
32.4.2 Thyroid Cancers 625

32.5 **Conclusions** 627

References 627

Abstract

Disorders of the thyroid are one of the most common endocrinopathies in childhood and adolescence. The thyroid hormone is not only essential for metabolism and organ function but also plays a key role in the regulation of myelination of the nervous system. It is therefore crucial for normal growth and development in children. Thyroid hormone release is regulated by the hypothalamus and the pituitary gland. Therefore problems in thyroid hormones can occur as a result of disruption in the hypothalamo-pituitary-thyroid axis at any level.

Problems with the thyroid axis usually manifest as an underactive (hypothyroidism) or an overactive (hyperthyroidism) gland. The

S. Uday
Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham, UK
e-mail: suma.uday@nhs.net

C. Davies (✉)
Department of Advanced and Integrated Practice, Children's Hospital for Wales, Cardiff and Vale UHB University Hospital of Wales (UHW), Cardiff, UK
e-mail: Christine.Davies8@wales.nhs.uk

H. Gleeson
Department of Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
e-mail: Helena.Gleeson@uhb.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_32

most common cause of an underactive thyroid in children is congenital hypothyroidism (CHT) followed by autoimmune hypothyroidism or Hashimoto's thyroiditis (HT), the incidence of which peaks in adolescence. Introduction of the newborn screening test for CHT has facilitated early diagnosis and treatment of CHT improving outcome related to intellectual disability. Other rare causes of hypothyroidism include TSH deficiency in cases of secondary hypothyroidism which can be part of multiple pituitary hormone deficiency or rarely isolated. Hypothyroidism can also occur following surgical removal of the gland for Graves' disease or damage following radiotherapy for cancer treatment.

The most common cause of hyperthyroidism is Graves' disease which is treated with anti-thyroid drugs (ATDs) in a block and replace or dose titration regimen. The right approach is heavily debated in the medical field. ATD treatment is followed by definitive treatment with surgery or radioactive iodine if the patient relapses after stopping ATD. Another rare but serious cause of hyperthyroidism which carries a significant mortality rate if undiagnosed is neonatal thyrotoxicosis (NT). NT occurs in babies born to mothers with Graves' disease or HT. This is a transient condition which may require treatment with ATDs. Hyperthyroidism can result from thyroid nodules such as toxic adenoma or multinodular goitre or rarely following radiotherapy and in McCune Albright syndrome.

Thyroid nodules can present as underactive or overactive thyroid but most frequently are not associated with thyroid dysfunction. Careful evaluation of nodules is critical due to the higher risk of these being cancerous in children compared with adults. Thyroid cancers can occur independently or as part of multiple endocrine neoplasias or familial neoplasias. Papillary thyroid carcinoma is the most common form of paediatric thyroid cancer. Other rare forms include follicular thyroid carcinoma and medullary thyroid carcinoma. It is important to consider the occurrence of thyroid cancers as part of multiple endocrine neoplasias.

Thyroid disorders are a common endocrinopathy in children and adolescents. Good clinical history and family history are vital in diagnosis, surveillance and planning follow-up in these patients.

Keywords
Thyroid · Hypothyroidism · Thyrotoxicosis · Thyroid nodule · Thyroid cancer

Abbreviations

ATDs	Anti-thyroid drugs
BR	Block and replace
CBZ	Carbimazole
CH	Central hypothyroidism
CHT	Congenital hypothyroidism
DBS	Dried blood spot
DT	Dose titration
ESPE	European Society for Paediatric Endocrinology
FTC	Follicular thyroid carcinoma
GD	Graves' disease
HT	Hashimoto's thyroiditis
L-T4	Levothyroxine
MTC	Medullary thyroid carcinoma
NT	Neonatal thyrotoxicosis
PTC	Papillary thyroid carcinoma
PTU	Propylthiouracil
SOD	Septo-optic dysplasia
T3	Tri-iodothyronine
T4	Tetra-iodothyronine or thyroxine
TFTs	Thyroid function tests
TPO	Thyroid peroxidase
TRAb	Thyroid receptor antibody
TRH	Thyrotrophin releasing hormone or TSH releasing hormone
TSH	Thyroid stimulating hormone
USS	Ultrasound scan

Key Terms

- **Congenital hypothyroidism:** low or inadequate thyroid at birth secondary to an genetic abnormality or error of thyroid metabolism or iodine deficiency
- **Hashimoto's thyroiditis:** an autoimmune form of hypothyroidism

- **Neonatal thyrotoxicosis:** is a rare condition in newborns of mothers with a history of Hashimoto's thyroiditis or Grave's disease
- **Thyroid nodules:** mostly benign masses in the thyroid
- **Multinodular goiter:** multiple benign masses in the thyroid
- **Thyroidectomy:** surgical removal of the thyroid gland
- **Thyroid ablation:** destruction of the thyroid tissue using radioactive iodine or radiofrequency treatment

Key Points

- Thyroid hormone is essential for regulation of growth, myelination of the nervous system, metabolism, and organ function.
- Congenital hypothyroidism is the most common condition of the thyroid affecting 1 in 3000 newborn children. It is diagnosed on a newborn blood spot screening test.
- Hashimoto's thyroiditis is the most common cause of autoimmune hypothyroidism in childhood, most common age at presentation is adolescence.
- The most common cause of thyrotoxicosis in children, adolescents, and adults is Graves' disease. Initial treatment is with anti-thyroid drugs with up to 60% requiring definitive treatment with surgery or radioactive iodine due to relapse after stopping anti-thyroid drugs.
- Neonatal thyrotoxicosis is a condition affecting babies born to mothers with Graves' disease or Hashimoto's thyroiditis. It is a rare but serious condition requiring close monitoring of the neonate due to a high mortality rate associated with it.
- Thyroid nodules in children and adolescents are more likely to be malignant and therefore careful evaluation is required.

32.1 Introduction

The thyroid is a butterfly-shaped gland located in the neck in front of the trachea just below the larynx. It comprises two lobes, which are attached by a band of thyroid tissue called the isthmus. Embryologically, the thyroid gland develops from the primitive pharynx and neural crest. Initially, the gland is located at the back of the tongue and during foetal development, migrates to the front of the neck before birth.

The thyroid gland produces two key hormones: tetra-iodothyronine or thyroxine (T4) and tri-iodothyronine (T3) which play a crucial role in the regulation of growth, myelination of the nervous system, metabolism, and organ function.

The thyroid gland uses iodine as its main source to synthesise thyroid hormones. Iodine deficiency can lead to thyroid problems such as underactive gland and enlarged gland (goitre) and is a common problem worldwide. Both T4 and T3 are produced by combining the iodine with the amino acid tyrosine. T4 is the predominant hormone (80%) which is then converted into T3, the more active hormone, in peripheral tissues. Thyroid hormone levels in the blood are regulated by the pituitary gland which is in turn regulated by the hypothalamus; both of which are situated centrally in the nervous system (see Fig. 32.1). Most hormonal axes are based on the negative feedback loop system. Low levels of circulating thyroid hormones stimulate the hypothalamus to release thyrotrophin releasing hormone (TRH) which in turn stimulates the pituitary gland to produce the thyroid stimulating hormone (TSH) which results in increased production of T4 and T3. Similarly high levels of circulating hormones feedback to the hypothalamus to suppress TRH and in turn TSH production.

Thyroid hormone levels vary widely during childhood (see Fig. 32.2). TSH and free T4 values decreased continuously with age, particularly during the first year of life with variance being greatest in the first month of life (Kapelari et al. 2008).

Hyperthyrotropinemia, i.e. raised TSH levels in the context of normal free T4 levels, has been noted in obese individuals. However, it has been heavily debated whether the raised TSH is the cause or effect of obesity.

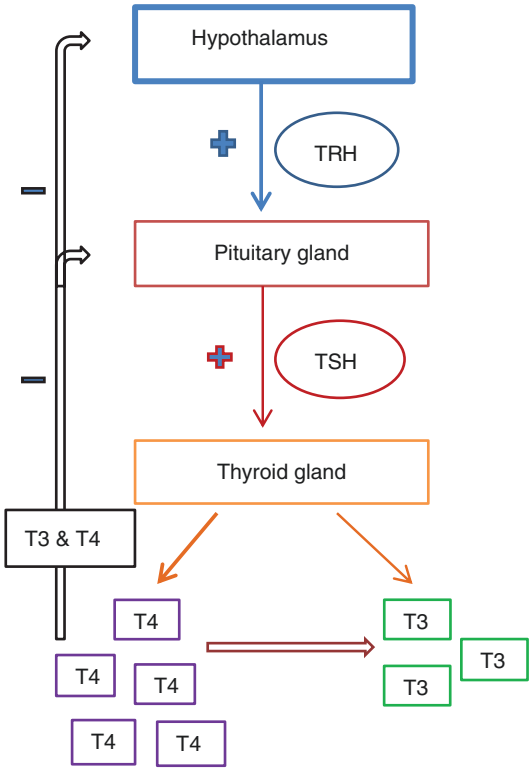


Fig. 32.1 Illustrates the hypothalamo-pituitary-thyroid axis. In response to low circulating levels of thyroid hormone tri-iodothyronine (T3) and tetra-iodothyronine (T4), the hypothalamus releases thyrotrophin-releasing hormone (TRH). The TRH stimulates the pituitary to produce thyroid-stimulating hormone (TSH) which in turn stimulates the thyroid to produce thyroid hormones. In the presence of high circulating levels of thyroid hormones, the T3 and T4 exert negative feedback control over the hypothalamus as well as anterior pituitary, thus controlling the release of both TRH and TSH

Disorders affecting the thyroid gland are common in childhood and adolescence. Early diagnosis and treatment are essential to prevent irreversible and permanent nervous system damage and developmental delay, especially in infants. Problems affecting the thyroid gland often manifest as an underactive gland (hypothyroidism) or an overactive gland (hyperthyroidism) with or without a swelling of the gland (goitre). Conditions affecting the thyroid gland are listed in the table below (Table 32.1).

We now discuss in detail some of the selected common endocrinopathies relating to thyroid dysfunction in children and adolescents using case studies.

32.2 Hypothyroidism

32.2.1 Congenital Hypothyroidism (CHT)

32.2.1.1 Introduction

CHT is a partial or complete loss of function of the thyroid gland (hypothyroidism) that affects infants from birth (congenital). The prevalence of CHT is 1 in 3000 live births.

32.2.1.2 Aetiology

The causes include:

1. Dygenesis (thyroid gland is absent, underdeveloped, or abnormally located)—80%
2. Dyshormonogenesis (abnormal biosynthesis of thyroid hormone)—20%

Commonest cause worldwide is maternal iodine deficiency, which is an essential element in the production of thyroid hormones.

A genetic cause may be present in 15–20% of the cases. Although the cause of thyroid dysgenesis remains unidentified in majority of the cases, 2–5% are said to be due to PAX8 and TSHR gene mutations. Thyroid dyshormonogenesis can occur due to mutation in one of the following genes: DUOX2, SLC5A5, TG, TSHB, and TPO (http://ghr.nlm.nih.gov/condition/congenital-hypothyroidism). Majority of the mutations are sporadic (new); however, a few children inherit it from their parents.

A very small percentage of patients have secondary hypothyroidism where the problem is in the hypothalamus or the pituitary (discussed later).

32.2.1.3 Diagnosis

CHT is diagnosed on dried blood spot (DBS) testing in the newborn. This is employed in all developed countries where blood is collected from a heel prick on all babies around day 5 of life. The diagnosis is mostly made on a raised TSH. The screening is aimed at identifying the more severe forms of primary CHT as early initiation of treatment (<3 months of age) minimises intellectual disability in children with CHT. In the UK, the aim is to start treatment within 21 days of birth. The flowchart (see Fig. 32.3) illustrates the screening and referral criteria and pathway.

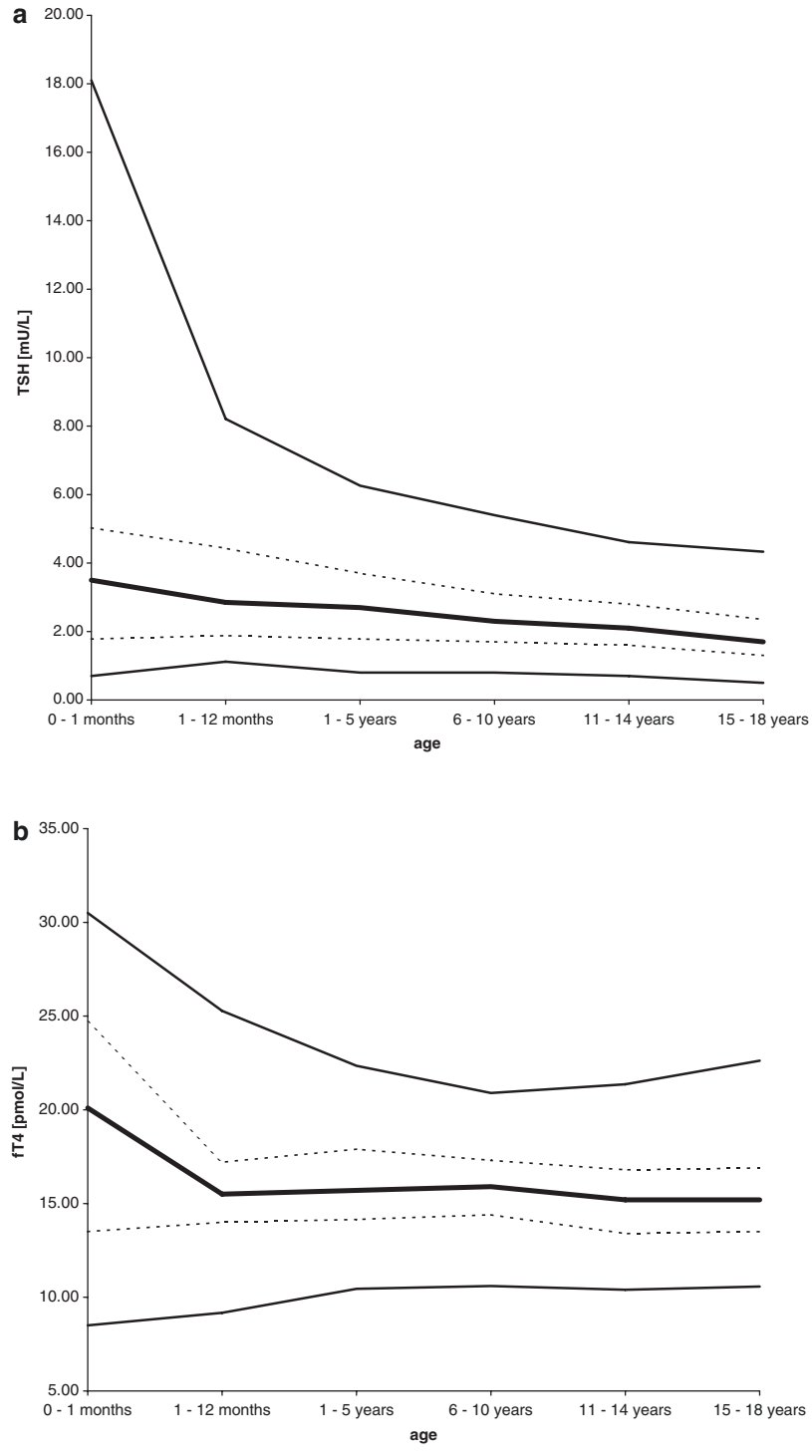


Fig. 32.2 Adopted from Kapelari et al. (2008): Age-related reference intervals for TSH (**a**) and free T4 (**b**). The central 95% range (2.5th, 25th, 50th, 75th, and 97.5th percentiles) are shown

Table 32.1 Conditions affecting the thyroid gland and hormones in the neonatal period, childhood and adolescence are listed below

	Hypothyroidism	Hyperthyroidism
Neonatal period	Congenital hypothyroidism	Neonatal thyrotoxicosis secondary to • Maternal Graves' disease • Maternal Hashimoto's thyroiditis
Childhood and adolescence	• Hashimoto's thyroiditis • Subacute thyroiditis • Following surgical removal of thyroid gland for Graves' disease or for thyroid nodule • Radiation damage to the thyroid gland following cancer treatment	• Graves' disease • Subacute thyroiditis • Hyperfunctioning thyroid nodule (toxic adenoma, toxic multinodular goitre) • McCune Albright syndrome
Rare	• TSH receptor defect causing congenital hypothyroidism • Congenital secondary hypothyroidism due to genetic mutations causing abnormal pituitary gland development	• Thyroid hormone ingestion (factitious or induced) • TSH hypersecretion secondary to pituitary tumours • Pituitary resistance to thyroid hormone • Activating mutation of the TSH receptor • Iodine induced hyperthyroidism

A second test should be considered in pre-term neonates, babies with very low birth weight and in babies who were ill at the time of first sample collection as TSH is known to be elevated.

Neonates may exhibit any of the symptoms and signs of CHT illustrated in the table below (Table 32.2) or may be asymptomatic and detected purely by a raised TSH on screening. A raised TSH on DBS should be confirmed on venous thyroid function tests at referral, prior to initiation of treatment.

The European Society for Paediatric Endocrinology (ESPE) consensus guidelines for CHT (Léger et al. 2014) suggest the following biochemical diagnostic criteria for initiation of treatment:

(a) If DBS reveals TSH of 40 mU/L, await serum results for 1–2 days before initiating treatment.
(b) Start treatment immediately if serum free thyroxine (FT4) concentration is below the normal range for age, regardless of TSH concentration.
(c) Start treatment if venous TSH concentration is persistently greater than 20 mU/L, even if serum FT4 concentration is normal.
(d) If TSH concentration is between 6 and 20 mU/L in a well-baby with normal FT4, consider diagnostic imaging to establish a definitive diagnosis.
(e) If TSH concentration remains high for more than 3–4 weeks, consider starting levothyroxine (L-T4) supplementation immediately (in discussion with the family) and retesting, off treatment, at a later stage; or retesting 2 weeks later without treatment.

32.2.1.4 Investigations

Thyroid ultrasound scan (USS) and scintigraphy are the recommended investigations for CHT. Often clinicians choose one of the two investigations; however, both should be considered in those with raised TSH to improve diagnostic accuracy.

An x-ray of the knee may be carried out to assess the severity of intrauterine hypothyroidism by the presence or absence of femoral and tibial epiphyses.

Treatment should not be delayed and can be initiated pending investigations.

Thyroid USS does not detect ectopic thyroid tissue and is user dependent. Thyroid scintigraphy can identify athyreosis (absence of uptake), hypoplasia of a gland, a normal or large gland in situ with or without abnormally high levels of uptake, and an ectopic thyroid at any point along the pathway of the normal embryological descent. It is ideal when performed within 7 days of starting L-T4 treatment.

32.2.1.5 Treatment

Treatment is with L-T4. It should be started before 2 weeks of age or as soon as a diagnosis is

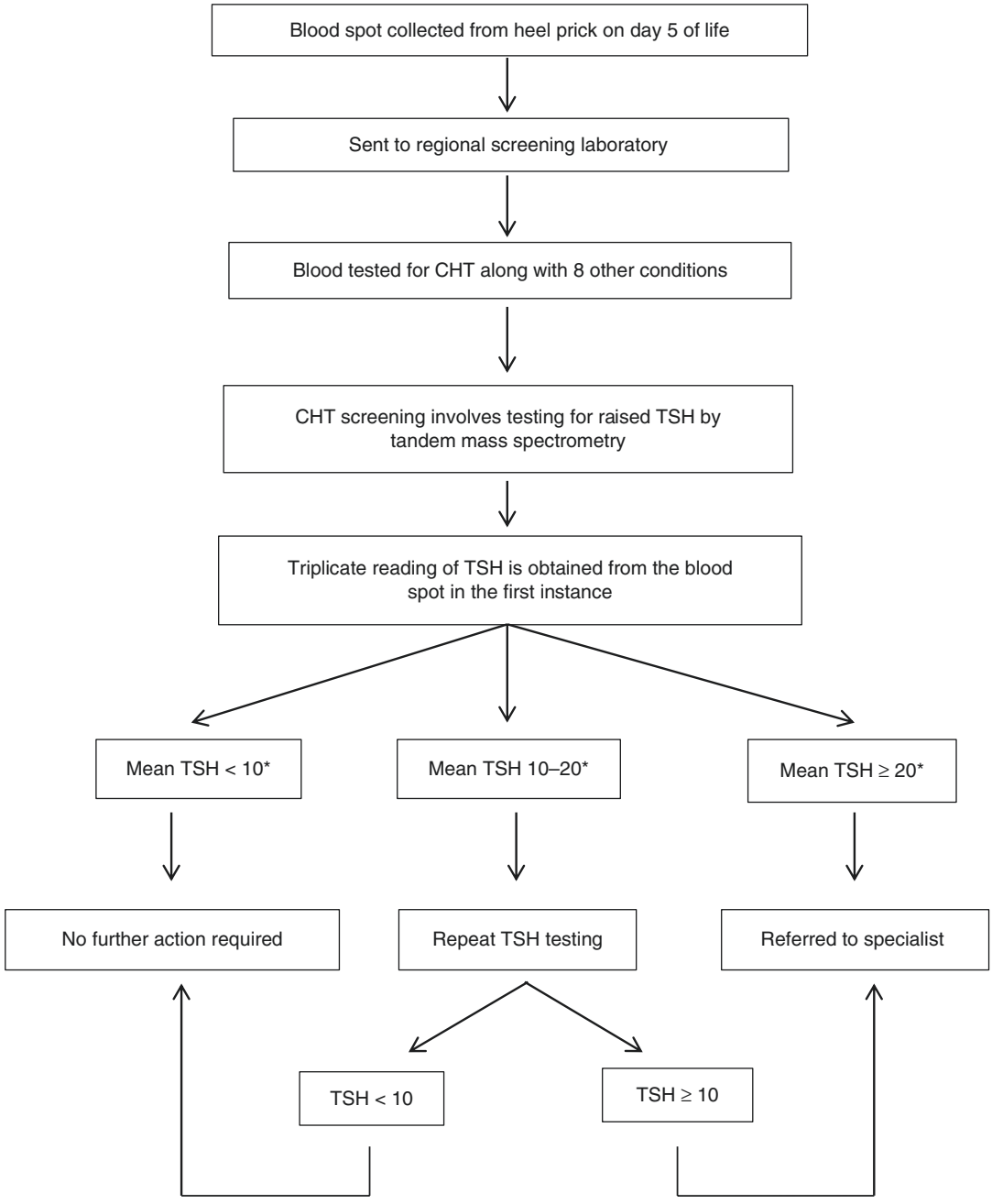


Fig. 32.3 Flowchart representing the screening and referral pathway in the UK. *Please note that different laboratories may have slightly different cut-off values for TSH for further screening and referral

made. The starting dose is 10–15 μg/kg/day. Treatment is monitored by thyroid function tests (TFTs) and tailored to maintain free T4 in the high end of normal range and TSH in the normal range.

32.2.1.6 Nursing Considerations

Levothyroxine is available in different strength solutions or tablets. The absorption is better with tablets. Nurses can be valuable in advising the parents on administering the medication. The

Table 32.2 Symptoms and signs of hypothyroidism in neonates

Symptoms	Signs
• Sleepiness • Constipation • Not waking for feeds • Poor feeding	• Prolonged neonatal jaundice • Cold extremities • Hypotonia • Macroglossia • Umbilical hernia • Dry skin • Coarse and puffy face • Large anterior fontanelle • Wide sagittal suture

majority of units suggest crushing and dissolving the tablets in milk and giving it via a teaspoon or a syringe. Crushed tablets are not to be added to a whole bottle of milk in case the baby does not complete the full feed. Other centres advise placing the tablet in the side of the baby's cheek at the beginning of a feed, which is then absorbed. Consideration must be given to the strength of tablet available when using the second method.

Parents should be provided with information leaflets. Where unit specific information leaflets are not available, in the UK, one can use generic leaflets available from British Thyroid Association or the UK National Screening Committee. Parents should also be directed towards support groups.

As with any other condition requiring lifelong treatment, it is crucial to emphasise on and ensure compliance at each visit.

32.2.1.7 Follow-Up

Regular 1–2 weekly follow-up is required initially to optimise treatment and achieve a normal TSH. Once TSH normalises, 3 monthly follow-up is recommended to monitor growth and development in the first year of life. More frequent visits may be required if there are clinical concerns.

Re-evaluation of the thyroid axis may be considered at the age of 3 years in those children where the aetiology remains unknown or in those where the presence of CHT is questioned either because treatment was commenced when the infant was unwell or in the presence of only slightly raised TSH at diagnosis.

32.2.1.8 Outcome

Since the introduction of newborn screening and early initiation of treatment, the neurocognitive outcome for children with CHT has improved (Grosse and Van Vliet 2011). Special measures must be put in place for those children in whom severe CHT affects motor development or school performance.

Case 1

The Paediatric team were notified that a baby girl had had a positive new born screening test result for congenital hypothyroidism with a blood spot TSH of 26.5 mU/L (mean of duplicate results). The family were contacted and the baby was reviewed in the Children's Assessment Unit on the same day.

Parents commented that she was a 'good' baby, and had to be woken up for the majority of her feeds. She was born at 40 weeks gestation by normal vaginal delivery with a birth weight of 2.8 kg. There was no family history of thyroid disease.

On clinical examination there were no dysmorphic features. She had no evidence of a goitre or lesion at the back of her tongue and was not jaundiced. She appeared clinically euthyroid and had no signs of cardiac abnormalities.

Abnormal TFTs with elevated TSH and low normal free T4 were confirmed on venous bloods (table below). Maternal thyroid functions were normal.

The baby was commenced on levothyroxine supplements at a dose of 25 mcgs daily. Thyroid ultrasound and thyroid uptake scan confirmed that the thyroid gland was in situ suggesting dyshormonogenesis as the cause of hypothyroidism.

The patient was seen for follow-up in the paediatric endocrine clinic in 2 weeks. The parents had noted that she was more awake and responsive and feeding well. Thyroid functions had improved.

Treatment	Pre	Post
Day	D9	D23
TSH mU/L (0.35–4.4)	55.2	7.99
Free T4 pmol/L (9–19.1)	13.4	24.2

Discussion: Careful examination of the infant with congenital hypothyroidism (CHT) should be carried out for presence of dysmorphic features and cardiac defects and vice versa. The prevalence of cardiac defects in children with CHT is higher than in the general population. Children with certain conditions such as Down's and Pendred syndrome and pseudohypoparathyroidism may have a slightly raised TSH in the neonatal period, which may not be picked up on new born screening test.

Points to Remember

- *Congenital hypothyroidism is diagnosed by a raised TSH or low T4 on a heel prick test done as part of the new born screening test.*
- *Early treatment, within 3 weeks of life, with levothyroxine minimises damage to the central nervous system and improves outcome.*
- *Close monitoring of growth and development in infants with CHT is essential.*

32.2.2 Autoimmune Hypothyroidism

32.2.2.1 Introduction

Autoimmune hypothyroidism also known as Hashimoto's thyroiditis (HT) or autoimmune thyroiditis is the commonest cause of acquired hypothyroidism in children and can present at any age but most frequently in adolescence. There are several forms of HT; however, the one in children is referred to as the juvenile form. Females are more affected than males and whites and Asians are more affected than other races. HT can occur in association with other autoimmune diseases such as type 1 diabetes mellitus, Sjögren syndrome, or other thyroid diseases such as papillary thyroid cancer, and is also more common in conditions associated with autoimmune conditions such as Turner Syndrome.

32.2.2.2 Clinical Features

The most common presenting feature of HT is that of a painless goitre and biochemical euthyroidism (normal thyroid functions). The next most common feature is subclinical hypothyroidism or overt hypothyroidism with clinical features of hypothyroidism (Table 32.3). A small proportion of patients present with features of thyrotoxicosis (Table 32.4) which is transient, known as hashitoxicosis (Htx), before developing permanent hypothyroidism. Htx is believed to result from unregulated release of stored

Table 32.3 Symptoms and signs of hypothyroidism in children and adolescents

Symptoms	Signs
• Muscular weakness • Fatigue • Sensitivity to cold • Constipation • Slowed mental processes • Poor memory • Reduced school performance • Sleep disturbance • Weight gain • Menstrual disturbance	• Low pulse rate and heart rate • Thick puffy skin • Coarse hair • Dry skin • Goitre (enlarged thyroid) • Delayed relaxation phase of deep tendon reflexes • Decreased growth velocity • Precocious (early) puberty • Delayed puberty • Raised prolactin levels

Table 32.4 Symptoms and signs of neonatal thyrotoxicosis

Symptoms	Signs
• Irritability • Jitteriness • Restlessness • Voracious appetite • Diarrhoea • Weight loss	• Goitre • Tachycardia and arrhythmias • Cardiac failure • Sweating and flushing • Acrocyanosis • Eye signs: periorbital oedema, lid retraction, and exophthalmos • Hepatosplenomegaly • Lymphadenopathy • Bruising and petechiae secondary to thrombocytopenia • Hyperviscosity • Craniosynostosis and microcephaly

thyroid hormones during inflammatory-mediated destruction of the thyroid gland. Children with long-standing hypothyroidism can occasionally present with iso-sexual precocious puberty (same sex early puberty) with delayed bone age and ovarian cysts, a triad referred to as Van Wyk Grumbach syndrome.

32.2.2.3 Diagnosis

The diagnosis of HT is currently established by a combination of clinical features, presence of serum antibodies against thyroid antigens (mainly to thyroperoxidase and thyroglobulin), and reduced echogenicity of the thyroid gland on USS. Antithyroid peroxidase (TPO) and antithyroglobulin (Tg) antibody titres are elevated in 90–95% of children with Hashimoto's thyroiditis (Grosse and Van Vliet 2011). A small proportion of children who are initially negative can become positive later. Around 20% of individuals who have antibody-positive test results do not develop hypothyroidism or hyperthyroidism (Catureglia et al. 2014).

32.2.2.4 Management

Treatment is by supplementation with L-T4 with a starting dose of 5 mcg/kg/day as a single dose. Children and adolescents with long-standing hypothyroidism should be started on a low dose of levothyroxine to prevent rapid overcorrection. Treatment is monitored by regular measurements of thyroid hormones and treatment is tailored to maintain a free T4 at the high end of normal and TSH in the normal range. Surgery is rarely required but must be considered if there are goitre-related pressure effects. It is essential to bear in mind that an increased prevalence of papillary thyroid carcinoma has been reported in patients with HT (Okayasu et al. 1995), although this remains debatable.

Around 20% of patients may return to a euthyroid state after completing puberty, therefore thyroid status should be re-evaluated at this stage by stopping treatment and monitoring using free T4 and TSH levels (De Luca et al. 2013).

Case 2

A 12½-year-old girl was reviewed in the endocrine clinic after recently being diagnosed with autoimmune hypothyroidism. She had first presented 2 months ago to her General Practitioner with a history of tiredness, dry skin, and weight gain. Parents had also reported that her teachers had noticed a decline in her energy levels. There was a family history of hypothyroidism in the maternal aunt.

On examination, the patient looked well and had a pulse of 86 beats per minute. Her height was on the 9th centile and her weight was just above the 50th centile. Previous measurements taken 2 years earlier from a community clinic had placed her height and weight on the 25th centile. There was a small, smooth goitre, not tender and not nodular. She was pre-pubertal.

Her initial TSH was raised with a low free T4 (table below) and TPO antibodies were positive at >1000 U/mL (normal <6.0). The GP had commenced her on levothyroxine 25 mcg daily. Her parents reported that there was a positive noticeable difference in their daughter since starting the medication.

Repeat thyroid function tests showed a reducing TSH and rising free T4. The dose of levothyroxine was increased to achieve a high normal free T4 and normal TSH. She was seen regularly in the endocrine clinic to review her progress and monitor her thyroid function tests.

Treatment	Pre	2 months post
TSH (0.35–4.4) mU/L	53.4	8.6
Free T4 (9–19.1) pmol/L	7.2	12.5

Discussion: Patients with autoimmune hypothyroidism may present with or without goitre. Increasing weight centile and decreasing height centile should always raise the suspicion of hypothyroidism. Treatment is aimed at maintaining a high normal free T4 and a normal TSH. The normal range for free T4 and TSH varies between laboratories and for different ages.

Points to Remember

- *Hashimoto's thyroiditis is the commonest cause of acquired hypothyroidism in children and commonly presents in adolescence.*
- *Majority of the children may be asymptomatic and biochemically euthyroid except for goitre at presentation.*
- *Tg and TPO antibodies may be absent at diagnosis and become positive later.*
- *Lifelong treatment with levothyroxine is required in the majority; a few children may be able to come off treatment once puberty is completed.*

32.2.3 Secondary or Central Hypothyroidism

Central hypothyroidism (CH) is defined as hypothyroidism due to insufficient stimulation by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland. CH can be congenital (present at birth) or acquired. Congenital CH (CCH) can occur in isolation but most often occurs in association with other pituitary hormone deficiencies. CCH is not identified on newborn screening test as the TSH levels in these neonates are low. The prevalence of CCH is said to be higher than previously known. Countries which use free T4 in the newborn screening report its incidence to be 1 in 16,000 (Schoenmakers et al. 2015). Mutations in transcription factors responsible for normal pituitary development (HESX1, LHX3, LHX4, SOX3, OTX2, PROP1, POU1F1) may cause central hypothyroidism with or without associated extra pituitary abnormalities (Schoenmakers et al. 2015). The other causes of CH in later childhood and adolescence include malignancies such as craniopharyngiomas, previous radiotherapy, previous pituitary surgery, traumatic brain injury, vascular defects, and infiltrative conditions such as histiocytosis.

Case 3

A baby girl born at 37 weeks by normal vaginal delivery was admitted to the neonatal unit due to poor tone (hypotonia) and suspected sepsis. Mum had had a normal pregnancy with normal antenatal scans.

The baby was treated with antibiotics for suspected sepsis. She was screened for prolonged jaundice at 2 weeks of age. Thyroid function tests done as part of screening revealed low TSH (2.9 mU/L) and low FT4 (8 pmol/L) raising suspicion of central hypothyroidism.

She was transferred to a tertiary centre for endocrinology review. Here she was screened for other pituitary hormone deficiencies. A short synacthen test demonstrated suboptimal cortisol response to ACTH revealing cortisol deficiency.

She was commenced on hydrocortisone replacement therapy followed by levothyroxine. Septo-optic dysplasia (SOD) as the cause of multiple pituitary hormone deficiency was suspected and further evaluated. Ophthalmology examination revealed right optic nerve hypoplasia and an MRI of the head showed an absent septum pellucidum, small anterior pituitary, and ectopic posterior pituitary, confirming the diagnosis of SOD.

Discussion: Central hypothyroidism is not diagnosed on new born screening test in countries where the screening programme uses high TSH levels to diagnose CHT. Countries measuring thyroxine levels in screening are more likely to detect babies with secondary hypothyroidism. However, measuring thyroxine is said to be less specific with high frequency of false positives and is therefore not universally practised. Presence of central hypothyroidism necessitates a thorough evaluation for the presence of other pituitary hormone deficiencies. Thyroxine replacement prior to hydrocortisone replacement in children with cortisol deficiency may precipitate an adrenal crisis.

32.3 Hyperthyroidism

32.3.1 Neonatal Thyrotoxicosis

32.3.1.1 Introduction

Neonatal thyrotoxicosis (NT) is the presence of an overactive thyroid (or hyperthyroidism) in the newborn. The prevalence of Graves' disease in pregnancy is 0.2% (Batra 2013). Of those pregnant patients with Graves' disease only 1–12.5% result in neonatal thyrotoxicosis (Batra 2013).

32.3.1.2 Aetiology

NT occurs due to transplacental passage of thyroid stimulating immunoglobulins (TSIs) from mothers with Graves' disease or Hashimoto's thyroiditis. The antibodies can persist despite previous treatment for Graves' disease in the mother. These antibodies which are IgG immunoglobulins cross the placenta and stimulate the foetal thyroid. Although this starts early in pregnancy the effect increases in the last trimester as the placental permeability increases, causing the foetal and maternal antibody levels to be equal.

Another rare cause of NT is an activating mutation of the TSH receptor. NT due to receptor mutation should be suspected if more than two generations in the family are affected by thyrotoxicosis and if there are difficulties in weaning ATDs. Rarely de novo (new) mutations have also been reported to occur. These individuals will need definitive treatment in the long term such as thyroidectomy.

32.3.1.3 Clinical Manifestations

Depending on the antibody levels and maternal control of the disease, the features of thyrotoxicosis may start as early as in the second trimester of pregnancy or not manifest in the neonate at all. Foetal growth can be restricted in utero due to hyperthyroidism and rarely a foetal goitre can be seen on antenatal scans in severe cases. There is an increased incidence of intrauterine death and premature delivery in pregnancies with maternal thyrotoxicosis.

Symptoms and signs (Table 32.3) of thyrotoxicosis may be apparent at birth or may be delayed due to the effect of maternal anti-thyroid drugs or coexistent blocking antibodies. In most cases, features are apparent by day 10 of life. Biochemically the neonate will have a raised free T4 and a suppressed TSH. TSH receptor antibodies (TRAbs) may be in high concentrations.

32.3.1.4 Management

Careful monitoring in pregnancy as detailed in the Endocrine Society Clinical Practice Guideline is essential (De Groot et al. 2012). Foetal thyrotoxicosis is treated by administering anti-thyroid drugs (ATDs), carbimazole or propylthiouracil (PTU) to the mother. These drugs act by preventing the synthesis of thyroid hormone and cross the placenta. Carbimazole is avoided, if possible, in the first trimester due to its association with congenital anomalies. Close monitoring of liver function on PTU is recommended due to its association with liver toxicity.

Neonatal thyrotoxicosis is treated with 0.5–1.5 mg/kg/day of carbimazole in the neonate. A beta blocker such as propranolol is used in a dose of 0.27–0.75 mg/kg 8 hourly in neonates who are symptomatic due to adrenergic stimulation (Ogilvy-Stuart 2002). Thyroid function must be monitored weekly in those on ATD.

In those neonates who are asymptomatic, thyroid function must be checked at birth, day 5–7 and then day 10–14. Parents should be warned of symptoms, as NT has been reported to occur as late as 45 days in certain cases.

32.3.1.5 Prognosis

Most neonates require treatment for no longer than 8–10 weeks. In those who require continued treatment, other causes must be considered. Craniosynostosis, intellectual disability, impaired growth and development have been reported in a small percentage of children with NT, although most of these are neonates with persistent thyrotoxicosis due to a genetic mutation rather than transient due to maternal antibodies.

Case 4

A baby boy was born at term by normal vaginal delivery. Mum had a history of hypothyroidism diagnosed 5 years prior to conception. She developed thyrotoxicosis in pregnancy and was treated with carbimazole. She had high levels of TPO

(2921 Ku/L; normal range 0–51) and thyroid receptor antibodies, TRAb (4.7 U/L; normal range 0–1).

The baby was observed in hospital for 48 h and was discharged home as he was feeding well and did not show any features of thyrotoxicosis such as weight loss, sweating, diarrhoea, tachycardia, or goitre. In an endocrine review on day 5 of life, the baby was tachycardic with a heart rate of 200 beats per minute. His weight was static and there was no goitre. NT was suspected and confirmed by biochemical tests (table below). Carbimazole (75 mcg/kg/day) treatment commenced. Propranolol (400 mcg/kg/day) was added in view of the tachycardia.

The TRAb (22 U/L; range 0–15) and TPO (675 Ku/L; range 0.0–5.6) antibodies were raised. TFTs were monitored and treatment weaned as below (table).

Treatment	Pre	1 week post	1 month post	3 months post	1 month off treatment	2 months off treatment
TSH (0.4–3.5) mU/L	<0.01	<0.01	0.3	0.3	0.35	0.5
FreeT4 (10.7–21.8) pmol/L	>77.2	18.4	9.8	15	14.5	14.2
Action	CBZ and propranolol	Propranolol stopped and CBZ halved	CBZ halved	CBZ stopped		

Discussion: Women with previous hypothyroidism can develop hyperthyroidism in pregnancy. Close monitoring of neonates with maternal Graves' disease or Hashimoto's thyroiditis is crucial. Treatment with anti-thyroid drugs (ATDs) can eventually be weaned.

Points to Remember

- *Neonatal thyrotoxicosis is caused by transplacental transfer of thyroid stimulating immunoglobulins in maternal Graves' or Hashimoto's thyroiditis.*
- *It is a rare and transient condition in the absence of genetic mutations.*
- *Close monitoring of neonates at risk of developing thyrotoxicosis is essential.*
- *Treatment with anti-thyroid drugs for a brief period may be required.*

32.3.2 Graves' Hyperthyroidism

32.3.2.1 Introduction

Hyperthyroidism is rare in children and adolescents. Majority of the cases are due to Graves' disease (GD). GD is an autoimmune disorder caused by an abnormal thyroid hormone production stimulated by thyroid stimulating immunoglobulins, the action of which mimics TSH. Inheritance is polygenic. GD is more common in some families. The production of immunoglobulins is thought to be triggered by certain infections involving the Yersinia series and also viruses. GD is associated with other autoimmune diseases such as diabetes mellitus, Addison disease, vitiligo, immune thrombocytopenic purpura (ITP), and pernicious anaemia. The incidence of GD is around 1 per 100,000 under the age of 15 years (Williamson and Greene 2010).

32.3.2.2 Clinical Features

The triad of GD includes goitre, thyrotoxicosis (Table 32.5), and ophthalmopathy (Table 32.5). However, not all patients present with ophthalmopathy. Fifty percent of patients with eye disease have a mild form and only 2–3% present with severe eye signs (Menconi et al. 2014).

32.3.2.3 Diagnosis

Diagnosis of GD includes elevated levels of serum thyroxine (T4) and tri-iodothyronine (T3), associated with undetectable serum TSH. Antibodies against the TSH receptor (TRAbs) are pathognomonic. They are detectable in the serum of about 98% of untreated GD patients (Menconi et al. 2014). TRAb measure-

Table 32.5 Symptoms and signs of hyperthyroidism and ophthalmopathy in children and adolescents

Symptoms	Signs
Hyperthyroidism	
• Weight loss • Increased appetite • Palpitations • Sweating • Heat intolerance • Tiredness and weak muscles • Nervousness, irritability, and shakiness • Mood swings or aggressive behaviour • Loose stools • Increased thirst and urination • Oligomenorrhoea	• Rapid pulse • Warm • Moist hands • Enlarged thyroid gland with or without a bruit • Tremor
Ophthalmopathy	
• Excess tearing • Irritation • Grittiness • Photophobia • Pain • Redness of the conjunctiva • Diplopia • Blurred vision • Reduced visual acuity	• Soft tissue involvement manifests as Swelling and redness of the eyelids Swelling of the caruncle Chemosis • Proptosis • Extraocular muscle involvement causing limitation of eye movement • Corneal involvement manifests as Stippling and ulceration • Optic nerve involvement • Lid lag

ment is not essential for diagnosing GD; however, it can be used when there is diagnostic uncertainty. Thyroid ultrasound demonstrates a hypoechoic picture with reduced colloid and increased vascularity. USS is also not essential for diagnosis but gives useful information about the size of the gland and detects any thyroid nodules not palpated clinically.

32.3.2.4 Management of GD

The initial management of GD includes anti-thyroid drugs (ATDs). The most appropriate regimen is highly debated. The goal of therapy is to render the patient euthyroid. This is not a cure and definitive treatment such as thyroidectomy or radioactive iodine is required in the long term in majority of the patients. Only half of the patients go into clinical remission following treatment with ATDs (Cheetham and Bliss 2016).

Anti-thyroid Drugs and Treatment Regimes

The most commonly used ATD in children and adults is carbimazole except in the first trimester of pregnancy or if carbimazole is not tolerated, when propylthiouracil (PTU) is used. Carbimazole is preferred to PTU, because of the evidence of a lower prevalence of severe side effects, especially idiosyncratic hepatitis and liver failure although this is rare. The other side effects of ATDs include skin rash and, very rarely, hepatitis, agranulocytosis, and vasculitis. It is important that all children and adolescents and their families are counselled about these potential side effects.

A beta blocker such as propranolol may be necessary in the initial stages to control the adrenergic symptoms of thyrotoxicosis. However, beta blockers are contraindicated in children with asthma and are therefore not used.

There are two main approaches to treatment with ATDs:

(a) *Block and replace* where high dose ATD is used to render the patient hypothyroid and levothyroxine is then added to treat hypothyroidism. Some clinicians believe that the side effects of ATDs are more with this regimen; however, others prefer this method as thyroid function is said to be more stable with this regimen and patients need fewer blood tests

and clinic follow-up visits initially (Cheetham and Bliss 2016).

(b) *Dose titration* where a titrating dose of ATD is used. This method is preferred by some due to reportedly fewer side effects and a simpler regimen; however, others report the need for frequent blood tests and dose adjustments due to unstable thyroid functions (Cheetham and Bliss 2016).

The relapse rate is reported to be similar with the two regimens, 51% in the block-replace group and 54% in the dose titration group (Abraham et al. 2010). The best approach remains debatable.

Surgery

For those that need definitive treatment, one option is thyroidectomy. Previously subtotal thyroidectomies were performed; however, now total thyroidectomy is increasingly recommended to prevent the recurrence of hyperthyroidism (<3%). The rate of complications with total thyroidectomy when performed by a skilled (high-volume) surgeon is said to be minimal. The most frequent complications include: pain and transient hypocalcaemia secondary to disruption of the parathyroid glands. Less frequent complications include haemorrhage, permanent hypoparathyroidism, and vocal cord paralysis.

Hypothyroidism, requiring levothyroxine replacement, is universal following total thyroidectomy.

Radioactive Iodine

The other option is radioactive iodine (I-131) which is increasingly being used in the treatment of GD and is gaining popularity. Radioiodine is preferably administered after achievement of euthyroidism with ATDs and ATDs are stopped 5–7 days prior to treatment.

The goal of the treatment is to induce hypothyroidism in order to achieve a stable remission. Oral I-131 targets and destroys the follicular cells in the thyroid gland; hence an initial rise in thyroid hormones may be noted. Beta blockers may be used to control symptoms of hyperthyroidism during this time. There is a risk of thyroid storm following I-131 treatment.

The dose of I-131 is calculated based on the gland size and radioiodine uptake by the gland. The reported doses in children and adolescents have ranged from 100–250 mCi/g thyroid tissue (Rivkees 2014). Treatment is less successful in patients with large goitre and high levels of circulating TRAb levels.

Very few short-term side effects are reported and are usually tolerable. Radiation thyroiditis can rarely cause pain and swelling of the neck and may require treatment with simple analgesia. The long-term persistence of hyperthyroidism and occurrence of hypothyroidism post treatment are variably reported and depend on the I-131 dose used. Both hypo- and hyperparathyroidism have been reported in the long term in a small percentage of patients. There is no evidence of an increased risk of thyroid cancer, other solid tumours, and leukaemia following I-131 therapy in adults with GD. Although the same has been shown in children, the numbers are small (1000 children) and the duration of follow-up (5–15 years) is short to make any definitive conclusions and long-term large studies are still required (Rivkees 2014). No long-term effects on the adult reproductive system in males and females have been described. Recent studies have focused on the association of I-131 therapy with the development or progression of ophthalmopathy, hence its use in patients with active Graves' ophthalmopathy is limited.

Case 5

A 7-year-old girl presented to her General Practitioner with symptoms of anxiety, poor sleep, and weight loss. On examination she was found to have an enlarged thyroid gland (goitre). She was not tachycardic and there were no eye signs.

Hyperthyroidism was suspected based on the history and clinical findings and confirmed on laboratory thyroid function tests. She had a raised FT4 (29 pmol/L) and a suppressed TSH (0.01 mU/L). She was positive for TPO (295 Ku/L; normal range 0–5.6) and TRAb (33 U/L; normal

range 0–15) confirming a diagnosis of Graves' hyperthyroidism. Thyroid USS showed multiple hypoechoic nodules and increased vascularity of the thyroid gland in keeping with the diagnosis.

She was treated with carbimazole (1 mg/kg/day in two divided doses). Treatment with propranolol was not indicated. Her free T4 normalised within 8 weeks although the TSH remained suppressed for longer. Following treatment she regained her weight and her sleep pattern was reported to have improved.

Treatment	Pre	2 weeks post	10 weeks post
TSH (0.4–3.5) mU/L	<0.01	0.01	0.03
FreeT4 (10.8–28) pmol/L	69.5	29	15.3

Discussion: Graves' hyperthyroidism is the most common cause of hyperthyroidism in children. Symptoms usually resolve following treatment with anti-thyroid drugs. In patients with increased adrenergic activity, namely increased heart rate and tremor, treatment with a beta blocker such as propranolol is indicated.

Points to Remember

- *GD is the most common cause of thyrotoxicosis in children and adolescents as well as adults.*
- *GD is a triad of thyrotoxicosis, goitre, and ophthalmopathy, although only a small proportion of patients present with all three features.*
- *Although the mainstay of initial treatment is with anti-thyroid drugs, the right regimen is highly debated (block and replace vs dose titration).*
- *In patients who relapse after stopping ATDs, the choice of long-term definitive treatment (surgery or radioactive iodine) depends on several factors such as disease severity, age of the patient, presence of ophthalmopathy, and the size of the goitre.*

32.4 Thyroid Nodules and Cancers

32.4.1 Thyroid Nodules

Thyroid nodules (TNs) are mostly benign and not cancerous, although a higher proportion of them are cancerous in children compared to adults (22–26% vs 5–10%, respectively) (Francis Gary et al. 2015). TN rarely present with clinical features, majority of them are incidentally picked up by physical examination, occasionally patients can present with a painless lump in the neck.

32.4.1.1 Evaluation of the Thyroid Nodule

Careful and thorough evaluation of TNs is essential due to the high risk of malignancy associated with it in childhood. This should include:

History: A detailed history focused on

1. Symptoms of hypothyroidism or hyperthyroidism (Tables 32.3 and 32.5)
2. Disturbance in voice
3. Swallowing difficulty
4. History of malignancy
5. Exposure to radiation
6. Family history of thyroid problems or other malignancies

Examination: A systematic physical examination should assess the thyroid gland, the lateral neck for surrounding lymph nodes, and if indicated, a laryngeal examination and systemic examination for signs of metastatic disease.

Investigations: should include thyroid function tests and ultrasound guided fine needle aspiration (FNA) biopsy.

The American Thyroid Association Guidelines (Rivkees 2014) provide detailed step by step guide on investigation and management of thyroid nodules, discussion of which is beyond the scope of this book.

Case 6

A 14-year-old girl was referred to the endocrine clinic with a 6 month history of feeling hot and shaky. She also had increased appetite and had felt her heart was racing for the past 2–3 months. She had lost weight and experienced irregular menstruation.

There was a family history of Graves' disease in the mother which was diagnosed 5 years ago and was treated with radioactive iodine. Paternal grandmother also had hypothyroidism.

On examination her heart rate was 104 beats per minute and she had mild tremor. She had a smooth, asymmetric, enlarged goitre which was bigger on the right compared to the left. She had no eye signs or lymphadenopathy.

Hyperthyroidism was suspected and confirmed on laboratory investigations. She had a raised FT4 (36 pmol/L) and suppressed TSH (<0.01 mU/L). She was commenced on carbimazole and propranolol to control adrenergic symptoms. Her TPO and TRAb were negative.

A thyroid USS identified a large well-defined solid and cystic lesion with increased vascularity. A fine needle aspiration biopsy was performed which showed normal thyroid tissue. The size of the goitre improved on carbimazole treatment. Technetium scintigraphy showed evidence of increased uptake within the single nodule suggesting a hot nodule amenable to surgery.

Discussion: Thyroid nodules must be evaluated thoroughly in children and adolescents due to the increased risk of cancer. In this case, further evaluation of the nodule with a technetium 99 scan to determine functionality indicated surgery would be the ideal definitive treatment.

32.4.2 Thyroid Cancers

Thyroid cancers are rare in children compared to adolescents. The annual incidence is 1 per million per year in children under 10 years compared to 15.4 cases per million per year in 15–19-year-olds (http://www.thyca.org/pediatric/about/). The two main types of paediatric thyroid cancers include differentiated thyroid cancer and medullary thyroid cancer.

1. **Differentiated Thyroid Cancer**: This includes papillary and follicular thyroid cancer and their variants.
   (a) *Papillary thyroid cancer* (PTC) is the most common type of thyroid cancer in both children, adolescents, and adults. The majority of children with PTC have local spread to the lymph nodes of the neck at the time of diagnosis and up to 20% have distant metastases (http://www.thyca.org/pediatric/about/). Recurrence of PTC is common. However, despite this the prognosis is excellent with appropriate treatment.
   (b) *Follicular thyroid cancer* (FTC) is rare in children, has aggressive characteristics and poorer prognosis.

The mainstay of treatment for both types of cancers is surgery aiming for a total thyroidectomy including resection of the surrounding affected lymph nodes. Radioactive iodine has also been employed followed by doses of L-T4 which suppress TSH levels for a period of time. Long-term follow-up and surveillance to detect recurrence is recommended.

2. **Medullary Thyroid Cancer (MTC)**: MTC is rare in childhood and accounts for 5–10% of all thyroid cancers (http://www.thyca.org/pediatric/about/). MTC comes from the parafollicular C-cells in the thyroid gland that produces a protein called calcitonin. Twenty-five percent of MTC cases are hereditary, the remainder are sporadic. MTC can occur as part of a multiple endocrine neoplasia. A family history of MTC, pheochromocytoma, or hyperparathyroidism may indicate multiple endocrine neoplasia 2A (MEN2A) or multiple endocrine neoplasia 2B (MEN2B), both of which are inherited in an autosomal dominant fashion. All family members should be genetically screened for this mutation. It can also occur by itself in familial medullary thyroid carcinoma (FMTC). MTC is treated with total thyroidectomy if diagnosed before metastatic

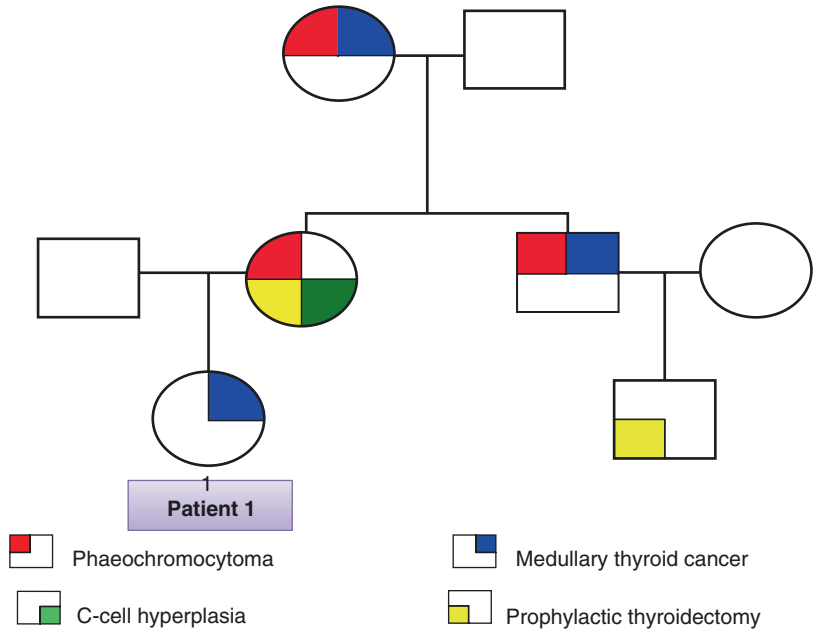
spread. Patients are monitored by serum measurement of calcitonin at follow up due to the risk of recurrence in the remnant thyroid tissue.

Case 7

A 14-year-old girl (patient 1) presents with a solitary neck lump. Thyroid function was normal. Ultrasound showed a left sided nodule. Fine needle aspiration (FNA) was inconclusive so she underwent left lobectomy of the thyroid which on histology was medullary thyroid cancer.

Calcitonin levels were checked postoperatively and were raised at 13.1 ng/L (<5 ng/L). Genetic screening was performed and she had a mutation in the RET gene. This mutation is associated with MEN2. The diagnosis of MEN 2A was made as she had no features like mucosal neuromas suggestive of MEN 2B. Plasma metanephrines were normal. She underwent a total thyroidectomy.

Four other family members were screened and were identified as having the same genetic mutation. One member of the family had been previously diagnosed with a phaeochromocytoma but this had not been followed up. Another two of the family members had biochemical and radiological evidence of medullary thyroid carcinoma and phaeochromocytoma.



Discussion: Children or adolescents found to have medullary thyroid cancer require genetic screening and if positive family screening. If a mutation is identified in the RET gene early prophylactic thyroidectomy (as medullary thyroid cancer occurs in 95%) is recommended along with ongoing screening for phaeochromocytoma (occurs in 40%) and hyperparathyroidism (occurs in 20%).

Points to Remember

- *Thyroid nodules are mostly benign; however, thorough evaluation is essential as 21–26% of these can be cancerous in children and adolescents.*

- *Papillary thyroid cancer is the most common type of thyroid cancer and has a good prognosis.*
- *Medullary thyroid carcinomas account for 5–10% of childhood cancers and can be inherited as part of multiple endocrine neoplasia or familial medullary thyroid carcinoma.*

32.5 Conclusions

Thyroid disorders of childhood are important endocrinopathies which need prompt investigation and treatment in order to allow for normal growth and development. Although rare, conditions such as foetal and neonatal thyrotoxicosis can be fatal necessitating careful maternal history and close monitoring of the foetus and the neonate. Thorough evaluation of thyroid nodules to exclude neoplasia is crucial. Knowledge of association of thyroid cancers with other endocrine neoplasias and a detailed family history are the key to diagnosing inherited thyroid cancers.

References

Abraham P, Avenell A, McGeoch SC, et al. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2010;(1):CD003420. https://doi.org/10.1002/14651858.CD003420.pub4.

Batra CM. Fetal and neonatal thyrotoxicosis. Indian J Endocrinol Metab. 2013;17(Suppl 1):S50–4. https://doi.org/10.4103/2230-8210.119505.

Catureglia P, De Remigisa A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13:391–7.

Cheetham T, Bliss R. Treatment options in the young patient with Graves' disease. Clin Endocrinol. 2016;85(2):161–4. https://doi.org/10.1111/cen.12871.

De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(8):2543.

De Luca F, Santucci S, Corica D, Pitrolo E, Romeo M, Aversa T. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. Ital J Pediatr. 2013;39:8.

Francis Gary L, Waguespack Steven G, Bauer Andrew J, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer. Thyroid. 2015;25(7):716–59. https://doi.org/10.1089/thy.2014.0460.

Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child. 2011;96:374–9.

http://ghr.nlm.nih.gov/condition/congenital-hypothyroidism.

http://www.thyca.org/pediatric/about/.

Kapelari K, Kirchlechner C, Högler W, Schweitzer K, Virgolini I, Moncayo R. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocr Disord. 2008;8:15. https://doi.org/10.1186/1472-6823-8-15.

Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. Horm Res Paediatr. 2014;81:80–103.

Menconi F, Marcocci C, Marinòl M. Diagnosis and classification of Graves' disease. Autoimmun Rev. 2014;13:398–402.

Ogilvy-Stuart AL. Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed. 2002;87:F165–71.

Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and White and African Americans. Cancer. 1995;76:2312–8.

Rivkees S. Pediatric Graves' disease: management in the post-propylthiouracil Era. Int J Pediatr Endocrinol. 2014;2014(1):10. https://doi.org/10.1186/1687-9856-2014-10.

Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT. Recent advances in central congenital hypothyroidism. J Endocrinol. 2015;227(3):R51–71.

Williamson S, Greene SA. Incidence of thyrotoxicosis in childhood: a national population based study in the UK and Ireland. Clin Endocrinol. 2010;72(3):358–63.

Key Reading

1. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G. European Society for Paediatric Endocrinology Consensus Guidelines on screening, diagnosis, and management of congenital hypothyroidism. Horm Res Paediatr. 2014;81:80–103.
2. Cheetham T, Bliss R. Treatment options in the young patient with Graves' disease. Clin Endocrinol. 2016;85(2):161–4. https://doi.org/10.1111/cen.12871.

3. Rivkees S. Pediatric Graves' disease: management in the post-propylthiouracil Era. Int J Pediatr Endocrinol. 2014;2014(1):10. https://doi.org/10.1186/1687-9856-2014-10.
4. Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158(3):273–85.
5. Francis Gary L, Waguespack Steven G, Bauer Andrew J, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer. Thyroid. 2015;25(7):716–59. https://doi.org/10.1089/thy.2014.0460.

Thyroid Disease in Pre- and Post-Pregnancy

33

Dev A. Kevat and Lucy Mackillop

Contents

33.1 **Physiology of Changes in Pregnancy Affecting Thyroid Function and Testing** 630

33.2 **An Approach to Abnormal Thyroid Function in Pregnancy** 631

33.3 **Thyroid Disorders During Pregnancy** 632
33.3.1 Gestational Hyperthyroidism 632
33.3.2 Pre-existing Hyperthyroid Conditions 633
33.3.3 Pre-existing Hypothyroidism 635
33.3.4 Subclinical Hypothyroidism 636
33.3.5 Positive Thyroid Peroxidase Antibodies with Otherwise Normal Thyroid Function 638

33.4 **Thyroid Disorders in the Puerperium (Post-partum) Period** 638
33.4.1 Introduction 638

33.5 **Conclusions** 640

Case Study 2–4. Answers 640

References 641

Abstract

Thyroid dysfunction affects approximately 3% of pregnant women. Adequate thyroid hormone levels are important for fetal development. Normal physiological changes of pregnancy can contribute to subclinical hypothyroidism which may require treatment with thyroxine during pregnancy. Pre-existing hypothyroidism requires an increase in thyroxine dosage. Pre-existing hyperthyroidism may or may not require continued treatment with anti-thyroid medication, though these medications can rarely cause adverse fetal effects. Gestational

D. A. Kevat
Monash Health and Western Health, Melbourne, VIC, Australia

Department of Endocrinology, Western Health, St Albans, VIC, Australia

L. Mackillop (✉)
Oxford University Hospitals NHS Foundation Trust and Nuffield Department of Women's and Reproductive Health, University of Oxford, Level 6, Women's Centre, John Radcliffe Hospital, Oxford, UK
e-mail: lucy.mackillop@ouh.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_33

hyperthyroidism must be distinguished from a new diagnosis of Graves' disease in pregnancy. Gestational hyperthyroidism does not require treatment with anti-thyroid medication. Graves' disease requires additional monitoring of mother and fetus and consideration of anti-thyroid medication. Post-partum thyroiditis is an underdiagnosed condition which can cause transient hyperthyroidism before recovery or hypothyroidism, or hypothyroidism without a hyperthyroid phase. Serial monitoring of thyroid function test is required. The vast majority of women with thyroid conditions can be managed to a successful pregnancy outcome.

Keywords
Pregnancy · Thyroid disease · Prenatal care · Postnatal care · Perinatal care

Abbreviations

bHCG	Beta human chorionic gonadotropin
IQ	Intelligence Quotient is an attempt to measure intelligence
T3	Free triiodothyronine
T4	Free thyroxine
TRAb	Thyroid receptor antibody levels
TSH	Thyroid stimulating hormone

Key Terms

- **Thyroid stimulating hormone (TSH):** a hormone made by the pituitary gland which stimulates the thyroid gland to make thyroxine (T4) and a small amount of tri-iodothyronine (T3).
- **Thyroxine (T4):** a hormone created by thyroid gland which travels in the circulation to the body's tissues.
- **Tri-iodothyronine (T3):** a more biologically active hormone mostly created by conversion of T4 to T3 in the body's tissues. A small amount is created by the thyroid gland itself.
- **Thyroxine-binding globulin:** a globulin protein, mostly created in the liver, that binds to T4 and T3 and carries it in the circulation.

Key Points

- The most common thyroid disorders in pregnancy include pre-existing disorders such as Hashimoto's hypothyroidism and Graves' disease as well as pregnancy-specific conditions such as gestational hyperthyroidism.
- The normal physiological changes of pregnancy play a key role in significant changes in thyroid hormone levels during gestation, including the development of subclinical hypothyroidism.
- Appropriate monitoring and management of thyroid conditions in pregnancy are important for health of both mother and fetus.
- Anti-thyroid medication improves the control of hyperthyroid conditions but may cause fetal adverse effects.
- The vast majority of women with thyroid conditions can be managed to a successful pregnancy outcome.

33.1 Physiology of Changes in Pregnancy Affecting Thyroid Function and Testing

The demands of pregnancy induce a number of significant physiological changes including profound cardiovascular adaptations, a 15% increase in basal metabolic rate, and a symphony of hormonal changes. Human chorionic gonadotropin levels increase greatly during the first trimester; oestrogen, progesterone, cortisol, and prolactin levels also increase, whilst lutenising and follicular stimulating hormone levels decrease. From an immunological perspective, a shift away from cell-mediated immunity (Th1 response) to humoral immunity (Th2 response) can result in some conditions such as Graves' disease improving during pregnancy.

Three key changes drive important changes in thyroid function (Glinoer 1998b)

1. **Increase in thyroid binding globulin levels**
   Thyroid binding globulin levels increase two- to threefold as a result of elevating oes-

trogen levels. As a greater proportion of thyroxine (T4) is bound to thyroid binding globulin, free thyroxine levels tend to decrease. Free triiodothyronine (T3) also tends to decrease. As is the case outside pregnancy, reduced thyroxine levels provide negative feedback to the hypothalamic-pituitary axis (Chap. 1) in order to try to maintain euthyroid equilibrium and steady state via a stimulus to increase in thyroid stimulating hormone (TSH). The increase in thyroid stimulating hormone is evident across trimesters. In women who have sufficient iodine intake, free thyroxine and triiodothyronine levels fall up to 15% during pregnancy.

2. **Action of human chorionic gonadotropin on the thyroid, particularly during the first trimester**
   Human chorionic gonadotropin is an essential hormone for a successful pregnancy. It is produced by the syncytiotrophoblast in the placenta and helps sustain the corpus luteum in the early stages of pregnancy. The corpus luteum produces progesterone which promotes the uterine thickening which allows the successful development of the implanted zygote/embryo.

   Absolute human chorionic gonadotropin levels vary between individuals, but increase exponentially after conception and Week 6 of pregnancy (beta human chorionic gonadotropin (bHCG) levels 1000–55,000 mIU/L), with further large increases to Week 12 (25,000–290,000 mIU/L), before decreasing to less than half the latter concentration by the time of delivery. There is evidence that human chorionic gonadotropin can directly stimulate the thyroid gland in a similar manner to thyroid stimulation hormone due to having a similar chemical structure known as molecular mimicry.

   In some women with bHCG levels greater than 50,000 mIU/L for more than 3 days, the stimulatory effect of human chorionic gonadotropin on the thyroid gland is sufficient to drive thyroxine and triiodothyronine levels high enough to cause symptomatic hyperthyroidism (e.g. with palpitations and tremor). There is a concomitant suppression of thyroid stimulating hormone production. Whilst most women do not suffer from hyperthyroidism in this manner, the effects of human chorionic gonadotropin do still exert a downward or blunting effect on thyroid stimulating hormone levels, particularly during the first trimester. Some research suggests that every 10,000 mIU/L increase in bHCG levels correlates with a 0.6 pmol/L increase in thyroxine levels and a decrease of 0.1 mIU/L in thyroid stimulating hormone level (Glinoer 1999).

3. **The placenta as an active endocrine organ**
   The placenta contains Type II deiodinase and Type III deiodinase. Type II deiodinase converts thyroxine (T4) to triiodothyronine (T3). It is also present in the thyroid gland. Type III deiodinase converts thyroxine and triiodothyronine to biologically inactive reverse triiodothyronine (reverse T3) and diiodothyronine (T2).

   The manner in which placental enzymatic activity regulates the hormonal environment for the developing fetus is not completely understood. It is generally agreed that the placenta plays a role in the need for increased maternal creation and turnover of thyroxine. This increased demand can result in women without sufficient iodine intake becoming hypothyroid.

33.2 An Approach to Abnormal Thyroid Function in Pregnancy

Iodine sufficiency should be ensured in all women, which usually requires supplementation of dietary sources (Box 33.1). Universal thyroid function testing is not currently recommended. Women with a personal history of thyroid disease should be tested when seeking to conceive and in the first trimester with management tailored to the particular condition. Women with a history of autoimmune disease should be considered for testing. Antibody testing is generally a useful adjunct to testing of thyroid function when patients have a history of autoimmune thyroid or other disease. Women who have a diagnosis of any thyroid disorder will require

Box 33.1 Practice Tips: Iodine Requirements in Pregnancy

Iodine is the key component for the biosynthesis of thyroid hormone. Inadequate intake predisposes a woman to hypothyroidism (Glinoer 1997). For both pregnancy and during breastfeeding, 250 μg/day is recommended by the World Health Organization and a number of key bodies, though not yet the United Kingdom Scientific Advisory Committee on Nutrition. This intake recommendation is higher than the 140–150 μg/day suggested for non-pregnant adults. Research has shown that iodine insufficiency does exist in developed countries including the United Kingdom.

Iodine is most often consumed in milk products, seafood, and shellfish. Organic milk contains less iodine. Grains may contain some iodine depending on the soil characteristics of cultivation, though levels vary. In some countries, salt is iodised.

All pregnant and breastfeeding women should be advised to take a supplement to ensure their intake of iodine is at least 250 μg/day. Different formulations of pregnancy vitamins can have different amounts of iodine and this should be scrutinised for adequacy prior to purchase and on clinical review. Consumption of more than 500 μg/day is not recommended.

monitoring throughout pregnancy though most conditions have a tendency to stabilise in the second and third trimesters.

33.3 Thyroid Disorders During Pregnancy

The two most common causes of hyperthyroidism in pregnancy are gestational hyperthyroidism and Graves' disease. Most women with Graves' disease are diagnosed before rather than during pregnancy. Rarer causes of hyperthyroidism can include the hyperthyroid phase of Hashimoto's disease, gestational trophoblastic disease (e.g. molar pregnancy), and exogenous taking of thyroxine tablets inappropriately or at the incorrect dose.

Hypothyroidism and subclinical hypothyroidism is most commonly caused by the physiological changes of pregnancy and is termed gestational (subclinical) hypothyroidism. Women with insufficient iodine intake are at greater risk of becoming hypothyroid. A second important cause is Hashimoto's disease which is an immune condition (See Chap. 30) can be diagnosed prior to or during pregnancy.

33.3.1 Gestational Hyperthyroidism

Gestational hyperthyroidism is due to the direct stimulatory effect of human chorionic gonadotropin on the maternal thyroid gland. It usually occurs during the first trimester and usually resolves by the end of the first half of pregnancy. This is because human chorionic gonadotropin levels are at their highest levels toward the end of the first trimester, and in some women are sustained at high enough levels to drive excess thyroxine (T4) production by the thyroid. Gestational hyperthyroidism is associated in some women with hyperemesis gravidarum which is characterised by severe nausea and vomiting. Both conditions are more common in twin pregnancy (Glinoer 1998a, b, c).

33.3.1.1 Diagnosis

Diagnosis of gestational hyperthyroidism is based on a combination of clinical features and laboratory investigations.

- Women often suffer from classical symptoms and signs of hyperthyroidism including palpitations, tremor, weight loss or lack of weight gain, anxiety and heat intolerance. On examination, they can be tachycardic. They do not have prominent eyes or an eye disease which is associated with Graves' disease. The thyroid gland is usually normal in size.

- On thyroid function testing, thyroxine and triiodothyronine levels are elevated beyond the reference range, and thyroid stimulating hormone production are usually less than 0.5 mIU/L and can be undetectably low.
- Thyroid receptor antibody levels (TRAb) are important to perform and are negative.

33.3.1.2 Maternal Concerns

Gestational hyperthyroidism can significantly diminish a women's quality of life (Glinoer 1998b).

Once a diagnosis is made, it is important to ask about symptoms of hyperemesis gravidarum, and seek specialist medical care for that condition if required. Even in the absence of hyperemesis gravidarum, weight loss and lack of weight gain caused by hyperthyroidism can be concerning for the patient, and increased caloric intake to compensate should be encouraged.

33.3.1.3 Fetal Concerns

Women who have gestational hyperthyroidism and hyperemesis gravidarum may not be able to meet nutritional requirements with consequent fetal risk of intrauterine growth retardation. The fetus of a woman with gestational hyperthyroidism only is not at significantly increased risk of adverse outcomes because of the transient nature of the condition.

33.3.1.4 Management

Steps in management include:

- Education and reassurance of the patient that the condition is usually self-limiting and very unlikely to cause any harm to the fetus
- Activate social supports including in cases of anxiety
- Encourage sufficient caloric intake
- Urgent referral to a specialist doctor if hyperemesis gravidarum is suspected
- Consideration of beta-blocker medication in severe cases, e.g. propranolol or labetalol. Side effects and safety in pregnancy should be discussed. Anti-thyroid medication is not required.
- Clinical review of the patient at 3–4 week intervals with repeat thyroid function tests until symptoms and thyroid function tests normalise

33.3.2 Pre-existing Hyperthyroid Conditions

Graves' disease is the most common cause of pre-existing hyperthyroidism. The condition is described fully in Chap. 28. Women of childbearing age with the condition should be counselled to use contraception until the disease is appropriately managed and disease activity levels are well controlled. Successful pregnancy is certainly possible for women with a history of the condition. Appropriate counselling should occur of the risks the condition poses for pregnancy, including the potential fetal effects of anti-thyroid drugs. Such pregnancies should not be considered "low risk". Women who have had a thyroidectomy to treat Graves' disease can still have circulating thyroid receptor antibodies which can affect a pregnancy. Antibody levels three times the upper limit of the normal reference range denote pregnancies of highest risk. Toxic (hyperfunctioning) nodules (see Chap. 28) can also cause hyperthyroidism in pregnancy.

33.3.2.1 Diagnosis

Diagnosis both in and outside of pregnancy is based on clinical symptoms and supporting investigation results. Women often present with symptoms of hyperthyroidism including weight loss, palpitations, hair loss, difficulty sleeping, and diarrhoea. Graves' disease can cause eye problems including exophthalmos (prominent or bulging eyes), slowed eye movements, and chemosis (swelling of the conjunctivae). Occasionally, women can present reporting that other people have told the patient that their eyes have changed.

- Thyroid receptor antibody (TRAb) levels can be measured in blood. The widely available test is accurate (both sensitive and specific)

Box 33.2 Case Example 1. Palpitations in Pregnancy

M.R is a 30-year-old lady who is 12 weeks into her first pregnancy. She reports suffering from palpitations and difficulty sleeping for a fortnight. She is anxious and concerned that she has not put any weight on for that period. M.R has no significant past medical history.

On examination she appears tired. Her heart rate is 118 beats per minute. The rest of the examination is unremarkable. Her thyroid function test results are TSH 0.1 mIU/L (Normal range-NR 0.5-4.0), T4 27 pmol/L (NR 10-20), and T3 5 pmol/L (NR 4-7).

What further test is it important to order? How would you counsel and manage M.R?

Please refer to the end of this chapter for answers related to this case

and is useful for diagnosis and as a marker of current disease activity.

- Thyroid uptake scans are a nuclear medicine scan which can also be used to diagnosis and assess the activity levels of Graves' disease. However, as the scan requires the use of a radionucleotide tracer which emits radiation, scans are not performed on pregnant women, and are generally avoided in the breastfeeding mother.

33.3.2.2 Maternal Concerns

Even when the condition is adequately treated, Graves' disease is associated with higher rates of miscarriage, pre-eclampsia, placental abruption, preterm delivery, and thyroid storm. Pregnancy carries with it a risk of worsening Graves' eye disease.

The medications used most commonly for Graves' disease in the United Kingdom are carbimazole and propylthiouracil. Methimazole is commonly prescribed in the United States. Both of these anti-thyroid drugs can cause disturbances in the production of red and white blood cells, with consequent anaemia and poor immune function. The medications can also cause disturbances in liver function, with rare cases of liver failure also reported particularly with propylthiouracil.

33.3.2.3 Fetal Concerns

Graves' disease is associated with intrauterine growth retardation, miscarriage, and pre-term delivery. The fetal thyroid develops from 6 weeks and produces thyroxine during the second half of pregnancy. The thyroid receptor antibodies associated with the Graves' disease can cross the placenta and stimulate the fetal thyroid causing hyperthyroidism. There is some evidence that hyperthyroidism may be associated with an increased risk of later seizure and neurobehavioural disorders.

Anti-thyroid medication reduces thyroxine and triiodothyronine levels in the maternal circulation with transmission to the fetus via the placenta which plays an active role in regulation of these hormones in the intrauterine environment. If such hormone levels are greatly reduced, the fetus can become hypothyroid. In rare cases, the fetus can develop a goitre as a consequence, which can put pressure on its trachea.

Anti-thyroid medication can also directly affect the fetus. Aplasia cutis (absence of a portion of skin, e.g. on scalp) and congenital abnormalities such as oesophageal atresia and dysmorphic facies have been reported with use of carbimazole (Yoshihara 2012). Face or neck cysts and urinary tract abnormalities in male offspring have been reported with propylthiouracil. As these abnormalities are not considered as severe as those with carbimazole, propylthiouracil is usually used during the first trimester, the key period of fetal organogenesis. Specialist medical advice should be sought on medication choice, as guidelines are being revised in a number of countries.

33.3.2.4 Management

Principles of management include:

- Pre-pregnancy counselling and disease control by a specialist physician.
- Regular clinical review with thyroid function tests during pregnancy—e.g. every 4–6 weeks if stable, every 2 weeks if medication changes are being made or the condition is not stable.

- In patients who require medication, use of the lowest dose of anti-thyroid medication required. Propylthiouracil Ideally 250 mg or less (total daily dose) is often used in the first trimester with consideration of patients being changed to Carbimazole Ideally 20 mg or less (total daily dose) in the second and third trimester. Remaining on a single type of medication throughout pregnancy is also appropriate in some cases. Although the potential fetal effects such as intrauterine growth retardation must be considered, beta-blocker medication such as Propranolol can be used to assist with hyperthyroid symptoms.
- Treatment is aimed to keep maternal thyroxine level at the upper limit of the normal range to minimise the risk of fetal hypothyroidism.
- Medication doses can often be reduced or ceased during the second and third trimester due to maternal immune system changes.
- Thyroidectomy can be considered in severe, resistant cases or in cases of allergies to medication.
- Thyroid receptor antibody levels should be performed regularly including at initial review, at 18–22, and at 30–34 weeks gestation to aid in estimating effects on the fetus.
- Post-partum review is essential as women are at risk of disease relapse particularly in the first 2 months after delivery.
- The neonate requires thyroid function tests at day 5 and day 10 and whilst mild abnormalities are often found, they are transient and rarely require treatment. However undiagnosed thyrotoxicosis in the neonate carries a high mortality rate, hence the need to perform these blood tests.
- Use of up to 20 mg of Carbimazole if needed is considered safe for breastfeeding.

Toxic Nodules

Toxic (hyperfunctioning) nodules are a rare cause of hyperthyroidism during pregnancy. Some women will have the nodules ablated using radioactive iodine prior to pregnancy and be euthyroid. Toxic nodules do not produce antibodies. Some women may need anti-thyroid medication through the pregnancy, usually at low doses. The risks of these medications are described in the previous section. There is no evidence that toxic nodules change their level of activity during pregnancy. Subclinical hyperthyroidism (suppressed thyroid stimulating hormone with thyroxine levels in the normal range) may not need treatment, but overt hyperthyroidism should prompt strong consideration of medication to avoid increased risks of miscarriage and other problems.

33.3.3 Pre-existing Hypothyroidism

Pre-existing hypothyroidism in pregnant women may be due to known Hashimoto's hypothyroidism, or an induced hypothyroid state consequent to the treatment of a hyperthyroid state (e.g. Graves' disease, toxic nodules) with radioactive iodine or thyroidectomy. Thyroidectomy may also have been performed as management for thyroid malignancy or multinodular goitre. Rarer causes of pre-existing hypothyroidism include pituitary dysfunction, previous pituitary surgery, and congenital hypothyroidism. Women with pre-existing hypothyroidism will likely already be on thyroxine replacement. Some will be seeing a specialist physician, though many will be managed at primary care level. The key issue in women with pre-existing hypothyroidism is the need for an increased thyroxine dose due to the physiological changes of pregnancy outlined above.

33.3.3.1 Diagnosis

The original cause of a women's hypothyroidism will usually have been diagnosed prior to pregnancy.

- If thyroxine doses are not increased, some women with pre-existing hypothyroidism will have an increase in their thyroid stimulating hormone levels in the first trimester.
- Women with pituitary dysfunction or previous pituitary surgery will not have such a rise as the pituitary is not able to respond to as

according to usual negative feedback principles (See Chap. 26).
- All women may have free thyroxine levels that reduce to the lower part of below the laboratory reference range. Even in the absence of conclusive evidence that thyroid stimulating hormone levels have risen or thyroxine levels have fallen, it is often the case that a greater dose of thyroxine is required.

33.3.3.2 Maternal Concerns

Women with pre-existing hypothyroidism who become pregnant can be asymptomatic or suffer the symptoms of over hypothyroidism such as tiredness and weight gain. However, symptoms of hypothyroidism may be confused with symptoms of normal pregnancy. Thyroid function testing is therefore essential. Profound untreated hypothyroidism is associated with an increased risk of maternal anaemia, heart failure, muscle weakness, pre-eclampsia, placental abruption, and post-partum haemorrhage.

33.3.3.3 Fetal Concerns

Severe maternal hypothyroidism, usually due to iodine deficiency in developing countries, can cause fetal cognitive, neurological, and developmental abnormalities including a constellation of these effects previously termed "cretinism". Many women with pre-existing hypothyroidism are at risk of milder hypothyroidism in pregnancy, therefore requiring early testing and an increase in the thyroxine dose as indicated. A large cohort study found a 7-point lower IQ in the offspring of undertreated hypothyroid mothers, with delays in motor skill development, language development, and attention at 7–9 years of age (Haddow et al. 1999). Maternal hypothyroidism is associated with an increased risk of a low birthweight baby and prematurity.

33.3.3.4 Management

- Women with pre-existing hypothyroidism should either have thyroid function tested as soon as possible after becoming pregnant with dose titration, or be instructed to increase their dose of Thyroxine by approximately 25% on becoming pregnant. As fetal brain development occurs predominantly in the first trimester, the dose increase should not be delayed whilst awaiting specialist review, or if thyroid function testing will cause undue delay.
- Thyroid function tests should ideally be done early in pregnancy and then 4–6 weekly during the first trimester, and then at least once in each of the second and third trimesters. Titration of Thyroxine dose to keep the thyroid stimulating hormone level at the appropriate trimester-specific range. Some women will need a 50% increase in dose. Rarely, after a significant dose increase, thyroid stimulating hormone levels may depress below the reference range. When this happens, the Thyroxine dose may need to be decreased slightly.
- Women should be re-educated in an ideal manner to take Thyroxine medication, on an empty stomach (usually morning), with a sip of water if required. Milk, including tea or coffee should not be consumed for an hour after taking Thyroxine, and other medication including pregnancy multivitamins should be taken at least an hour later.
- On delivery of the baby, the mother should be instructed to return to her pre-pregnancy dose of Thyroxine. No wean or gradual reduction is required.
- The mother should be asked to have repeat thyroid function testing 6–8 weeks post-partum, ideally with her primary care practitioner who will be managing her ongoing care.

33.3.4 Subclinical Hypothyroidism

Subclinical hypothyroidism is common in pregnancy due to the physiological changes of pregnancy outlined above. Treatment thresholds can vary and are in a state of change. Consequently, it is worthwhile consulting local guidelines and clinical leadership for any established management practices. Gestational subclinical hypothyrodism is a transient condition in which the requirement for treatment with thyroxine ceases on delivery. The condition may reoccur in future pregnancies.

Subclinical hypothyroidism is defined as an elevated thyroid stimulating hormone level with thyroxine and triiodothyronine levels in the normal range. Pregnancy and trimester-specific reference ranges should be used when available. Thyroid peroxidase antibodies should be tested to help determine whether the woman has hitherto undiagnosed hypothyroidism or is likely to develop long-term hypothyroidism due to Hashimoto's disease.

33.3.4.1 Diagnosis

In all cases of subclinical hypothyroidism, thyroxine and triiodothyronine levels should be in the normal range. If these levels are lower than the reference range, the patient has overt hypothyroidism and will also require treatment with Thyroxine.

- Total or free hormone level reference ranges can be used and ideally should be pregnancy specific. Usually, the normal range is defined as being between the 2.5th and 97.5th centiles of the relevant normal population (Table 33.1).

33.3.4.2 Maternal Concerns

Subclinical hypothyroidism has been associated with impaired fertility; with the use of thyroxine in women undergoing treatment with assisted reproductive technology becoming common. An association with miscarriage has also been a concern though more recent data has not supported this finding.

There have been studies and meta-analyses of the relationship between subclinical hypothyroidism and the risks of gestational diabetes, placenta previa, placental abruption, and/or pre-eclampsia. Results have differed considerably, partly because of variability in inclusion of overtly hypothyroid women.

Table 33.1 Thyroid stimulating hormone levels that prompt a diagnosis can vary depending on the guidelines being used

	Trimester			
	1	2	3	
TSH (mIU/L)	Pregnancy/ trimester-specific ranges			
TSH (mIU/L)	>2.5	>3.0	>3.5	European Thyroid Association 2014 (Lazarus et al. 2014)
TSH (mIU/L)	>4.0	>4.0	>4.0	American Thyroid Association 2017 (Alexander et al. 2017)

33.3.4.3 Fetal Concerns

As overt hypothyroidism has been associated with lower IQ in children, there has been concern that the offspring of women with subclinical hypothyroidism may also suffer adverse cognitive effects. Studies have reported conflicting results (Williams 2012). Treating pregnant women to a thyroid stimulating hormone level of <1.0 mIU/L did not improve IQ tested at 3 years of age (Lazarus et al. 2012).

One meta-analysis found an increased risk pre-term delivery and perinatal mortality with subclinical hypothyroidism (Van De Bougard et al. 2011) though many individual studies have not concluded this.

33.3.4.4 Management

- Women should be re-educated in an ideal manner to take Thyroxine medication, on an empty stomach (usually morning), with a sip of water if required. Milk, including tea or coffee should not be consumed for an hour after taking Thyroxine, and other medication including pregnancy multivitamins should be taken at least an hour later.
- On a diagnosis of subclinical hypothyroidism, Thyroxine should be commenced at a dose of 50 mcg. If the thyroid stimulating hormone level is grossly elevated (e.g. >10 mIU/L), and/or the patient is obese or has a high weight, a higher commencement dose can be considered.
- Further thyroid function testing should occur 4–6 weeks after dose commencement or change, at least once a trimester. Dosages can be titrated to achieve the required target thyroid stimulating hormone. In general, the dosage of Thyroxine will be more stable in the second and third trimester.
- Thyroid peroxidase antibody levels should be tested. If they are positive, strong consideration should be given to continuing Thyroxine after delivery with instructions for testing and titration 6 weeks post-partum by the primary care practitioner.
- If thyroid peroxidase antibodies are negative, and the woman thus has uncomplicated sub-

clinical hypothyroidism, the woman should be instructed to return to cease Thyroxine after delivery. No wean or gradual reduction is required (Negro et al. 2011).

Box 33.3 Case Example 2. Anxiety and Explanations

K.P is a 26-year-old lady who is 8 weeks into her second pregnancy. Her first child has Autism Spectrum Disorder. K.P is well and without symptoms. After missing her period, she visited her primary care practice. The GP registrar ordered a number of blood tests including thyroid function tests before referring her to your clinic. K.P is a little anxious about her results. She has no significant past medical history.

Examination is unremarkable. Thyroid function test results are TSH 5.5 mIU/L (NR 0.5-4.0), T4 13 pmol/L (NR 10-20), and T3 5 pmol/L (NR 4-7).

What further test is it important to order? How would you counsel and manage K.P?

Please refer to the end of this chapter for answers related to this case

33.3.5 Positive Thyroid Peroxidase Antibodies with Otherwise Normal Thyroid Function

Some women who are seeking to conceive or are pregnant will have positive thyroid peroxidase antibodies but will have thyroid stimulating hormone and thyroxine levels in the normal range. Whilst some research has suggested that commencing such women on Thyroxine will assist with fertility success, a greater number of studies have not supported such a finding. Whilst it is not necessary to cease Thyroxine if it has been commenced by another clinician, it is not desirable to commence Thyroxine in such women. There is a reported association between positive thyroid peroxidase antibodies and spontaneous miscarriage and premature delivery though guidelines do not recommend commencing thyroxine as there is insufficient evidence that this changes outcomes (De Leo and Pearce 2017).

33.3.5.1 Management

- When necessary, counsel women that the majority of the evidence indicates that commencing Thyroxine in their situation is unnecessary and does not change outcomes.
- Inform that the positive antibodies suggest a higher background risk of becoming or developing hypothyroidism in the future
- Monitor the woman's thyroid function tests 4–6 weekly until mid-gestation and then if stable at 30 weeks
- Inform the woman and communicate with her primary care doctor that she should have her thyroid function tested at 6 weeks post-partum, and thereafter 4–6 monthly for at least a year and then as her doctor guides. A woman with positive thyroid peroxidase antibodies is at a higher risk of post-partum thyroiditis and a long-term risk of hypothyroidism

33.4 Thyroid Disorders in the Puerperium (Post-partum) Period

33.4.1 Introduction

The most common thyroid disorder during the post-partum period is post-partum thyroiditis which affects approximately 5% of the population (Stagnaro-Green 2015). Unfortunately, this autoimmune condition is underdiagnosed, with symptoms often being attributed to the challenges of caring for a newborn child.

Approximately a quarter of women with post-partum thyroiditis will experience the "classical" course of hyperthyroidism followed by hypothyroidism. Half will develop hypothyroidism without a hyperthyroid phase. The remainder will have isolated hyperthyroidism only. Some women who become hypothyroid will remain so for the long term.

33.4.1.1 Diagnosis

Women can suffer from hyper- or hypothyroid symptoms (Chaps. 3 and 5) depending on the subtype of hypothyroidism.

- Common hyperthyroid symptoms in the condition are palpitations, heat intolerance, irritability, and fatigue.
- Tiredness, cold intolerance, dry skin, and impaired memory are common in those women who become hypothyroid.
- Post-partum thyroiditis is strongly associated with positive thyroid peroxidase antibodies, which is a useful adjunct test together with thyroid function tests. Women who test positive for thyroid peroxidase antibodies have greater than a 30% chance of developing post-partum thyroiditis.
- Thyroid receptor antibodies should also be tested to exclude Graves' disease—there is also an increased risk of the new development of Graves' disease in the post-partum period. The presence of thyroid receptor antibodies is very likely to indicate Graves' disease.
- Thyroglobulin antibodies may also be positive but provide limited further diagnostic value in the modern context.
- A nuclear medicine thyroid uptake scan (I-131, Tc-99m) can be used to help distinguish different types of thyroid disease. Such imaging is possible in the post-partum period provided breast milk is discarded for the required interval (4 days I-131, 1 day Tc-99m), but in practice other diagnostic methods are strongly preferred.
- Given the common nature of post-partum thyroiditis, there should be a low threshold for thyroid function testing during this time. Women are particularly at risk of developing the disorder 6–10 weeks after delivery but it can occur up to 12 months post-partum. Serial thyroid function testing every 2–3 months is often helpful in determining the subtype of disorder.
- Women with autoimmune diseases such as Type 1 diabetes and systemic lupus erythematosus have a two- to threefold increased over-background risk of developing post-partum thyroiditis. Women with Graves' disease are also at higher risk of developing post-partum thyroiditis. Such women should ideally be reviewed clinically approximately 6 weeks post-partum, with some clinicians reasonably opting to test thyroid function tests in this group regardless of symptomatology.

33.4.1.2 Maternal Concerns

Both the symptoms of hyperthyroidism and hypothyroidism can obviously make caring for a newborn or infant child even more challenging. Given hypothyroidism can cause low mood, particular interest has been focused on the relationship between post-partum thyroiditis and depression. The evidence is conflicting with some studies indicating increased risk whilst other studies have not demonstrated this link. It is prudent to screen women for common depressive symptoms (Table 33.2) and refer appropriately. Research has specifically not shown increased risk of the rarer condition of depression with psychotic features.

33.4.1.3 Neonatal Concerns

There is some evidence that selenium can reduce the risk and severity of post-partum thyroiditis in women who have positive thyroid peroxidase antibodies in pregnancy. However, commencing selenium in this context has yet to become clinical practice, pending further studies to replicate findings.

Table 33.2 Common depressive symptoms in post-partum period

Anhedonia—markedly diminished interest or pleasure in almost all activities
Low mood
Fatigue
Feeling restless or slowed down
Feelings of worthlessness or guilt
Poor sleep—sleeping excessively, difficulty sleeping, and/or early morning wakening
Poor appetite
Thoughts or preoccupation with death or dying including suicide
Irritability
Significant weight loss or weight gain
Difficulty with concentration/memory

Women with autoimmune conditions (e.g. Type 1 diabetes) should receive a clinical review and strong consideration of testing of thyroid function tests and thyroid peroxidase antibodies approximately 6 weeks post-partum.

33.4.1.4 Management

- Management of hyperthyroid phase in affected individuals who are significantly symptomatic is with beta-blocker medication, usually propranolol 10–20 mg three to four times a day.
- Women with post-partum thyroiditis require long-term follow-up to monitor for the emergence of hypothyroidism.

Box 33.4 Case Example 3. Post-partum Struggles

H.O is 5 weeks post-partum, having delivered her first child who was born healthy at term. Her thyroid function tests (thyroid stimulating hormone and thyroxine/T4) during pregnancy were normal though her thyroid peroxidase antibodies were on the upper limit of the normal range. H.O was not started on thyroxine. Her sister and mother have had Hashimoto's hypothyroidism for a number of years.

H.O phones you as you reviewed her during her pregnancy. She says she is struggling to sleep and noticed she is losing hair. H.O says she is often worried about her baby's feeding and sleeping and feels overwhelmed. Her husband works long hours, and her own family are overseas.

How would you manage H.O in this situation?
What tests would you organise and what would you expect to find?

Please refer to the end of this chapter for answers related to this case

33.5 Conclusions

Thyroid disease can have a diverse range of causes and presentations during pregnancy. The most common conditions of subclinical hypothyroidism and pre-existing hypothyroidism can be well managed with thyroxine commencement and adjustment, with regular thyroid function test monitoring. Gestational hyperthyroidism is a self-limiting condition which should be distinguished from Graves' disease. Graves' disease requires specialist input throughout pregnancy and surveillance in the post-partum period. Post-partum thyroiditis can cause hypothyroidism or hyperthyroidism. The condition is common and underdiagnosed. Thyroid function tests should be organised if there is clinical suspicion, and patients will require long-term follow-up.

Case Study 2–4. Answers

Case study 2: M.R symptoms of palpitations, difficulty sleeping, and not putting on weight are consistent with hyperthyroidism. Her thyroid function tests support this with an elevated thyroxine/T4 and supressed thyroid stimulating hormone levels. As she is in the first trimester, gestational hyperthyroidism caused by BHCG stimulation of the thyroid is the probable diagnosis. Although the condition is considered "benign" in that it does not cause fetal problems or long-term maternal problems, women can be significantly symptomatic. It is important to test for thyroid receptor antibodies to distinguish from the serious condition of Graves' disease. A positive result for such antibodies should prompt immediate contact with a specialist. M.R should be counselled that the condition is self-limiting and likely to improve in the next 2–6 weeks as BHCGs levels fall in the second trimester. She should be encouraged to eat more and to activate social supports. Beta-blocker medication can be considered in severe cases for short-term use with the involvement of a medical practitioner.

Case study 3: K.P has subclinical hypothyroidism as defined by her thyroid stimulating hormone being marginally elevated and her thyroid stimulat-

ing hormone being in the normal range. Most women with this condition are asymptomatic. In the context of having a child with Autism Spectrum Disorder, K.P may be particularly concerned about anything she has read or heard regarding a link between "low thyroid levels" and "intellectual problems". It is important to reassure K.P that this generally occurs in cases much more severe than her situation. K.P should be tested for thyroid peroxidase antibodies, the presence of these may indicate that she would benefit from post-partum monitoring for the development of post-partum thyroiditis or hypothyroidism. During pregnancy, a small dose of thyroxine (e.g. 50mcg daily) should be started with titration to the pregnancy-specific thyroid stimulating hormone targets outlined in this chapter, or as per local guidelines.

Case example 4: H's symptom of losing hair is consistent with hyperthyroidism. Her difficulty in sleeping and concern about her child's welfare may be expected with a newborn child, but may also be due or worsened by hyperthyroidism. It can be difficult to distinguish such a situation clinically, and therefore thyroid function and thyroid antibody tests, especially thyroid peroxidase antibodies, should be requested. Together these results (supressed thyroid stimulating hormone, elevated thyroxine/T4, positive thyroid peroxidase, and thyroglobulin antibodies) may indicate a diagnosis of post-partum thyroiditis. Serial clinical and biochemical monitoring of women with post-partum thyroiditis is required. In the long-term, hypothyroidism may develop and require treatment with thyroxine.

References

Alexander EK, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315–89.

De Leo S, Pearce E. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol. 2017. http://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587(17)30402-3.pdf, https://www.ncbi.nlm.nih.gov/pubmed/29246752. Accessed 22 March 2018.

Glinoer D. Maternal and fetal impact of chronic iodine deficiency. Clin Obstet Gynecol. 1997;40(1):102–16.

Glinoer D. Thyroid hyperfunction during pregnancy. Thyroid. 1998a;8(9):859–64.

Glinoer D. The systematic screening and management of hypothyroidism and hyperthyroidism during pregnancy. Trends Endocrinol Metab. 1998b;9(10):403–11.

Glinoer D. Iodine supplementation during pregnancy: importance and biochemical assessment. Exp Clin Endocrinol Diabetes. 1998c;106(Suppl 3):S21.

Glinoer D. What happens to the normal thyroid during pregnancy? Thyroid. 1999;9(7):631–5.

Haddow JE, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341(8):549–55.

Lazarus JH, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012;366(6):493–50.

Lazarus J, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J. 2014;3(2):76–94.

Negro R, et al. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. J Clin Endocrinol Metab. 2011;96(6):E920–4.

Stagnaro-Green A. Chapter 4: Approach to the patient with postpartum thyroiditis. In: Wartofsky L, editor. Clinical approach to endocrine & metabolic diseases; 2015.

Van De Bougard E, Vissenburg R, Land JA, Van Wely M, VanDerPost JA, Goddijn M, Bisschop PH. Significance of (sub)clinical thyroid dysfunctionand and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human Reprod Update. 2011;17(5):605–19.

Williams F, et al. Mild maternal thyroid dysfunction at delivery of infants born ≤34 weeks and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab. 2012;97(6):1977–85.

Yoshihara A, et al. Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. J Clin Endocrinol Metab. 2012;97(7):2396–403.

Key Reading

1. Alexander EK, Pearce EN, Brent GA. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315–89. https://doi.org/10.1089/thy.2016.0457.
2. Lazarus J, Brown RS, Daumerie C, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Thyroid J. 2014;3(2):76–94. https://doi.org/10.1159/000362597.
3. Cignini P, et al. Thyroid physiology and common diseases in pregnancy: review of literature. J Prenat Med. 2012;6(4):64–71.

Part V

The Adrenal Gland

Sofia Llahana

34 Anatomy and Physiology of the Adrenal Gland

Phillip Yeoh

Contents

34.1 **Adrenal Development in Fetal and Postnatal Stage** 646
34.2 **Anatomy of Adrenal Glands** 647
34.3 **Functions of the Adrenal Glands** 648
34.3.1 Aldosterone 648
34.3.2 Cortisol 649
34.3.3 Androgens 652
References 654

Abstract

The adrenal glands are important endocrine organ that produces corticosteroids including glucocorticoids, mineralocorticoids and androgens. These are important hormones that regulate sodium retention, blood pressure, fluid volume, the immune system, metabolism and behaviour. The adrenals also exert negative feedback mechanism in the hypothalamus and pituitary through the hormone cortisol. High levels of cortisol suppress the pituitary hormone ACTH whereas low cortisol stimulates ACTH secretion by increasing the release of hypothalamic hormones CRH and AVP. The adrenal medulla, which is located in the central part of the adrenal, forms part of the sympathetic nervous system and is referred as the sympatho-adrenomedullary system. It secrets epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine in response to stimulation by the sympathetic nervous system.

Keywords

Adrenal · Hypothalamic-pituitary axis · Zona glomerulosa · Zona fasciculata · Zona reticularis · Adrenal cortex · Adrenal medulla · Aldosterone · Cortisol · Androgen

P. Yeoh (✉)
The London Clinic, London, UK
e-mail: p.yeoh@thelondonclinic.co.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_34

Abbreviations

ACTH	Adrenocorticotropic hormone
AGP	Adrenogonadal primordium
AngII	Angiotensin II
AR	Androgen receptor
AVP	Arginine vasopressin
CAH	Congenital adrenal hyperplasia
CBG	Corticosteroid-binding globulin
CRH	Corticotropin releasing hormone
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
DHT	Dihydrotestosterone
GC	Glucocorticoid
GR	Glucocorticoid cell receptor
HPA	Hypothalamic pituitary axis
PAPS	3′-phosphoadenosine-5′-phophosulfate
PCOS	Polycystic ovarian syndrome
SCN	Hypothalamic suprachiasmatic nucleus
zF	Zona fasciculata
zG	Zona glomerulosa
zR	Zona reticularis

Key Terms

- **Outer layers of adrenal cortex:** This is made up of the zona glomerulosa (zG), zona fasciculata (zF) and zona reticularis (zR), comprising of 90% of the gland.
- **Inner layer of adrenal cortex:** The adrenal medulla is located in the middle of the adrenal gland beyond the zona reticularis (zR).

Key Points

- The adrenal consist of three outer zones: zona glomerulosa, zona fasciculata and zona reticularis. The inner layer is the adrenal medulla.
- The adrenal is a major endocrine gland in the human body.

34.1 Adrenal Development in Fetal and Postnatal Stage

The embryonic adrenal development derives from neural crest cells and intermediate mesoderm. The early stage of adrenal development appears as an adrenogonadal primordium (AGP) at 28–30 days post-conception in humans. Neural crest cells develop into the adrenal medulla while intermediate mesoderm regresses into the definitive adrenal cortex. During the embryonic stage, the neural crest cells differentiate into neuroblasts (sympathoblasts) and become sympathetic and autonomic ganglion cells as well as phaeochromoblasts, which later become phaeochromocytes or mature chromaffin cells. Phaeochromocytes which form the adrenal medulla are enveloped by mesenchymal primitive adrenal cortex.

During the fetal stage, the zone of adrenal cortex of is called the fetal zone; 80% of it consists of fetal zone cells. These cells produce large quantities of DHEA and DHEAS, which are converted to oestrogen by the placenta for the maintenance of normal pregnancy. Adrenocortical cells emerge by the 8th week of gestation to form the definitive zone that later develops into the adrenal cortex. During the last 6 weeks of gestation, the majority of the prenatal growth is due to the enlargement of the fetal cortex which is the largest zone at birth.

After birth, the fetal zone undergoes changes under the influence of the hormones angiotensin II (AngII) and ACTH, whereby the zona glomerulosa (zG) and zona fasciculata (zF) mature. Unlike the zona glomerulosa and fasciculata, the zona reticularis does not function actively between 6–8 years old in females and 7–9 years old in males. It begins to emerge between the zona fasciculata and the medulla in a process known as ‘adrenarche’, which involves the proliferation and production of adrenal androgens. Adrenarche is independent of ACTH or gonadotropins. Secondary sexual characteristics also begin to occur at adrenarche. The mechanisms

involved in postnatal adrenal formation and the maintenance of these distinct zones remain poorly understood.

34.2 Anatomy of Adrenal Glands

The adrenal glands weigh 4–5 g each in a normal healthy adult and sit on the upper end of the right and left kidneys (Fig. 34.1). The centre of the adrenal gland, the medulla, weighs around 1 g. The outer layer, the zona glomerulosa (zG), is composed of ovoid-shaped cells. The zona fasciculata forms the majority of the adrenal cortex and is organised in fascicles or bundles. There is no anatomical demarcation between medulla and cortex. The medulla is composed of chromaffin cells and contains small vesicles 100–300 nm in diameter in which catecholamines (adrenaline and noradrenaline) are stored and released. In the human, adrenaline accounts for 80% of adrenal catecholamine release into the circulation system and has effects on multiple organs.

The adrenal cortex synthesises corticosteroids, including over 50 distinct steroid hormones. Under normal condition in the absence of stress, the adult adrenal cortex produces approximately 10–15 mg of cortisol per day.

The adrenal glands are highly vascular, with three critical arteries supplying each adrenal gland. The superior suprarenal artery, the superior suprarenal artery and the middle suprarenal artery. Blood flows into the adrenal cortex and drains into the adrenal medulla before entering the inferior vena cava via the central vein on the right adrenal. On the left, the adrenal vein blood drains into the left renal vein. The drainage system of the adrenal gland plays a complex role in steroid synthesis and regulation. The adrenal gland is also well innervated. The nerve supply originates from the coeliac plexus and thoracic splanchnic region of the sympathetic autonomic nervous system, as well as some parasympathetic contributions from the phrenic and vagal nerves. The nerve supply also reaches the chromaffin cells in the medulla, and the innervation has been

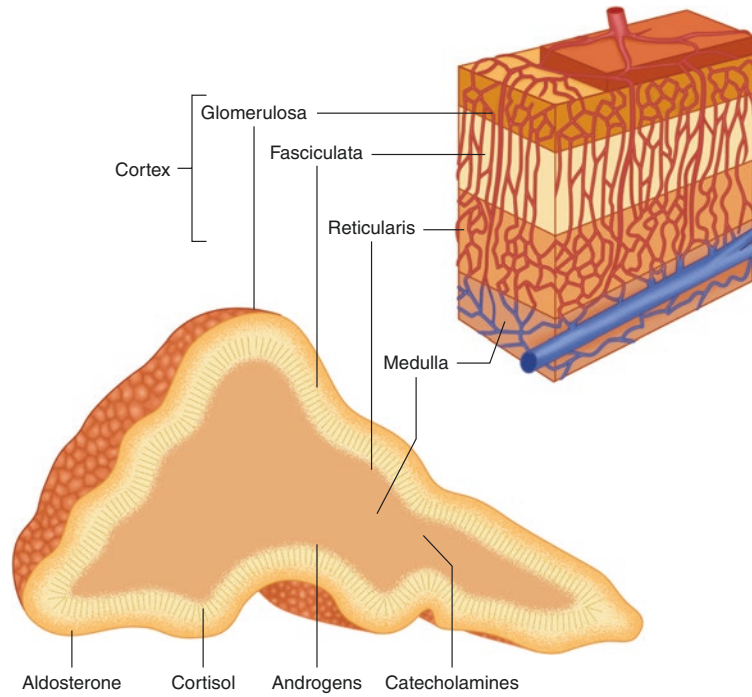


Fig. 34.1 Anatomy and hormones secretion of adrenal gland

suggested to reach the cortisol arteriolar and capillary bed to regulate cortisol blood flow. Chromaffin cells are also found in the vagus nerve, carotid arteries, bladder, prostate and liver. Besides secreting catecholamine and dopamine, the adrenal medulla also secretes other stress hormones such as enkephalins and neuropeptide Y. One of the most important actions of catecholamine is the fight-or-flight response which leads to an increase in respiration, heart rate, blood pressure and blood vessel constriction (in the skin and gut).

34.3 Functions of the Adrenal Glands

The adrenal cortex is responsible for the production of three major classes of steroid hormones: glucocorticoids, mineralocorticoids and androgens (Fig. 34.2). The zona glomerulosa synthesises the mineralocorticoids aldosterone, the zona fasciculata produces cortisol, while the inner layer zona reticularis secretes androgen steroids such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), androstenedione and 1β-hydroxyandrostenedione. Glucocorticoids, such as cortisol, are secreted in high amounts around 10–50 mg/day whereas mineralocorticoids, such as aldosterone, are much less at around 100–200 μg/day. Surprisingly, DHEAS is also secreted in large quantities.

34.3.1 Aldosterone

First isolated in 1953, aldosterone has a plasma half-life of under 20 min and is weakly bound to plasma proteins. The adrenal secretes an average of 100–200 μm of aldosterone in 24 h. Its secretion is mainly stimulated by angiotensin II and an increase of extracellular potassium concentration, compared to other minor modulators such ACTH, stretch receptors in the heart, serum sodium and serotonin. Angiotensin II is converted in the lung from angiotensin I, which is stimulated by the release of the enzyme renin in the kidney (Fig. 34.3). Aldosterone promotes sodium and water retention and lowers plasma potassium levels by binding to mineralocorticoid receptors in the renal tubules. After binding to the receptor, the complex translocates to genomic DNA which causes gene transcription expression and in turn leads to reabsorption and retention of sodium and excretion of potassium and hydrogen. The sequence also affects blood pressure and extracellular fluid volume. This system is called the renin-angiotensin-aldosterone system and also has a small diurnal rhythm mediated by ACTH.

Aldosterone and corticosterone share the first part of their biosynthesis pathways. They are synthesised from cholesterol catalysed by enzyme of cytochrome P450 family located in the mitochondria (Fig. 34.3). The last part of the aldosterone pathway is mediated by aldosterone synthase, found only in the zona glomerulosa in the adrenal where pregnenolone is transformed to progesterone and then to aldosterone. Aldosterone is catabolised in the liver and kidney and a small amount is excreted in the urine. Aldosterone level in plasma is also affected by the time of the day and posture.

34.3.1.1 Aldosterone Dynamic

Aldosterone excess has a profound impact on blood pressure due to the increase in sodium and fluid retention, including extracellular fluid expansion as well as suppression of plasma renin activity. This chronic hypervolaemic state leads to hypertension. Aldosterone excess is found in primary hyperaldosteronism where excess secretion of aldosterone leads to suppression of renin, hypokalaemia and hypertension. In congenital adrenal hyperplasia (CAH), C21-hydroxylase deficiency caused by 21-hydroxylase gene mutation leads to increased ACTH levels and androgens but loss of major mineralocorticoids. Classic form of CAH presented with salt-losing and virilisation.

Conversely, patients with primary and secondary adrenal failure may present with low blood pressure, low sodium and hyperkalaemia, but only in primary adrenal failure there is loss of mineralocorticoids. Replacement with mineralocorticoid will rectify the electrolyte imbalance in such patients.

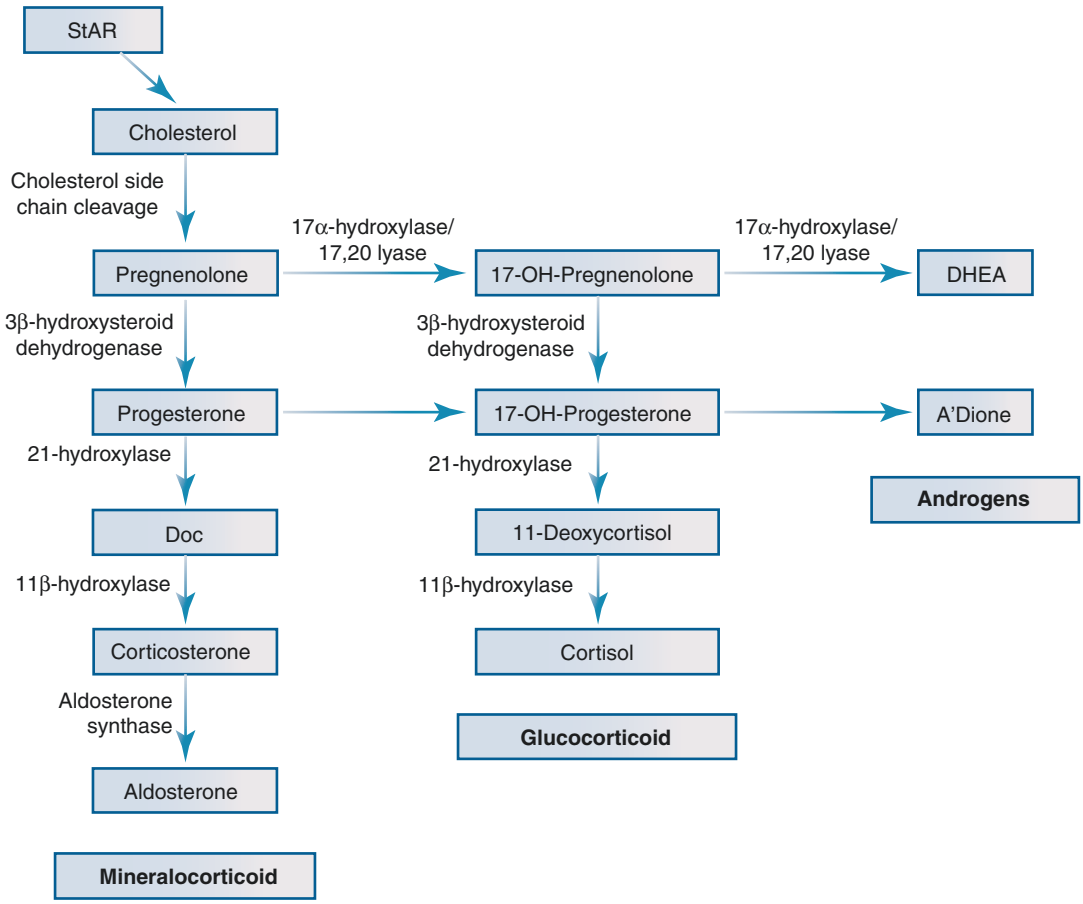


Fig. 34.2 Adrenal steroidogenesis. (Used with permission from Stewart P.M. (2008) The adrenal cortex, chapter 14. In: Kronemberg H.M., Melmed S., Polonsky K.S. and Larsen P.R. (Eds) Williams Textbook of Endocrinology, 11th Edition. Saunders Elsevier, Philadelphia, pages: 445–503)

34.3.2 Cortisol

The 'stress hormone' cortisol plays a major role in the hypothalamic-pituitary-adrenal HPA axis (Fig. 34.4) (please read the Chap. 12 in Part III for more details). Cortisol exerts numerous effects including blood sugar control through gluconeogenesis, affects blood pressure through salt and water regulation and regulates the immune system through its anti-inflammatory effects. It also affects memory, emotion and cognition.

Cortisol production is stimulated by the pituitary hormone ACTH, which itself is regulated by corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus. ACTH is a 39 amino-acid peptide secreted by the anterior pituitary gland. Its secretion also occurs in response to low circulating cortisol, anxiety and stress, as well as the underlying circadian rhythm. It is inhibited by high endogenous and exogenous circulating cortisol or other glucocorticoids, and thus forms a homeostatic loop.

Cortisol is produced in circadian manner (Fig. 34.5), peaking around 8–9 am and at several points throughout the day including following meals. At a cellular level, cortisol binds to the glucocorticoid cell receptor (GR). Once bound to the receptor, it is translocated to the nucleus and leads to changes in metabolism particularly on carbohydrate, fat and protein metabolism. The GR complex also up-regulates the expression of

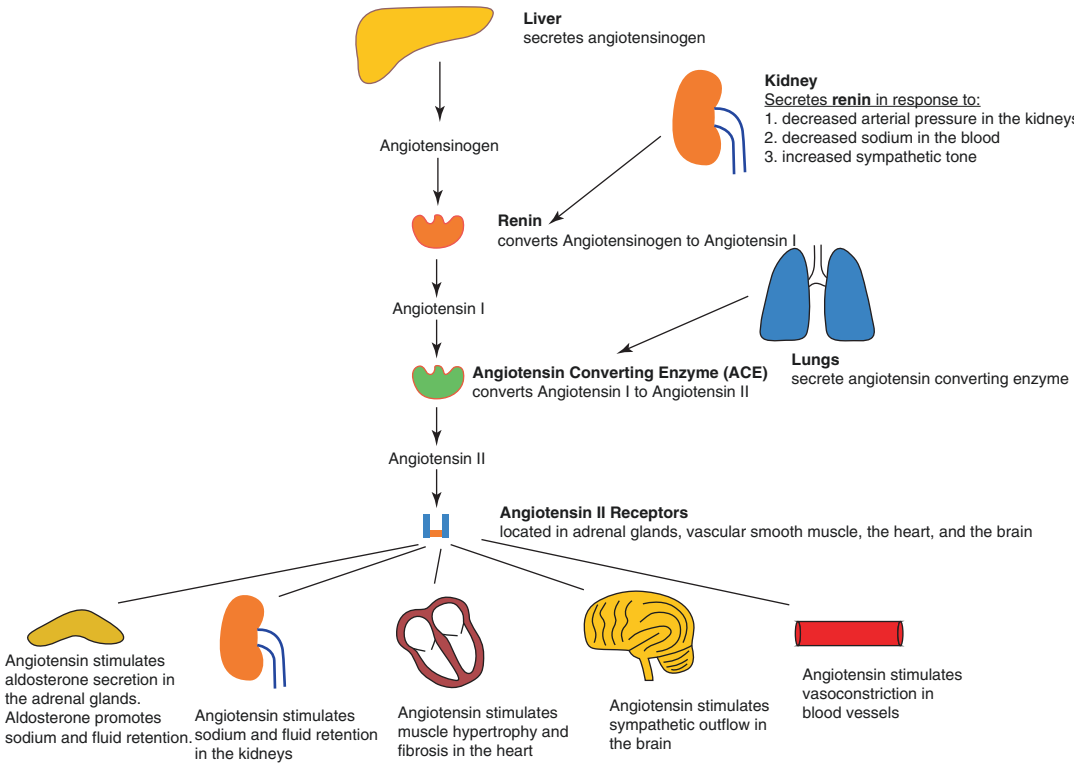


Fig. 34.3 The renin-angiotensin-aldosterone system

anti-inflammatory proteins in which represses the expression of pro-inflammatory proteins.

34.3.2.1 Body Circadian Rhythm of Cortisol Production

The circadian rhythm of cortisol secretion is shown in Fig. 34.5. ACTH is secreted in a pulsatile manner. Peak levels usually occur in the morning coinciding with peak cortisol production with a 30–60 min delay. It has a short life and the response is closely related to physical demands and environmental influences.

This circadian system is controlled by central clock in the hypothalamic—the suprachiasmatic nucleus (SCN)—which synchronises subsidiary cellular peripheral clocks. The SCN is located in the anterior part of the hypothalamus immediately dorsal, or superior (hence supra), to the optic chiasm. The intracellular mechanisms interlock negative and positive transcriptional-translational feedback loops that oscillate over a 24-h period.

34.3.2.2 Pharmacodynamics of Cortisol

Cortisol is circulated in three forms: protein bound, free cortisol and cortisol metabolites. The largest group is protein-bound cortisol which constitutes approximately 92% of the total cortisol in the circulation. It has a better affinity to corticosteroid-binding globulin (CBG) than to albumin. The free cortisol or unbound fraction is the active hormone that dictates physiological activity. When the cortisol secretion reaches a saturation point with normal CBG secretion, this leads to increased free or unbound cortisol in circulation. Most synthetic glucocorticoids have less affinity to CBG. Prolonged elevation of free or unbound cortisol in circulation adversely produces Cushingoid symptoms.

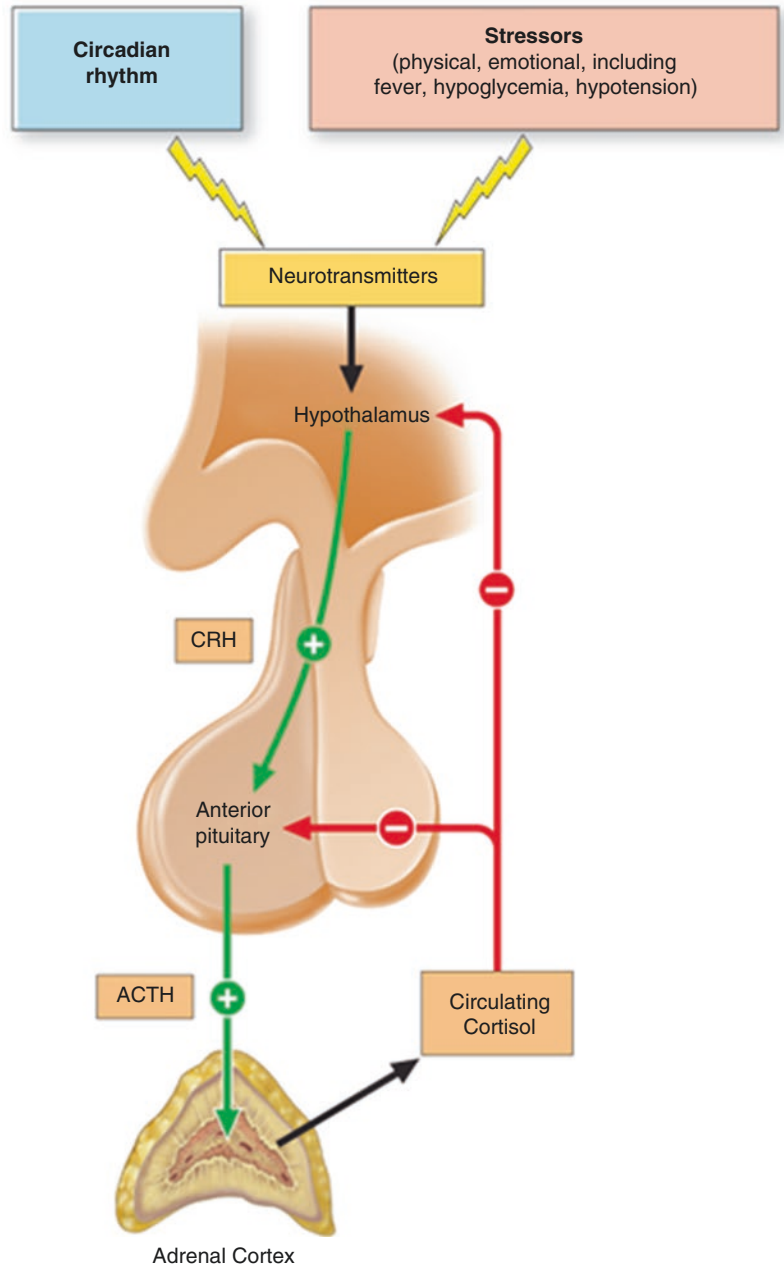


Fig. 34.4 The hypothalamic-pituitary-adrenal (HPA) axis and regulation of adrenal glucocorticoid secretion. (Used with permission from Arlt W (2017) Disorders of the adrenal cortex, chapter 8. In: Jameson JL (Eds) Harrison's Endocrinology, 4th Edition, McGraw Hill Education, New York, pages 107–135)

Cortisol is metabolised in the liver and metabolites are excreted via the kidneys.

Standard laboratory assays for serum cortisol levels include protein-bound and the free or unbound fractions in order to determine the total concentration. Cortisol can also be measured in the saliva and urine. Salivary cortisol reflects the amount of free unbound cortisol that escapes binding proteins and enters the tissues throughout the body. Salivary cortisol measures cortisol collected at that particular time: 24 h urinary free cortisol (UFC) captures total amount of free and

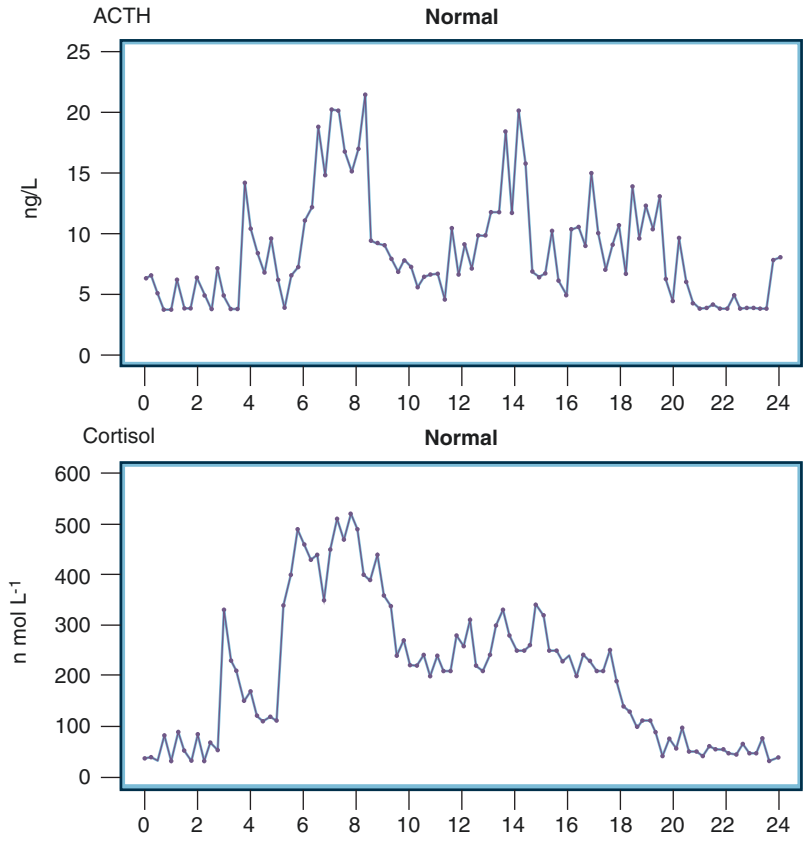


Fig. 34.5 The circadian rhythm of the cortisol production. (Used with permission from Stewart P.M. (2008) The adrenal cortex, chapter 14. In: Kronemberg H.M., Melmed S., Polonsky K.S. and Larsen P.R. (Eds) Williams Textbook of Endocrinology, 11th Edition. Saunders Elsevier, Philadelphia, pages: 445–503)

unbound cortisol excreted in urine over 24 h period. It should be emphasised that many cortisol assays will also measure, to some extent, other corticosteroids or their metabolites.

34.3.3 Androgens

Adrenal androgens are synthesised from cholesterol through a series of intracellular and extracellular actions involving oxidases and dehydrogenases. Unlike glucocorticoids, adrenal androgens have little activity at androgen receptors. Instead, they function as precursor molecules ready to be metabolised peripherally to potent androgens such as DHT or aromatised to oestradiol. The C_{19} steroids include DHEA, DHEAS, androstenedione and 11β-hydroxyandrostenedione. They are produced in adrenal gland and gonads in both men and women. Circulating levels of dehydroepiandrosterone (DHEA), DHEA-sulphate (DHEAS), androst-5-ene-3 beta, 17 beta-diol (5-diol), 5-diol-sulphate, 5-diol-fatty acid esters and androstenedione in both men and women were found to decline from the age of 20–80 years old (Labrie et al. 1997). The majority of DHEA and DHEAS comes from the adrenals, including 50% of secreted androstenedione. The conversion to potent androgens such as testosterone or dihydrotestosterone occurs in tissues that express HSD3-B1 and HSD17-B1/5 such as adipose tissue and the skin.

The adrenal gland secretes a small amount of testosterone. In men, testosterone is predominantly produced by Leydig cells in the testes. In women, DHEA can be taken up by ovarian theca cells to synthesise testosterone and may be converted to dihydrotestosterone in peripheral tissues once converted to androstenedione, without requiring transformation to testosterone (Nakamura et al. 2009). In healthy men, circulating testosterone levels are approximately ten times higher than women (Taieb et al. 2003).

DHEA is converted to DHEA-sulphate (DHEAS), an inactive steroid, through the enzyme DHEA sulfotransferase SULTA2-A1. When required, DHEAS is reactivated back to DHEA with the presence of the sulphate donor 3′-phosphoadenosine-5′-phophosulfate (PAPS). PAPS is synthesised by the two isoform of PAPS synthase, PAPSS1 and PAPSS2. The sulphation process is important to prevent excess androgen formation, which could in turn lead to increased androstenedione or testosterone.

However, the regulation of adrenal androgens remain poorly understood. It is thought that ACTH may play a role. This is from data collected from patients with ACTH stimulation during adrenal venous sampling (Rege et al. 2013) where ACTH administration increases DHEAS by fivefold, DHEA by 21-fold, androstenedione by sevenfold and 11β-hydroxyandrostenedione by fivefold. Whether this is physiologically relevant remains unclear.

Androgens play a critical role for the development and maintenance of the male reproductive system. They also influence insulin sensitivity as well as bone and muscle metabolism. It exerts its effects by a genomic mechanism by involving the hormones binding to androgen receptor (AR) resulting in the modulation of gene expression. The androgen receptor is a nuclear receptor that is activated by androgenic hormones such as testosterone or dihydrotestosterone in the cytoplasm, and then translocate into the nucleus. During male sexual development, testosterone is responsible for primary sexual characteristic development, while dihydrotestosterone is responsible for secondary male characteristics, particularly male genital development to form the penis scrotal pouches as well as hair follicle development.

Androgen increases the rate of bone remodelling by prolonging the lifespan of osteoclasts and shortening the lifespan of osteoblasts. This leads to slow the maturation of bone, but the more potent epiphyseal effect comes from oestrogen which is aromatised from androgens.

Androgens also impair adipose tissue to proliferate and differentiate. This in turn induces adipose tissue dysfunction and affects glucose uptake and leads to insulin resistance, intracellular stress and inflammation (Klöting and Blüher 2014). Treatment of androgen excess has been shown to reduce fasting insulin and improve the insulin sensitivity (Banaszewska et al. 2016).

34.3.3.1 Testosterone

Testosterone has a direct impact in body composition of men by increasing lean body mass and this leads to increase insulin sensitivity. Low testosterone independently affects insulin resistance. Androgen replacement therapy improves insulin sensitivity, diabetes and the metabolic syndrome in hypogonadal men (Haider et al. 2014; Traish et al. 2014).

High levels of testosterone correlate with high androstenedione levels in women with polycystic ovary syndrome (O'Reilly et al. 2014) who were found to have an adverse metabolic phenotype. However, Lerchbaum et al. (2014) argued contrarily that high androstenedione and the free testosterone index have a beneficial metabolic effect.

On the other hand, patients with adrenocortical carcinoma often present with Cushing's syndrome and androgen excess including DHEA/DHEAS, androstenedione and testosterone. High testosterone in women may cause hirsutism, acne, deepening of the voice, hair loss and amenorrhoe. However, testosterone excess in men raised haematocrit, seborrhoea, acne and some mood changes.

34.3.3.2 DHEA/DHEAS

Sulphation is an important pathway of DHEA metabolism. Any disruption in this pathway, including patients with PAPSS2 mutations, can lead to high active DHEA and a low DHEAS levels (Oostdijk et al. 2015). A similar pattern was found in two thirds of polycystic ovarian syndrome patients showing an increase in the DHEA/DHEAS ratio with significantly increased excretion of both major androgen metabolites, androsterone and aetiocholanolone (Kempegowda et al. 2016); 20–30% of PCOS women were found to have excess DHEAS levels (Goodarzi et al. 2015). In Asian women with PCOS, high serum

DHEAS is associated with the presence of acne and a significantly reduced risk of abdominal obesity, independent of serum testosterone concentration and insulin resistance (Chen et al. 2011). The study showed that DHEAS and total testosterone have different relationships with body weight, abdominal obesity and dyslipidaemia. A lower prevalence of acne was found in obese PCOS women with lower DHEAS concentrations (Afifi et al. 2017). Asian patients with PCOS have a lower prevalence and severity of hirsutism and obesity which might be attributed to genetic and environmental differences.

34.3.3.3 Conclusions

The adrenals play an important role in the dynamics of the endocrine system. Its complex interactions with hormone pathways, genetic factors, environmental influences and the body's circadian rhythm all play a vital role in its secretion, excretion and homeostasis. Excess and insufficient adrenal secretions underpin the balance between health and disease. Feedback mechanisms are often involved in the synthesis and pathway of the adrenal system.

References

Afifi L, Saeed L, Pasch LA, Huddleston HG, Cedars MI, Zane LT, Shinkai K. Association of ethnicity, Fitzpatrick skin type, and hirsutism: a retrospective cross-sectional study of women with polycystic ovarian syndrome. Int J Womens Dermatol. 2017;3(1):37–43. Published online 2017 Mar 13. https://doi.org/10.1016/j.ijwd.2017.01.006.

Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L, Duleba AJ. Effects of resveratrol on polycystic ovary syndrome: A double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2016;101(11):4322–8. Epub 2016 Oct 18.

Chen ML, Chen CD, Yang JH, Chen CL, Ho HN, Yang WS, Yang YS. High serum dehydroepiandrosterone sulfate is associated with phenotypic acne and a reduced risk of abdominal obesity in women with polycystic ovary syndrome. Hum Reprod. 2011;26(1):227–34. https://doi.org/10.1093/humrep/deq308.

Goodarzi MO, Carmina E, Azziz R. DHEA, DHEAS and PCOS. J Steroid Biochem Mol Biol. 2015;145:213–25. https://doi.org/10.1016/j.jsbmb.2014.06.003. Epub 2014 Jul 5.

Haider A, Yassin A, Doros G, Saad F. Effects of long-term testosterone therapy on patients with "Diabesity": results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes. Int J Endocrinol. 2014;2014:683515. https://doi.org/10.1155/2014/683515.

Kempegowda P, O'Reilly MW, Hassan-Smith Z, Storbeck KH, Taylor AE, Arlt W. Impaired DHEA sulfation defines androgen excess in women with polycystic ovarian syndrome (PCOS). Endocr Abstr. 2016;41:GP184. https://doi.org/10.1530/endoabs.41.GP184.

Klöting N, Blüher M. Adipocyte dysfunction, inflammation and metabolic syndrome. Rev Endocr Metab Disord. 2014;15(4):277–87. https://doi.org/10.1007/s11154-014-9301-0.

Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997;82(8):2396–402.

Lerchbaum E, Schwetz V, Rabe T, Giuliani A, Obermayer-Pietsch B. Hyperandrogenemia in polycystic ovary syndrome: exploration of the role of free testosterone and androstenedione in metabolic phenotype. PLoS One. 2014;9(10):e108263. https://doi.org/10.1371/journal.pone.0108263. eCollection 2014

Nakamura Y, Hornsby PJ, Casson P, Morimoto R, Satoh F, Xing X, Kennedy MR, Sasano H. Rainey WE Type 5 17beta-hydroxysteroid dehydrogenase (AKR1C3) contributes to testosterone production in the adrenal reticularis. J Clin Endocrinol Metab. 2009;94(6):2192–8. https://doi.org/10.1210/jc.2008-2374. Epub 2009 Mar 31.

O'Reilly MW, Taylor AE, Nicola J, Crabtree NJ, Hughes BA, Capper F, Crowley RK, Stewart PM, Tomlinson JW, Arlt W. Hyperandrogenemia predicts metabolic phenotype in polycystic ovary syndrome: the utility of serum androstenedione. J Clin Endocrinol Metab. 2014;99(3):1027–36. Published online 2014 Jan 7. https://doi.org/10.1210/jc.2013-3399.

Oostdijk W, Idkowiak J, Mueller JW, House PJ, Taylor AE, O'Reilly MW, Hughes BA, Mde Vries MC, Kant SG, Santen GWE, Verkerk AJMH, Uitterlinden AG, Wit JM, Losekoot M, Arlt W. PAPSS2 deficiency causes androgen excess via impaired DHEA sulfation—in vitro and in vivo studies in a family harboring two novel PAPSS2 mutations. J Clin Endocrinol Metab. 2015;100(4):E672–80. Published online 2015 Jan 16. https://doi.org/10.1210/jc.2014-3556.

Rege J, Nakamura Y, Fumitoshi S, Morimoto R, Kennedy MR, Layman LC, Honma S, Hironobu S, Rainey WE. Liquid Chromatography-Tandem mass spectrometry analysis of human adrenal vein 19-cardon steroids before and after ACTH stimulation. J Clin Endocrinol Metab. 2013;98(3):1182–8.

Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, Lacroix I, Somma-Delpero C, Bouloux

P. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. Clin Chem. 2003;49(8):1381–95.

Traish AM, Haider A, Doros G, Saad F. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. Int J Clin Pract. 2014;68(3):314–29. https://doi.org/10.1111/ijcp.12319. Epub 2013 Oct 15.

Key Reading

1. Stewart PM. The adrenal cortex, chapter 14. In: Kronemberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th ed. Philadelphia: Saunders Elsevier; 2008. p. 445–503.

35 Diagnosis and Management of Congenital Adrenal Hyperplasia in Children and Adults

Alessandro Prete, Chona Feliciano, Irene Mitchelhill, and Wiebke Arlt

Contents

35.1 **Introduction** 659

35.2 **Pathophysiology of Congenital Adrenal Hyperplasia** 659

35.3 **Classification and Manifestations of Congenital Adrenal Hyperplasia** 661

35.4 **Assessment, Care, and Management of Patients with Congenital Adrenal Hyperplasia** 662

35.4.1 Diagnosis 662

35.4.2 Classic Congenital Adrenal Hyperplasia: Medical Treatment 663

35.4.3 Classic Congenital Adrenal Hyperplasia: Treatment and Prevention of Adrenal Crisis 665

35.4.4 Classic Congenital Adrenal Hyperplasia: Monitoring 667

35.4.5 Classic Congenital Adrenal Hyperplasia: Management in the Neonatal Period 667

35.4.6 Classic Congenital Adrenal Hyperplasia: Management During Infancy and Childhood 669

35.4.7 Classic Congenital Adrenal Hyperplasia: Management During Adolescence 671

A. Prete
Institute of Metabolism and Systems Research, University of Birmingham and Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
e-mail: A.Prete@bham.ac.uk

C. Feliciano
Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
e-mail: Chona.Feliciano@uhb.nhs.uk

I. Mitchelhill
Department of Endocrinology, Sydney Children's Hospital (SCHN), Randwick, NSW, Australia
e-mail: Irene.mitchelhill@health.nsw.gov.au

W. Arlt (✉)
Institute of Metabolism and Systems Research (IMSR), College of Medical and Dental Sciences, University of Birmingham and Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
e-mail: w.arlt@bham.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_35

35.4.8 Classic Congenital Adrenal Hyperplasia: Management in the Adult Care Setting 671
35.4.9 Classic Congenital Adrenal Hyperplasia: Fertility 672
35.4.10 Classic Congenital Adrenal Hyperplasia: Management of a Genetic Diagnosis 672
35.4.11 Management of Nonclassic Congenital Adrenal Hyperplasia 672
35.4.12 Additional Aspects of Optimal Care 673

35.5 Role of Patient Advocacy Groups in Improving Patient Care and Education in CAH 673
35.5.1 The CAH Support Group (Reprinted Permission from CAH Support Group (UK) Patient Advocacy Group) 673
35.5.2 The CARES Foundation (Reprinted Permission from CARES Foundation (USA) Patient Advocacy Group) 674

35.6 A Patient Perspective (Published with Patient Consent) 675

35.7 Conclusions 676

References 676

Abstract

The adrenal cortex produces the steroid hormones, glucocorticoids, mineralocorticoids, and androgens, required for normal metabolic function. They are specifically involved in supporting the stress response, salt and water balance, and sex development. Congenital adrenal hyperplasia (CAH) is a group of genetic disorders caused by enzyme deficiencies in adrenal steroid production. More than 90% of CAH cases are caused by a deficiency of the adrenal steroid enzyme 21-hydroxylase (CYP21A2). Depending on the severity of deficiency, patients can have a variable spectrum of clinical presentation. Classic CAH is the most serious form and is life-threatening, due to severe glucocorticoid and mineralocorticoid deficiency (the so-called salt-wasting classic CAH), or isolated glucocorticoid deficiency but largely preserved mineralocorticoid deficiency (the so-called simple virilising classic CAH). Androgen excess leads to ambiguous genitalia in girls (also termed 46,XX disorder of sex development, 46,XX DSD) and precocious sexual maturation in childhood. Nonclassic CAH is associated with androgen excess and either normal glucocorticoid capacity or borderline glucocorticoid deficiency; it can present as precocious sexual maturation in childhood and hirsutism and irregular menses in adolescents and adult women. Classic CAH requires treatment to correct hormone deficiencies (glucocorticoids and mineralocorticoids) and mitigate androgen excess. In childhood, treatment focuses on issues of gender assignment, genital surgery, and optimisation of growth and pubertal development. Priorities change with increasing age, typically focusing on fertility in early adult life and prevention of metabolic syndrome and bone loss in middle and older age. Prevention of life-threatening adrenal crisis remains paramount throughout the life of these patients. Management of CAH is complex and involves multidisciplinary expertise throughout the life of these patients. This chapter provides endocrine nurses with a synopsis of the approach, evaluation, and management of patients with CAH. Particular emphasis is placed on providing comprehensive coordinated care that includes patient and family education and the understanding of the physical and psychological consequences of the condition.

Keywords

21-hydroxylase deficiency · Adrenal insufficiency · Adrenal crisis · Androgen excess Ambiguous genitalia

Abbreviations

17OHP	17-hydroxyprogesterone
46,XX DSD	46,XX disorder of sex development
ACTH	Adrenocorticotropic hormone
CAH	Congenital adrenal hyperplasia
FSH	Follicle-stimulating hormone
IM	Intramuscular
IV	Intravenous
LH	Luteinising hormone
SHBG	Sex hormone-binding globulin
TARTs	Testicular adrenal rest tumours

Key Terms

- **ACTH stimulation test:** diagnostic test to assess the adrenal steroid production after the administration of the synthetic ACTH analogue Tetracosactide (Synacthen®, Cortrosyn®, Cosyntropin).
- **Adrenal crisis:** life-threatening emergency caused by inadequate production of the adrenal hormone cortisol in situations of stress.
- **Adrenal insufficiency:** condition in which the adrenal glands do not produce adequate amounts of steroid hormones, primarily the stress hormone cortisol.
- **Ambiguous genitalia:** condition in which an infant's external genitals don't appear to be clearly either male or female.
- **Hirsutism:** excessive terminal hair that appears in a male pattern in women.
- **Virilisation:** abnormal development of male sexual characteristics in females or in prepubertal age boys.

Key Points

- Steroid 21-hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia. It accounts for most of the cases of primary adrenal insufficiency in children.
- Severe congenital adrenal hyperplasia causes insufficient production of the adrenal hormones cortisol and aldosterone. Cortisol and aldosterone are necessary for life and patients need lifelong replacement.
- Congenital adrenal hyperplasia causes androgen excess, which can lead to problems in newborns (ambiguous genitalia), children (virilisation and short stature), and adults (hirsutism, infertility, and menstrual irregularities).
- Cortisol deficiency predisposes patients with congenital adrenal hyperplasia to life-threatening adrenal crisis. This is a medical emergency that requires immediate treatment with injectable hydrocortisone (equivalent to the endogenous hormone cortisol).

35.1 Introduction

Congenital adrenal hyperplasia (CAH) is an inherited condition with many physical and psychosocial dimensions. The enzyme deficiency responsible for this condition affects hormone production of the adrenal gland, resulting in a combination of cortisol and aldosterone deficiency and androgen excess, which have detrimental effects both pre- and postnatally (El-Maouche et al. 2017; White and Bachega 2012). In this chapter, we will focus on CAH due to steroid 21-hydroxylase deficiency, which is the most common cause of the condition. We will review pathophysiology, diagnosis, and management, focusing on age-specific challenges associated with this chronic condition.

35.2 Pathophysiology of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic disorders and is the most common cause of primary adrenal

insufficiency in children (1:10,000 to 1:20,000 live births) (White and Speiser 2000; Speiser et al. 2010). The most frequent genetic abnormality is a mutation in the *CYP21A2* gene, which encodes the enzyme 21-hydroxylase; this accounts for more than 90% of cases (White and Speiser 2000). CYP21A2 is a key enzyme of adrenal steroidogenesis (Fig. 35.1a).

Adrenal steroidogenesis takes place in the adrenal cortex and leads to the production of **glucocorticoids** (i.e. cortisol, required for normal metabolic function and involved in the response to stress), **mineralocorticoids** (i.e. aldosterone, regulating the level of electrolytes and water in the body), and **adrenal androgens** (serving as sex steroid precursors). Adrenocorticotropic hormone (ACTH) is released by the anterior lobe of the pituitary gland, regulated via negative feedback from circulating glucocorticoids, and is an important stimulus of glucocorticoid and adrenal androgen production, promoting uptake and utilisation of cholesterol from the adrenal cortex. Cholesterol is the substrate of all steroid hormones (Fig. 35.1a).

CYP21A2 is crucial for the production of glucocorticoids and mineralocorticoids. As a consequence, the synthesis of cortisol and aldosterone is impaired when this enzyme is defective. A lack of cortisol drives increased ACTH secretion from the pituitary; ACTH then stimulates the adrenal gland to produce excessive amounts of androgens, the only pathway not affected by the lack of CYP21A2 (Fig. 35.1b). Several mutations of *CYP21A2* have been described in CAH. The severity of the condition relates to the degree to which the mutations compromise 21-hydroxylase activity (El-Maouche et al. 2017), reflected by different levels of impairment in cortisol and aldosterone production. The common feature of all

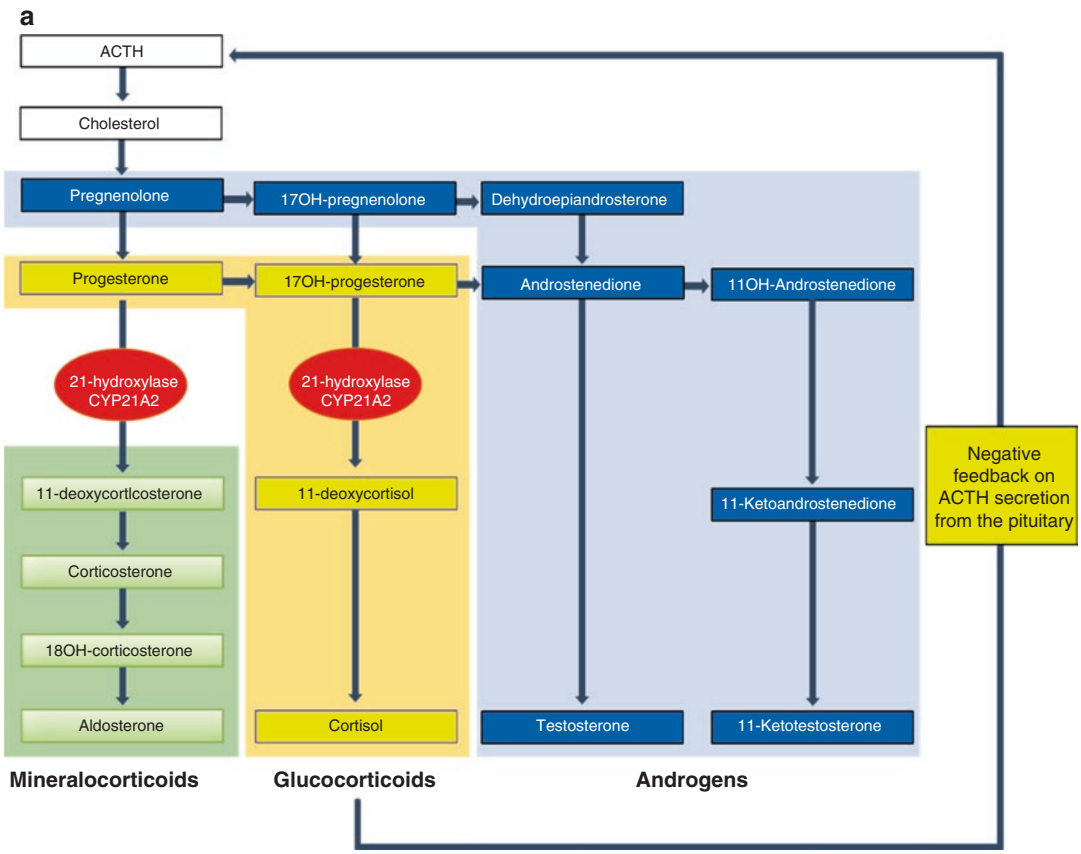


Fig. 35.1 Pathways of adrenal steroid synthesis. (**a**) Normal adrenal steroid synthesis. (**b**) Abnormal adrenal steroid synthesis in classic CAH (see next page); dotted arrows show the pathways affected by the lack of the enzyme 21-hydroxylase

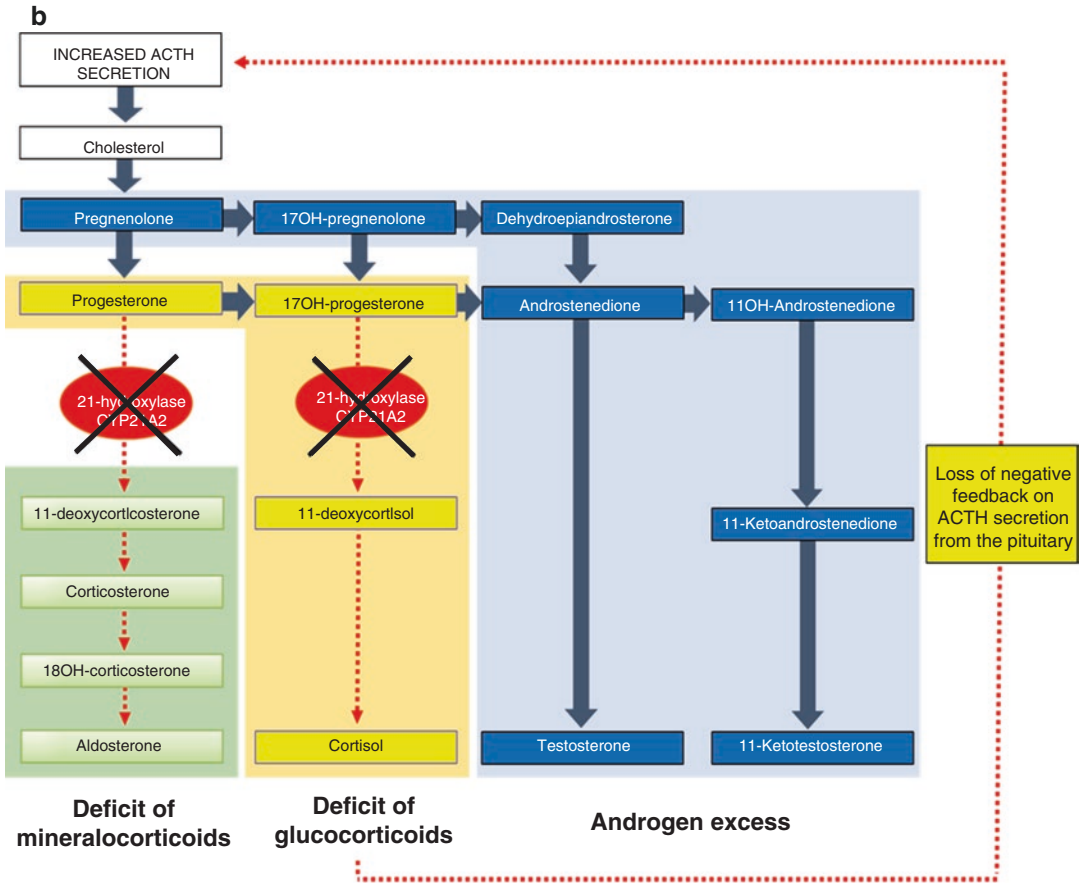


Fig. 35.1 (continued)

forms of CAH due to 21-hydroxylase deficiency is androgen excess.

35.3 Classification and Manifestations of Congenital Adrenal Hyperplasia

Depending upon the degree of cortisol and aldosterone deficiency and androgen excess, CAH can be classified as follows (White and Bachega 2012):

- **Classic CAH**: Severe deficiency of cortisol and androgen excess. Newborn females present with genital ambiguity (=46,XX disorder of sex development, 46,XX DSD). ~75% of newborns who are not identified at birth but harbour the most severe CYP21A2 mutations develop a salt-wasting crisis 7–14 days after birth (="salt-wasting" CAH—both cortisol and aldosterone deficiency). This is particularly relevant for newborn males, who do not present with genital ambiguity. Children with slightly less severe mutations and therefore largely preserved mineralocorticoid production also present with 46,XX DSD in affected girls at birth. However, affected boys are often only diagnosed in early childhood with signs of increased bone age and virilisation (="simple virilising" CAH—cortisol deficiency only). Children with classic CAH require glucocorticoid replacement (as well as mineralocorticoid replacement in "salt-wasting" genotypes), and this prevents further virilisation through excess androgen production via downregulation of the negative feedback and consequently diminished ACTH stimulation of the adrenal glands.
- **Nonclassic CAH**: It is the most common form of CAH and affects 0.1% of the general

population, with higher rates among Hispanics and Yugoslavs (1–2%) and Ashkenazi Jews (3–4%) (White and Speiser 2000). Patients with nonclassic CAH produce relatively normal amounts of cortisol and aldosterone at the expense of mild-to-moderate androgen excess. However, some patients may have borderline glucocorticoid deficiency and require glucocorticoid replacement during major stress; hence, all nonclassic patients warrant initial assessment of their glucocorticoid capacity through an ACTH stimulation test. They have no signs at birth and present later in childhood, adolescence, or adult life due to symptoms of androgen excess.

Table 35.1 describes the clinical manifestations of classic and nonclassic CAH.

35.4 Assessment, Care, and Management of Patients with Congenital Adrenal Hyperplasia

35.4.1 Diagnosis

In 2010, the Endocrine Society recommended universal newborn screening for CAH, and many countries have implemented this recommendation (Speiser et al. 2010), though there is no screening implemented in the UK at present. In many other countries, screening is done by measuring 17-hydroxyprogesterone (17OHP) in dried blood spots. Abnormal results should be confirmed by a second measurement (White 2009); specificity is increased by additional measurement of 21-deoxycortisol, a steroid only generated in large amounts in 21-hydroxylase

Table 35.1 Manifestations of congenital adrenal hyperplasia

Classic CAH	Nonclassic CAH (late-onset CAH)
Neonates: • Females: ambiguous genitalia (=46,XX DSD) • Males may have subtle findings such as scrotal hyperpigmentation or penile enlargement *~75% of patients present in a salt-wasting adrenal crisis 7–14 days after birth*: • History: failure to thrive; persistent poor feeding; excessive sleepiness; significant weight loss (>10%); vomiting; persistent jaundice • Observations: jaundice; hypothermia; tachypnoea; dyspnoea; dehydration (sunken fontanelle, poor skin turgor) • Hypovolaemic shock, cardiovascular collapse • Laboratory abnormalities: hypoglycaemia; hyponatraemia; hyperkalaemia; metabolic acidosis *Childhood*: • History of rapid growth (crossing centiles) • Advanced bone with reduced height prediction • Early pubic hair development or sexual precocity (typically at 2–4 years of age) • Clitoromegaly • Increased body odour • Oily skin and hair *Adolescence and adulthood*: • Hirsutism • Hair loss and receding hair line (male-patterned baldness in women) • Oily skin and hair • Excessive acne • Menstrual irregularities • Infertility in both men and women	Nonclassic CAH is usually associated with milder signs and symptoms of androgen excess. Patients can be diagnosed anywhere from early childhood to adulthood. Adolescent girls and adult women can have a clinical picture that is indistinguishable from the polycystic ovarian syndrome. Men are often asymptomatic. Affected females do not have ambiguous genitalia. *Late childhood*: • Early pubic hair development or sexual precocity (before the age of 8 years in girls or 9 years in boys) • Clitoromegaly (rare, mild) • Accelerated growth • Advanced bone age • Increased body odour *Adolescence and adulthood*: • Menstrual irregularities • Hirsutism • Hair loss and receding hair line (male-patterned baldness in women) • Excessive acne *Fertility*: Subfertility is milder in comparison to classic CAH. Men usually have a normal testicular function.

deficiency. If 17OHP is elevated, blood sodium, potassium, and glucose must be checked. The measurement of 17OHP after an ACTH stimulation test can be used to confirm the diagnosis (White 2009). Abnormal results should then be complemented with DNA analysis for *CYP21A2* mutations.

In females, the diagnosis of **classic CAH** is most commonly made at birth because of the ambiguity (atypical development) of their genitalia (=46,XX DSD). In males who don't undergo newborn screening and do not develop a salt-wasting crisis in the neonatal period, the diagnosis may be delayed and only present when they develop signs of androgen excess.

Most cases of **nonclassic CAH** are not picked up at neonatal screening (White 2009). The diagnosis of nonclassic CAH can be made at any time from childhood to adulthood, including asymptomatic individuals identified during genetic screening because of affected relatives. The initial assessment is done by measuring early morning 17OHP. Abnormal results should be followed up by an ACTH stimulation test for 17OHP and cortisol (Witchel and Azziz 2010).

35.4.2 Classic Congenital Adrenal Hyperplasia: Medical Treatment

Treatment includes glucocorticoid replacement which aims to normalise hormone balance and reduce excess androgen production from the adrenal glands. Treatment is required lifelong, and adherence to treatment is essential for normal growth and development throughout the lifespan (El-Maouche et al. 2017). It is crucial that families, children, and adult patients with CAH are able to learn the necessary skills to manage the condition and understand why treatment is needed and how it is managed (please refer to Chap. 37 for more information on how to support patients and improve their adherence to treatment in adrenal insufficiency).

The mainstay of treatment of classic CAH are glucocorticoids (**hydrocortisone [=cortisol] or, if difficult to control in adulthood, long-acting synthetic glucocorticoids such as prednisolone**) and mineralocorticoids (**fludrocortisone**). Glucocorticoids must be given in sufficient doses to replace cortisol deficiency and downregulate excessive production of ACTH from the pituitary and over-secretion of adrenal androgens. Fludrocortisone is given to keep electrolytes and intravascular fluid volume normal. Table 35.2 reports treatment goals and typical regimens in patients with classic CAH (El-Maouche et al. 2017; Speiser et al. 2010; Han et al. 2013a; Joint Lecahwg 2002). These should be seen only as a guide; treatment must be individualised after clinical and laboratory assessment.

Daily treatment in children includes hydrocortisone three to four times daily and fludrocortisone one to two times daily, with additional salt replacement in the newborns:

- For children with CAH, hydrocortisone is the drug of choice. The daily dose per m^2 body surface is higher compared to those children who have other causes of adrenal insufficiency because of the need to downregulate excess ACTH production and mitigate the androgen excess. Daily doses must be prepared from tablets when each dose is due, crushed, and administered in a small quantity of water prior to a feed—the use of oral hydrocortisone suspensions is discouraged, as they are not bioequivalent to the tablets (Speiser et al. 2010). The European Medical Agency has recently granted a paediatric use marketing authorisation for Alkindi® (Diurnal Ltd), a formulation of hydrocortisone granules that allows for more accurate and age-appropriate dosing in children and masks the bitter taste of conventional tablets.
- Fludrocortisone can be administered together with hydrocortisone. Neonates often require higher doses in the first months of life. Blood pressure should be monitored and doses minimised to prevent hypertension.
- Any need to increase treatment to maintain normal sodium and potassium levels can be addressed by the addition of salt (sodium chloride). Solutions of 20% (made by

Table 35.2 Medical treatment of classic congenital adrenal hyperplasia

Treatment goals	**All patients:** • Correct cortisol deficiency and prevent adrenal crisis • In patients with "salt-wasting" CAH: correct aldosterone deficiency to promote normal electrolyte balance • Mitigate androgen excess while avoiding iatrogenic glucocorticoid excess **Children:** • Promote normal growth, development, and final height outcome • Obtain normal sexual maturation **Adolescents and adults:** • Ameliorate hirsutism, acne, and menstrual irregularities in adolescents and women • Preserve fertility • Achieve positive sexual outcomes for females requiring genital reconstructive surgery
Neonates and infants	Medical treatment needs to be adjusted on an individual basis with frequent clinical and biochemical monitoring over the first months of life. Typical doses are initially: • Hydrocortisone: starting dose 20–30 mg/m^2/day in three divided daily doses. Higher doses may be used for initial reduction of markedly elevated androgens, but it is important to very rapidly reduce the dose when target hormone levels are achieved • Fludrocortisone: starting dose 50–100 mcg twice daily • Salt: starting dose 1–2 g/day of sodium chloride divided into several feedings. Salt supplementation can be discontinued as the child begins to eat table food and the taste for salty food increases • Fludrocortisone and salt supplements are balanced carefully with monitoring of blood pressure and electrolytes
Children	Medical treatment needs to be adjusted on an individual basis with frequent clinical and biochemical monitoring over time. Typical maintenance doses are: • Hydrocortisone: maintenance dose 10–15 mg/m^2/day in three divided daily doses • Fludrocortisone: maintenance dose 50–200 mcg/day • Encourage salt intake with exposure to hot weather or with intense exercise
Older adolescents and adults	• Glucocorticoids: hydrocortisone is the treatment of choice. However, long-acting glucocorticoids are often used in adults. Typical glucocorticoid regimens include one of the following: – Hydrocortisone: 15–25 mg/day in two to three daily doses – Prednisolone: 3–7 mg/day in one or two doses – Dexamethasone: 0.25–0.5 mg at bedtime • Fludrocortisone: usual maintenance dose 50–200 mcg/day. It is important to reassess mineralocorticoid requirements when the patient transitions from paediatric to adult care because they can differ significantly between these phases • Encourage salt intake with exposure to hot weather or with intense exercise • Oral contraceptive pills can be considered as an adjunct treatment in women to regularise menses and ameliorate the cosmetic effects of androgen excess (hirsutism and acne). Direct hair removal methods are also an option (e.g. photoepilation, electrolysis, eflornithine cream)

compounding pharmacies for accuracy) can be used to minimise the volume given, with the dose given neat just before a feed or mixed in a small amount of breast milk or formula. Babies adapt fairly quickly to the taste, and simple administration strategies need to be developed to enhance adherence to treatment. Children with classic CAH are salt–losers and therefore have a preference for salty foods. As toddlers, salt should be added to their cooked foods to balance their intake, with older children having the ability to balance their own by "adding salt".

Long-acting glucocorticoids (prednisolone or dexamethasone) are often used in adults instead of hydrocortisone due to convenience of less frequent dosing (Table 35.2). When possible, hydrocortisone should be favoured because of the lower risk of over-replacement; both prednisolone and in particular dexamethasone are long-acting, and activate the glucocorticoid receptor

for much longer including evening and nighttime when circulating cortisol concentrations in healthy individuals are physiologically low. A novel modified-release formulation of hydrocortisone (Chronocort®, Diurnal Ltd) has been designed to mimic physiological cortisol secretion and improve control of the androgen excess (Mallappa et al. 2015). A phase-III clinical trial is currently evaluating its efficacy in adult patients with classic CAH.

35.4.3 Classic Congenital Adrenal Hyperplasia: Treatment and Prevention of Adrenal Crisis

Patients with classic CAH have primary adrenal insufficiency and do not have the capacity to secrete extra cortisol in situations of stress. If the dose of glucocorticoids is not increased in these situations, a patient with classic CAH can develop a life-threatening adrenal crisis. If not promptly recognised and treated, an adrenal crisis rapidly leads to systemic collapse, hypovolaemic shock, and death (Table 35.3) (Bornstein et al. 2016).

Adrenal crisis is a common occurrence in patients with classic CAH (Hahner et al. 2015; Reisch et al. 2012). Precipitating factors include intercurrent illness, infections (particularly gastroenteritis and respiratory infections), persistent vomiting or diarrhoea, fever, significant pain, trauma (e.g. fractures), emotional distress, and strenuous physical activity (Hahner et al. 2015). Surgery requiring general anaesthesia, preparation for invasive diagnostic procedures (e.g. colonoscopy), and oral surgery (e.g. dental extractions) are further risk factors. Patients with CAH can also become acutely unwell if they do not have good adherence to medical treatment or do not follow the simple sick day rules outlined below (refer to Chap. 62 for more information on prevention and management of adrenal crisis).

A patient with a suspected adrenal crisis must be promptly treated with lifesaving injectable hydrocortisone (IM as priority pending IV access). Diagnostic measures should never delay treatment. If an adrenal crisis is suspected, act immediately and refer to hospital emergency management guidelines, if available. As a guide (Joint Lecahwg 2002; Bornstein et al. 2016):

- STEP 1: Give hydrocortisone immediately (injection of hydrocortisone IM or IV): 25 mg in those <3 years of age; 50 mg in those

Table 35.3 Adrenal crisis and signs and symptoms of over- and under-replacement

Adrenal crisis	Adrenal crisis is a life-threatening emergency. Patients present with at least two of the following: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, fever, somnolence, confusion, and coma. Laboratory evaluation can show hyponatraemia, hyperkalaemia, hypoglycaemia, increased serum creatinine, and metabolic acidosis. Hypoglycaemia is common in children
Glucocorticoid treatment	*Over-replacement*: insomnia, increased appetite, proximal muscle weakness, skin thinning, easy bruising, red stretch marks, weight gain and central obesity, disproportionate supraclavicular and dorsocervical fat pads, facial and upper neck plethora, facial rounding. Reduced growth rates and weight gain in children can be an indication of glucocorticoid over-replacement *Under-replacement*: fatigue, weakness, nausea, lack of appetite, dizziness, hypotension, weight loss, skin hyperpigmentation (due to ACTH excess)
Mineralocorticoid treatment	*Over-replacement*: hypertension, peripheral oedema *Under-replacement*: orthostatic hypotension (e.g. dizziness, lightheadedness, and fainting when standing up); postural blood pressure drop on examination (lying to standing); fatigue, leg cramps, salt craving
Inadequate androgen suppression	*Children*: increased growth rate (before epiphyseal closure); early pubic hair development; early sexual development; clitoromegaly; increased sebaceous secretions; increased body odour *Adolescent and adult women*: hirsutism; excessive acne; oily skin; menstrual irregularities; male-patterned baldness in females

3–12 years of age; 100 mg in those >12 years of age.
- STEP 2: Start rapid rehydration with isotonic saline infusion according to protocols for age and weight.
- STEP 3: Correct hypoglycaemia, if present (IV dextrose). Hypoglycaemia can be common in children with adrenal crisis.
- STEP 4: Start continuous IV infusion of hydrocortisone after the bolus injection: 25–30 mg per 24 h in those ≤3 years of age; 50–60 mg per 24 h in those 3–12 years of age; 100 mg per 24 h in children >12 years of age; 200 mg per 24 h in adults. Alternatively, the total daily dose can be split and administered IM or IV every 6 h.
- STEP 5: Treat the precipitating factor of the crisis, if possible (e.g. infection, trauma).
- STEP 6: Contact an endocrinologist for urgent review of the patient and advice on further tapering of hydrocortisone.

In order to prevent an adrenal crisis, several measures need to be in place (Bornstein et al. 2016). These are simple and are lifesaving:

- Educate parents, patients, and partners regarding correct adjustment of glucocorticoid replacement in case of stress ("sick day rules"):
  - **Sick day rule 1**: double or triple daily oral glucocorticoid dose during illness that requires bed rest and/or antibiotics or is associated with high fever (>38 °C) until recovery. Children should get hydrocortisone in three to four doses and given sweet drinks and salt supplements if off their food. Double or triple the dose on the day of any minor procedure/surgery that do not require fasting (e.g. procedures requiring local anaesthesia and tooth extraction).
  - **Sick day rule 2**: administer hydrocortisone per IM or IV injection during severe illness, prolonged vomiting or diarrhoea, acute trauma and if the patient is confused, drowsy, or unconscious. Hydrocortisone per IM or IV injection must be given in preparation for surgery/procedures requiring general anaesthesia and during prolonged fasting (e.g. preparation for colonoscopy). In adults, the recommended dose is 100 mg via bolus injection, followed by 200 mg/24 h.
- Educate patients, parents, and partners regarding symptom awareness and possible precipitating factors of adrenal crisis. They should be advised that "if in doubt" they should give a hydrocortisone emergency injection and seek medical advice.
- Ensure patients have an additional supply of tablets so that they can double/triple their dose for at least 7 days, for example, when travelling abroad. If a patient is unable to tolerate tablets, hydrocortisone should be given IM and medical advice promptly sought.
- Provide patients and caregivers with a hydrocortisone emergency injection kit. Check regularly that their kit is up to date.
- Educate patients, parents, and partners on how to self-administer and inject hydrocortisone IM (for example: www.pituitary.org.uk/information/treating-a-pituitary-condition/hydrocortisone/how-to-give-an-emergency-injection-of-hydrocortisone; www.CAHPepTalk.com).
- Provide the patient with a steroid emergency card (for example: www.endocrinology.org/adrenal-crisis) and encourage them to wear medical alert bracelets or necklaces. Patients must keep the steroid emergency card with them at all times and show it to any health professional they are dealing with.
- Instruct parents of school-aged children affected by CAH to inform school staff about the condition. An emergency letter and response plan can be of use (as an example: www.cah.org.au/products-resources; www.CAHPepTalk.com).
- Provide patients and caregivers with emergency phone numbers for on-call services and the ambulance service (register with their consent onto the red flagged ambulance emergency service, if available locally).
- Instruct patients and caregivers to inform the endocrinologist before surgical procedures so that proper advice can be given to the hospital staff.
- Encourage salt intake with exposure to hot weather or with intense exercise. Before major

physical activity (e.g. long distance running, major sports, or competitive dancing), patients might benefit from taking a small dose of extra hydrocortisone.
- Regular review of the patient by health professionals to reinforce the sick day rules and adherence to treatment.

35.4.4 Classic Congenital Adrenal Hyperplasia: Monitoring

Patients with classic CAH require lifelong care. While the correction of cortisol and aldosterone deficiency and the control of androgen excess are common aims in children and adults, treatment goals do change over time (Table 35.2). In children with CAH prevention of early puberty and achievement of an acceptable final height are paramount. Upon completion of pubertal development and attainment of adult height, continued monitoring of symptoms of androgen excess (menstrual irregularities, hirsutism), quality of life, sexual health, and fertility become increasingly more important. The avoidance of the long-term side effects of excess glucocorticoid treatment is also crucial (e.g. stunted linear growth in children and, in particular in adults, metabolic syndrome, increased cardiovascular risk and osteoporosis) (Reisch et al. 2011; Arlt and Krone 2007).

Medical treatment of CAH can be challenging and is a fine balance between over- and under-treatment (Table 35.3). The goal is achieving the best clinical results with the lowest possible daily glucocorticoid dose. Regular clinical assessment and blood tests are required to monitor the effectiveness of treatment (Table 35.4 and Fig. 35.2) (Escobar-Morreale et al. 2012). The frequency and modalities of monitoring need to be tailored to the individual patient. Management can be complex and should involve multiple heath care professionals including endocrinologist, endocrine nurse specialist, genetic counsellors, gynaecologists, urologists and surgeons, fertility specialists, mental health providers, and social services. The endocrinologist and the specialist endocrine nurse play a pivotal role in coordinating management to guide the patients and their carers to achieve satisfactory health outcomes.

35.4.5 Classic Congenital Adrenal Hyperplasia: Management in the Neonatal Period

A female newborn with 46,XX DSD requires urgent consultation with the paediatric endocrine team and specific management strategies to provide the family with appropriate information and support to manage the shock and grief process until gender is determined. Placating comments and judgements regarding the gender of the baby should not be made. The focus should be on "your baby" who is "well and beautiful" with positivity expressed about the labour and delivery. Parents are advised that specialist endocrine team will be consulted immediately to explain the situation and assist in ascertaining the gender of their baby.

The paediatric endocrinologist will direct the plan to determine the diagnosis and gender and develop a treatment strategy to manage the glucocorticoid and mineralocorticoid deficiencies. The initial assessment is made on the physical findings, electrolyte and hormone analysis, radiological investigations, and genetic testing. The severity of genital malformation is assessed according to the Prader scale (Fig. 35.3) (White and Speiser 2000).

The surgical management of children born with 46,XX DSD is complex. Patients should be referred to centres with substantial experience and a team of paediatric surgeons, paediatric endocrinologists, mental health professionals, and social work services (Speiser et al. 2010).

Boys with classic CAH who did not undergo neonatal screening can present aged 1–3 weeks of life with a salt-wasting adrenal crisis—a state of systemic collapse which can lead to death if not managed quickly (Table 35.1). Because of the serious state of circulatory collapse, intravenous access may be difficult an intraosseous access may be required. A blood gas will give an immediate indication of the blood glucose, electrolytes, and assess for acidosis. At any stage of concern,

Table 35.4 Monitoring of patients with classic congenital adrenal hyperplasia

Frequency of monitoring	• At least monthly during the first 3 months of life • Every 3 months in the neonate and infant • Every 3–6 months in children and adolescents • Every 6–12 months in adults on stable medical treatment
Clinical assessment	• History taking, including current medications and comorbidities • Assess the adherence to medical treatment • Monitor growth velocity in children • General physical examination • Vital signs and body measurements: height; weight; waist circumference; blood pressure sitting and standing (to look for hypertension and orthostatic hypotension) • Look for signs and symptoms of over- or under-replacement (Table 35.3) • Examination of the genitalia to look for any signs of virilisation in children (e.g. clitoromegaly and precocious pubic hair development) and assess the outcome of reconstructive surgery in girls. It is imperative that such examinations are discussed with the parents and child and are undertaken discretely, particularly as children become older. Testicular examination should be performed periodically in adolescents and adults, looking for palpable masses or testicular atrophy • Assess the menstrual function in adolescents and premenopausal women • Assess women for hirsutism, using the modified Ferriman–Gallwey score (Fig. 35.2) • Assess health-related quality of life. Questionnaires can be used in older children and adults (e.g. PedsQL™ Generic Core Scale, PedsQL™ Fatigue Scale, WHOQoL-BREF scale, MAF scale, SF-36®; EQ-5D™). Investigate psychological, social, and sexual health issues, as well as current health concerns • Ask if the patient had any sick days since the previous visit and needed to increase the dose of glucocorticoids or required hospitalisation • Reinforce the sick day rules and confirm that measures are in place to prevent and treat promptly adrenal crisis (e.g. hydrocortisone emergency injection kit, steroid emergency card, medical alert bracelet) • Investigate family plans in patients of reproductive age
Laboratory assessment	*Hormonal evaluation*: • CHILDREN: morning serum 17-hydroxyprogesterone and androstenedione. Testosterone measurement is sometimes useful in patients whose disease is not well controlled. Adrenal androgen secretion should not be completely suppressed; normal levels of 17-hydroxyprogesterone generally indicate overtreatment • MEN AND WOMEN: morning serum 17-hydroxyprogesterone and androstenedione. The goal is individualised to achieve patient goals, but androstenedione should not be suppressed • MEN: morning serum testosterone, sex hormone-binding globulin (SHBG), and gonadotropins (FSH and LH) • WOMEN: morning follicular-phase progesterone should be checked in those seeking fertility. Testosterone measurement is sometimes useful in patients whose disease is not well controlled *Plasma renin activity or direct renin concentration*: it is used to monitor fludrocortisone replacement. Reference intervals are based on postural state and age, and data should be evaluated accordingly. A suppressed result reflects overtreatment and increases the risk of hypertension *Other tests*: • Blood sodium, potassium, and kidney function • Fasting plasma glucose: in neonates and young children glucose must be monitored because of the risk of hypoglycaemia, particularly if the child is unwell or requiring salt replacement. Conversely, adults are at risk of developing diabetes mellitus • In adults: lipid panel; glycated haemoglobin (HbA1c); vitamin D
Radiological assessment	• Regular bone age assessment in children (X-ray of the hand) • Regular testicular ultrasound in males from adolescence onwards • Monitor adults periodically for low bone density (DEXA scan)

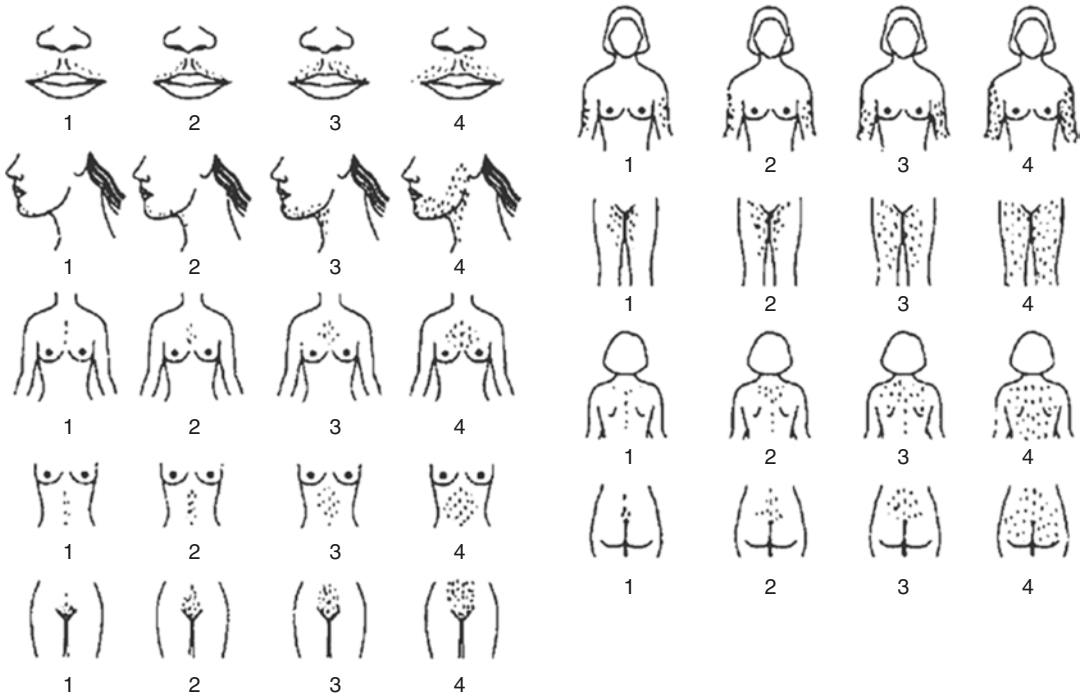


Fig. 35.2 Modified Ferriman–Gallwey score is the gold standard for the evaluation of hirsutism, scoring nine body areas (upper lip, chin, chest, upper and lower abdomen, arm, thigh, upper and lower back). Ferriman–Gallwey total scores that define hirsutism in women of reproductive age are: US and UK black or white women, ≥8; Mediterranean, Hispanic, and Middle Eastern women, ≥9 to 10; South American women, ≥6; Asian women, a range of ≥2 for Han Chinese women to ≥7 for Southern Chinese women. Reproduced with permission from Escobar-Morreale et al. (2012). Copyright Oxford University Press, 2011

or if there is a delay in obtaining intravenous access, hydrocortisone followed by glucagon should be administered IM for suspected adrenal insufficiency and hypoglycaemia. Once intravenous access is established, IV hydrocortisone, dextrose, and normal saline should be administered to correct hypovolaemia, hypoglycaemia, and the electrolyte abnormalities.

35.4.6 Classic Congenital Adrenal Hyperplasia: Management During Infancy and Childhood

The psychosocial adjustment of the parents to the diagnosis of CAH initially, and later for the child, is critical to achieving a positive outcome for the child and the family in the long term. Having a child with a complex chronic condition is a life-altering experience, with the impact on parents and family members depending greatly on individual coping abilities, and also influenced by social background, cultural and family beliefs (Patterson et al. 1990). A family's adjustment to a new diagnosis can be greatly enhanced by a health professionals' approach to the situation through counselling, education, and support (Hatton et al. 1995). By facilitating a process of understanding and adjustment health professionals can increase the likelihood of families having the knowledge, understanding, and confidence to manage difficult situations when they occur, such as a possible adrenal crisis. This education process should be reviewed regularly at clinical follow-up.

Psychological support is important for the parents but also for the children as they grow and adapt to living with a complex condition and its physical and emotional consequences. Managing intercurrent illness in order to prevent serious

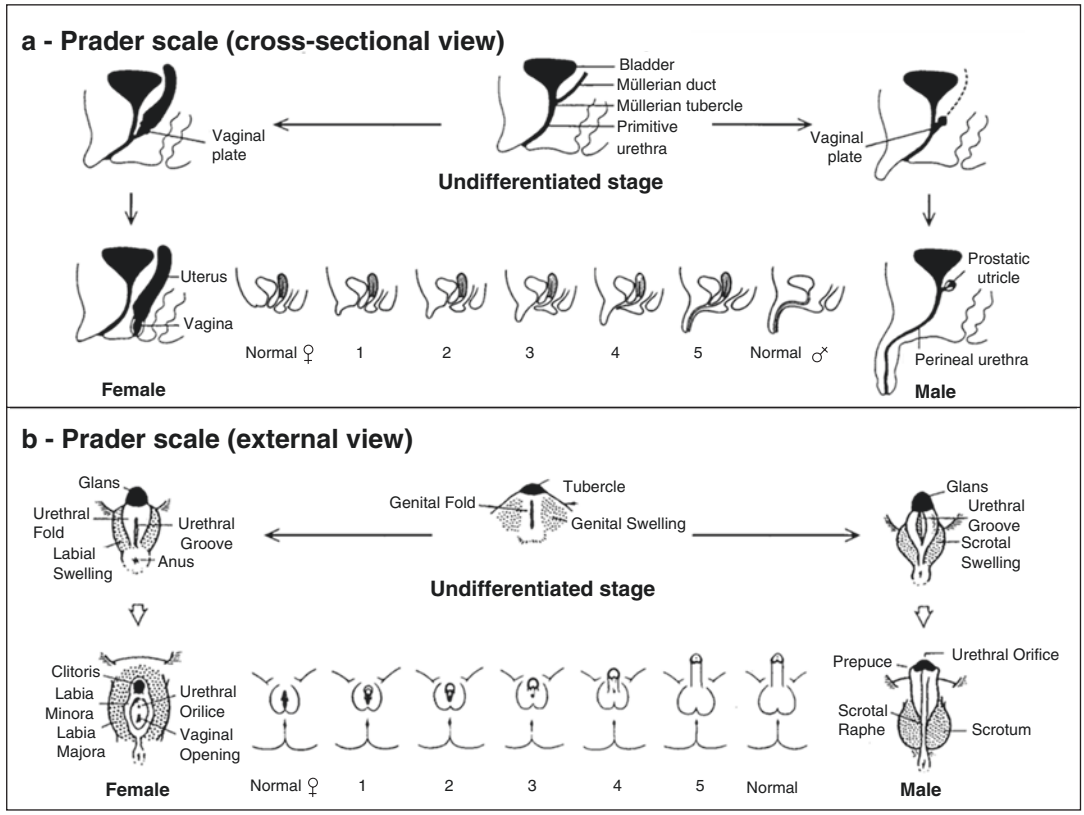


Fig. 35.3 Prader scale. The severity of virilisation is often quantitated using the five-point Prader scale. (**a**) Normal and abnormal differentiation of the urogenital sinus and external genitalia (cross-sectional view). (**b**) Normal and abnormal differentiation of the external genitalia (external view). Reproduced and edited with permission from White et al. (2000). Copyright The Endocrine Society, 2000

deterioration to a possible life-threatening adrenal crisis is a serious concern for parents and always at the forefront of their minds. They have to adapt their daily routine around their child's medication plan, attendance for regular medical reviews, and routine investigations. Health professional should aim to help families adapt the care required for these children into their daily lives in order to ensure positive health outcomes in the long term.

CAH has an element of androgen exposure in utero, which can affect brain development and function (Webb et al. 2018). Girls can have male-typical childhood play and more interest in male-typical activities during childhood and adolescence (Dittmann et al. 1990). Health professionals need to be aware of parental concerns regarding this variation to the norm and guide parents appropriately. Counselling with a psychologist will assist in this process for both the parents and the child. Autism, which is more often found in males than females, has been found to be more prevalent in patients with CAH of both sexes (Knickmeyer et al. 2006).

Support groups are important for parents and extended families, enabling them to share with others their experiences and difficulties in having a child with a diagnosis of CAH. Not all parents are ready to meet other families and will do so in their own time. Support groups can be invaluable in providing families with a sense of normality, and being able to meet other children who have grown up having the diagnosis of CAH. It is important that patients themselves are able to share their experiences in confidence with others with the same diagnosis.

35.4.7 Classic Congenital Adrenal Hyperplasia: Management During Adolescence

Adolescence is the phase of transition from childhood to adulthood. Managing CAH at this stage of development can be challenging, with a rapidly changing body and the impact of the hormonal changes of puberty (Merke and Poppas 2013). Adolescence is also a time of significant emotional change and often adherence to medical treatment is an issue.

Adolescent females can struggle with hormonal control at puberty, which often requires an increase in routine hydrocortisone doses. They may also need the addition of an oral contraceptive pill to regulate their monthly cycle and reduce acne and excess body hair. The outcome of reconstructive genital surgery carried out in infancy should be reviewed in adolescence and discussed with an appropriately skilled surgeon. If (additional) surgery is desired, particular expertise is imperative to ensure comprehensive understanding, appropriate consent by the adolescent and parents for adequate surgical outcomes.

In adolescent males with classic CAH, ACTH hypersecretion can cause hyperplasia of ACTH-sensitive cells present in the testes. This leads to the development of testicular nodules known as "testicular adrenal rest tumours" (TARTs), which can cause infertility (see section on fertility below) (El-Maouche et al. 2017). Poor adherence to hydrocortisone treatment and severe loss-of-function CAH genotypes have been identified as risk factors for the development of TARTs, which should be actively monitored for by ultrasound starting in adolescence, at the latest at the point of transition to adult care.

35.4.8 Classic Congenital Adrenal Hyperplasia: Management in the Adult Care Setting

With adolescence, the patient with CAH must gradually assume primary responsibility for his/her care and eventually transition to adult care. The adolescent's needs and concerns shift to a more adult focus on quality of life, long-term health and eventually relationships, fertility, and family planning (Reisch et al. 2011; Han et al. 2013b; Auchus and Arlt 2013). As patients with classic CAH often require higher doses of glucocorticoids to control the androgen excess, they are at increased risk of obesity, diabetes mellitus, dyslipidaemia, cardiovascular disease, and bone loss during adult life (Auchus and Arlt 2013; Arlt et al. 2010; Han et al. 2014). Consequently, a key priority when managing adults with CAH is to minimise long-term consequences of both the condition itself and its treatment.

The transition of care from a paediatric to an adult care setting remains a major challenge and many patients are lost to follow up (Gleeson et al. 2013). Ideally, patients should be jointly reviewed by the paediatric endocrinologist, the newly introduced adult endocrinologist, a clinical nurse specialist, and a geneticist on their first appointment. Apart from clinical and laboratory assessment, the initial evaluation should also focus on the following:

- Get to know the patient and understand their childhood journey.
- Assess the patient's understanding of the condition, goals of, and adherence to treatment.
- If available medical records are incomplete, these few questions are helpful: "At what age were you diagnosed?" "When did you stop growing?" and "Did you have any genital surgeries?" (Auchus and Arlt 2013).
- If indicated, an external genital examination may be necessary. Discuss sexual health with the patient and consider referral to a gynaecologist or urologist, if appropriate.
- Discuss family plans. Refer the patient to a fertility clinic, if appropriate.
- Consider the need for psychological counselling.

Ongoing follow-up will depend on this baseline assessment. Patients can have both or alternating appointments with their endocrinologist and the clinical nurse specialist, usually on yearly basis if they are on stable medical treatment (Table 35.4). Establishing a good nurse–patient relationship can enhance continued engagement for ongoing care.

35.4.9 Classic Congenital Adrenal Hyperplasia: Fertility

High rates of infertility can occur in patients with classic CAH (Reichman et al. 2014). Fertility correlates with the severity of the condition and can be reduced in both sexes.

Women have low fertility rates mainly due to androgen excess and menstrual irregularities with anovulatory cycles. 46,XX DSD and related surgical outcomes can also impact on sexual relationships and the chance of a positive pregnancy experience. Women seeking a pregnancy often need to intensify glucocorticoid treatment to obtain a more stringent control of the androgen excess and, consequently, promote their ability to ovulate and conceive. They should also be referred for review of the outcomes of previous genital reconstruction surgery; women with complex genital surgery should deliver by Caesarean section.

About 30–50% of men with classic CAH develop TARTs (Auchus and Arlt 2013), hyperplastic adrenal-like tissue, which can compress the surrounding testicular structures and cause oligospermia. Moreover, the adrenal-derived androgens can suppress gonadotropins and cause testicular atrophy. Men should be taught to self-examine their testes and have regular testicular ultrasound examinations to assess atrophy and the presence of TARTs. The term "tumour" should not be interpreted as a neoplasm because these masses actually represent hyperplastic tissue and do not show increased proliferation. It is therefore important not to confuse TARTs with primary testicular tumours when discussing a case with the patient and colleagues from other disciplines (Auchus and Arlt 2013). Poor adherence to glucocorticoid treatment is an important risk factor for the development of TARTs and intensified treatment is sometimes required, but not always effective for decreasing the size of the masses and restore fertility. Adult males with TARTS should be offered semen analysis and counselled on sperm banking.

35.4.10 Classic Congenital Adrenal Hyperplasia: Management of a Genetic Diagnosis

Once a child has been diagnosed with CAH, genetic testing will identify the specific mutation present. This should be arranged following referral for genetic counselling, firstly to determine the mutation in the neonate, and then the carrier status of the family members. This will have an impact on their pregnancy planning in the future.

CAH is autosomal recessive. Parents of a baby with CAH both have one of their two 21-hydroxylase DNA alleles affected and thus have a one-in-four chance of having another baby with CAH and one-in-eight chance of having a female baby with CAH and 46,XX DSD. Treating the mother with dexamethasone before the major period of fetal sexual differentiation (6–8 weeks post-conception) can help to prevent the 46,XX DSD in the female fetus. However, dexamethasone can have adverse effects on the mother receiving treatment during pregnancy and also possible long-term effects on the baby, which require discussion before starting treatment (Speiser et al. 2010). Previously, there was also concern of treating unaffected pregnancies as treatment had to be initiated before the sex of the child was known and before there was clarity about whether or not the child was affected, which previously could only be found out after invasive measures. However, nowadays both the chromosomal sex of the fetus and whether it is affected by 21-hdyroxylase deficiency can be readily detected through analysis of fetal cells circulating in maternal blood, offered by specialist genetic units. A pregnancy undergoing dexamethasone treatment requires frequent monitoring by endocrine and obstetric specialists.

35.4.11 Management of Nonclassic Congenital Adrenal Hyperplasia

Patients with nonclassic CAH do not need continuous glucocorticoid replacement; however, some patients may require glucocorticoid replacement in major stress, such as surgery, trauma, or ICU treatment. If glucocorticoids are needed to control the detrimental effects of androgen excess, they should be given up to the achievement of the treatment goal and then stopped (Auchus and Arlt 2013). Treatment can be considered in:

- Children with progressive signs of virilisation and accelerated growth.
- Women with anovulatory infertility.

If fertility is not desired, glucocorticoids should be avoided in women with bothersome hirsutism and/or menstrual irregularities. In such cases, treatment with oral contraceptives including an anti-androgenic progestin component (e.g. drospirenone or cyproterone) is preferred (Speiser et al. 2010).

35.4.12 Additional Aspects of Optimal Care

Health care professionals have a vital role in assessing and guiding individual and family adjustment to the diagnosis of CAH (Auchus et al. 2010). It is essential that health care professionals understand the need to provide a clear and simple explanation about the diagnosis in a positive way. Information needs to be given in limited amounts at a time, remembering that it may need to be repeated a number of times for it to be retained. Evaluating the information given is understood is an important step in this process. Using a timely approach will ensure that patients and families will acquire the appropriate information they need to manage the condition and assist in allaying any anxieties which may persist (Hatton et al. 1995). Continuous reinforcement of health information is also key.

The nurse–patient relationship is an extremely important factor in achieving effective health education for patients and families (Auchus et al. 2010). The nurse needs to be sensitive to the emotional needs of patients and caregivers, and assess their readiness for learning. For families with a child with a chronic condition such as CAH, the education process takes place over a continuous period of time as the child progresses through the developmental stages of childhood, adolescence, and into adulthood.

Finally, consistency and continuity of care by staff are considered one of the most important factors for patients with CAH, with transition from paediatric to adult care carefully planned (Merke and Poppas 2013; Auchus et al. 2010; Kruse et al. 2004). Adolescence and early adulthood are crucial times in the life of these patients and associated with significant physical and psychological adjustment. It is important to support the young person in making decisions which build confidence to direct their own care over time. Patient education and assumption of responsibility are critical for adherence to treatment, continuity of care, and successful outcomes.

35.5 Role of Patient Advocacy Groups in Improving Patient Care and Education in CAH

Patient advocacy groups are a highly valuable resource for patients and their families, not just as a clinical and supportive tool, but by also enabling empowerment and enriching the relationship between patients, families, and their health care providers. The advent of social media, with websites and online support groups can add to this, and patients have a reliable and trusted resource for peer support. Most PAGs work very closely with clinical teams to develop evidence-based information and support clinical research; they can form a useful resource and can reach patients and health care teams across the globe especially for rare conditions such as CAH.

35.5.1 The CAH Support Group (Reprinted Permission from CAH Support Group (UK) Patient Advocacy Group)

Robin Brett had CAH and was just 18 years old when he sadly died in 2014. He was taken to hospital with vomiting and unable to keep his medication down; this preceded by constipation which was treated by a large dose of enema. Although an IM injection of hydrocortisone was administered on admittance to hospital, no further medication was given on the ward and few checks were made. Just over 16 h after admittance, he went into an adrenal crisis and subsequently a cardiac arrest from which he could not be revived.

Robin's parents had been members of the CAH Support Group since shortly after he was

born and regularly attended conferences so were knowledgeable about his condition but, despite raising concerns about his treatment, were not listened to.

We were very saddened to hear of his death, the cause of which was not originally recorded accurately, which the family found particularly upsetting. However, his brave mother was determined to discover the truth and the support group put her in touch with one of our medical advisors who agreed to view the Coroner's report. After he read this, he issued his own report categorically stating that death was obviously caused by "*acute adrenal insufficiency consequent on a lack of adequate steroid replacement*". His conclusion was then confirmed by another specialist who was instructed by the Coroner's Office and the death certificate was altered accordingly.

Although nothing could bring Robin back, his mother was determined that her son's death would not be in vain and was keen to work with the support group to try and ensure the mistakes that occurred at the hospital where Robin was admitted would not happen again and cause another family to suffer as they had. We put her in touch with another eminent endocrinologist (who agreed to help) and she tirelessly wrote to the medical director of every hospital trust in the UK, explaining what had happened to her son and asking them to put measures in place to prevent another tragedy. In particular, she asked that a note be added to a patient's medication, requesting to utilise a note function on the current electronic prescribing system, highlighting the importance of administering steroids and also requesting measures are put in place to ensure patients with adrenal insufficiency receive appropriate care, to prevent any more unnecessary deaths.

Mrs. Brett received a fantastic response from these letters, with medical directors promising to make changes as suggested and to better educate staff about adrenal insufficiency/crisis. Robin even featured in a very poignant and moving training video as a result, which we believe helped highlight how fragile life can be for those with CAH and other steroid-dependent conditions.

The primary aims of the CAH group are to support all families affected by CAH and to increase awareness of the condition to the public and the medical profession. We believe the above tragic account of just one of our members is evidence on how we work together with families and the medical profession in order to do this. We provide a variety of information booklets and leaflets, organise conferences, social meetings as well as a regular newsletter to keep our members up to date. We also encourage and contribute to research projects.

Please contact us for any information:
Sue Elford
Chair: CAH Support Group
E-mail: sue@cah.org.uk

Website: www.livingwithcah.com
Sallyann Blackett
Treasurer: CAH Support Group
E-mail: sallyann@theblacketts.co.uk

35.5.2 The CARES Foundation (Reprinted Permission from CARES Foundation (USA) Patient Advocacy Group)

The Leight family founded CARES Foundation in 2001 after their daughter was diagnosed with Congenital Adrenal Hyperplasia (CAH), a rare disorder of the adrenal gland. When attempting to learn more about the disorder, they found that there was no support for families and affected individuals and few resources for information. Today, CARES Foundation serves as a global resource for patients and families affected by CAH.

In 2001, only 27 states in the USA were screening newborns for CAH. CARES initiated a grass-roots campaign to advocate for the inclusion of CAH in the newborn screening panel in all 50 states. As of 2008, every state in the USA tests for CAH, saving numerous lives. In 2009, CARES Foundation embarked on another national campaign to establish EMS (emergency medical service) protocols for adrenal crisis which are currently available in nearly 30 states.

CARES Foundation has an extensive support network for patients and families that includes one-on-one support; regional and specialised support groups; regularly scheduled teleconference calls with participation from expert providers, and private support groups on social media. CARES provides referrals to expert physicians

and access to online expert via the "Ask the Expert" service.

Education is a key component of our mission. Our educational efforts include:

- Annual education conferences for patients, families, and health care professionals
- A newsletter containing information on new treatments, research studies, and other valuable information
- Guides for educating school and camp personnel
- A guide for travelling with CAH
- Emergency instructions
- Educational packet for school nurses
- Website containing valuable information

Providing patients with access to quality health care is another cornerstone of CARES Foundation. To this end, CARES designated four centres of excellence across the USA where expert care is provided by a multidisciplinary team addressing patient needs throughout their lifecycle. These centres are also conducting research to advance patient care. CARES is also where patients and researchers turn for participation, recruitment, and information on clinical trials.

Since 2001, CARES has established itself as a global resource for not only patients with CAH and their families but also for health care professionals. We encourage all health care professionals to offer CARES as a resource for their patients. Professionals are also encouraged to take advantage of our services.

For more information about CARES Foundation, contact Dina Matos, Executive Director of CARES Foundation, at dina@caresfoundation.org or Tel: 866-227-3737 (USA). You can also visit our website www.caresfoundation.org

35.6 A Patient Perspective (Published with Patient Consent)

I am a 30-year-old woman who is lucky enough to be in a loving relationship but who does have long-term medical conditions to cope with every day. I recently tried to deal with fertility treatment and had two unsuccessful rounds of intrauterine insemination (IUI). Dealing with infertility is emotionally and physically draining. It makes you feel inadequate and alienated from life. I can't express how much I yearn to be called mummy and dream of a future with my own family. I'm having a break from it now and want to share my story with you as this is the most recent in a long series of medical battles in my life.

I was diagnosed with CAH at birth and salt-wasting CAH a few weeks later when I had a salt crisis which nearly put me in a coma. I will always be under the care of an endocrinologist and managed with steroid replacement therapy.

I had surgery at the age of one and then again at four, I remember the later vividly. The surgery for girls with CAH is very painful and sensitive as it involves cosmetic changes to the vagina and clitoris to normalise the genitals. Although cosmetic the extent of these surgeries was enormous and resulted in psychological problems for many years to come, in my case without any professional support. Put simply this isn't something you can speak about freely or easily.

My teens were particularly difficult, not only was I dealing with regular hospital appointments and medication but I also had the underlying problem of knowing I wasn't "normal" and believing there was absolutely no way I could *ever* have sex, which in my young mind equated to *never* being loved (my vaginal entrance was the size of my little finger; need I say more?). I began asking myself if I was asexual and taught myself to avoid all situations which may compromise me and bat away any attention. That way I could ignore the problem and live in denial. I continued with this approach into my early 20s.

My periods started a bit late at age 14 (and have gone on to cause me many problems over the years) and I went into hospital again for vaginal stretching under anaesthetic. The aim: to enable me to use a tampon. The timing: it could not have been worse. Can you imagine experiencing this during puberty in addition to all the usual ups and downs? Constantly being asked by kids at school if you're a lesbian because you're not interested in boys? If only it were that simple. I have never felt as isolated as I did at secondary school. All I can say is I'm pleased I had a happy

childhood and loving parents to look back on; it wasn't all bad but it was very challenging!

And the fun didn't stop there. When I was 16 I was diagnosed with Crohn's disease and had surgery a few months later; a right hemicolectomy removing my ascending colon and some of my small intestine all of which had become ulcerated and was causing me incredible pain, nausea, and diarrhoea. Again I was managed with yet more steroids which this time brought along the added frustration of unwanted weight gain and associated difficulties as a teenager. I ended up missing most of year 11 but am pleased to say I did really well in my exams, which I took at home and went on to sixth form college, and later to university. I eventually let my hair down, had a LOT of fun forgetting all that I had been through and enjoying being with people who didn't know me or my past. That said I know now that I was avoiding dealing with my issues by partying all the time rather than seeking help.

In 2005, I moved to another city and finally got up the courage to see a gynaecologist. I desperately wanted to have sex and enjoy my sexuality which I had oppressed for so many years. After an initial period of overdoing "it" I met my partner and we are planning to get married next year…as they say, the rest is history!

Learning points:

- The struggles to live and lead a normal healthy life continue in patients with CAH hence, lifelong monitoring, support, and individualised approach is required.
- Education in the prevention and management of adrenal crisis is paramount for everyone involved in the multispecialty care of patients with CAH.
- The positive patient-health care engagement, empowerment of patients and their families/carers in voicing their concerns, and active involvement of patient support groups will improve all aspects of care being received.

35.7 Conclusions

Classic CAH is a rare and life-threatening chronic condition that needs lifelong adrenal replacement therapy. Patients and families are required to have a good knowledge and understanding of the condition and its management needs in both the short and long term. Their involvement with the health system will be lifelong and requires regular review and ongoing treatment and medial management. Health professionals have a crucial role in coordinating the care of patients with CAH. Treatment goals must be agreed with family and, as soon as possible, with the patient. The management plan is individualised and needs to be modulated throughout the patient's lifetime. For a patient with CAH, a sense of feeling connected and understood within the health system is one of the most important aspects in achieving positive health outcomes and satisfaction with their life's journey.

Aknowledgments With special thanks to Sue Elford, Chair, and Sallyann Blackett, Treasurer, from *The CAH Support Group*, website: www.livingwithcah.com and Dina Matos, Executive Director, from the CARES Foundation, website www.caresfoundation.org for their contributions with patient case studies and details on information and resources available through their Patient Advocacy Group.

References

Arlt W, Krone N. Adult consequences of congenital adrenal hyperplasia. Horm Res. 2007;68(Suppl 5):158–64. https://doi.org/10.1159/000110615.

Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010;95(11):5110–21. https://doi.org/10.1210/jc.2010-0917.

Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2013;98(7):2645–55. https://doi.org/10.1210/jc.2013-1440.

Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, Bachega TA, et al. Guidelines for the development of comprehensive care centers for congenital adrenal hyperplasia: guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol. 2010;2010:275213. https://doi.org/10.1155/2010/275213.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89. https://doi.org/10.1210/jc.2015-1710.

Dittmann RW, Kappes MH, Kappes ME, Borger D, Stegner H, Willig RH, et al. Congenital adrenal hyperplasia. I: gender-related behavior and attitudes in female patients and sisters. Psychoneuroendocrinology. 1990;15(5–6):401–20.

El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet. 2017;390(10108):2194–210. https://doi.org/10.1016/S0140-6736(17)31431-9.

Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2012;18(2):146–70. https://doi.org/10.1093/humupd/dmr042.

Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years. Clin Endocrinol. 2013;78(1):23–8. https://doi.org/10.1111/cen.12053.

Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100(2):407–16. https://doi.org/10.1210/jc.2014-3191.

Han TS, Stimson RH, Rees DA, Krone N, Willis DS, Conway GS, et al. Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia. Clin Endocrinol. 2013a;78(2):197–203. https://doi.org/10.1111/cen.12045.

Han TS, Krone N, Willis DS, Conway GS, Hahner S, Rees DA, et al. Quality of life in adults with congenital adrenal hyperplasia relates to glucocorticoid treatment, adiposity and insulin resistance: United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE). Eur J Endocrinol. 2013b;168(6):887–93. https://doi.org/10.1530/EJE-13-0128.

Han TS, Conway GS, Willis DS, Krone N, Rees DA, Stimson RH, et al. Relationship between final height and health outcomes in adults with congenital adrenal hyperplasia: United Kingdom congenital adrenal hyperplasia adult study executive (CaHASE). J Clin Endocrinol Metab. 2014;99(8):E1547–55. https://doi.org/10.1210/jc.2014-1486.

Hatton DL, Canam C, Thorne S, Hughes AM. Parents' perceptions of caring for an infant or toddler with diabetes. J Adv Nurs. 1995;22(3):569–77.

Joint Lecahwg. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. J Clin Endocrinol Metab. 2002;87(9):4048–53. https://doi.org/10.1210/jc.2002-020611.

Knickmeyer R, Baron-Cohen S, Fane BA, Wheelwright S, Mathews GA, Conway GS, et al. Androgens and autistic traits: a study of individuals with congenital adrenal hyperplasia. Horm Behav. 2006;50(1):148–53. https://doi.org/10.1016/j.yhbeh.2006.02.006.

Kruse B, Riepe FG, Krone N, Bosinski HA, Kloehn S, Partsch CJ, et al. Congenital adrenal hyperplasia—how to improve the transition from adolescence to adult life. Exp Clin Endocrinol Diabetes. 2004;112(7):343–55. https://doi.org/10.1055/s-2004-821013.

Mallappa A, Sinaii N, Kumar P, Whitaker MJ, Daley LA, Digweed D, et al. A phase 2 study of Chronocort, a modified-release formulation of hydrocortisone, in the treatment of adults with classic congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2015;100(3):1137–45. https://doi.org/10.1210/jc.2014-3809.

Merke DP, Poppas DP. Management of adolescents with congenital adrenal hyperplasia. Lancet Diabetes Endocrinol. 2013;1(4):341–52. https://doi.org/10.1016/S2213-8587(13)70138-4.

Patterson JM, McCubbin HI, Warwick WJ. The impact of family functioning on health changes in children with cystic fibrosis. Soc Sci Med. 1990;31(2):159–64.

Reichman DE, White PC, New MI, Rosenwaks Z. Fertility in patients with congenital adrenal hyperplasia. Fertil Steril. 2014;101(2):301–9. https://doi.org/10.1016/j.fertnstert.2013.11.002.

Reisch N, Arlt W, Krone N. Health problems in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Horm Res Paediatr. 2011;76(2):73–85. https://doi.org/10.1159/000327794.

Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M, et al. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. Eur J Endocrinol. 2012;167(1):35–42. https://doi.org/10.1530/EJE-12-0161.

Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(9):4133–60. https://doi.org/10.1210/jc.2009-2631.

Webb EA, Elliott L, Carlin D, Wilson M, Hall K, Netherton J, et al. Quantitative brain MRI in congenital adrenal hyperplasia: in vivo assessment of the cognitive and structural impact of steroid hormones. J Clin Endocrinol Metab. 2018;103(4):1330–41. https://doi.org/10.1210/jc.2017-01481.

White PC. Neonatal screening for congenital adrenal hyperplasia. Nat Rev Endocrinol. 2009;5(9):490–8. https://doi.org/10.1038/nrendo.2009.148.

White PC, Bachega TA. Congenital adrenal hyperplasia due to 21 hydroxylase deficiency: from birth to adulthood. Semin Reprod Med. 2012;30(5):400–9. https://doi.org/10.1055/s-0032-1324724.

White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev. 2000;21(3):245–91. https://doi.org/10.1210/edrv.21.3.0398.

Witchel SF, Azziz R. Nonclassic congenital adrenal hyperplasia. Int J Pediatr Endocrinol. 2010;2010:625105. https://doi.org/10.1155/2010/625105.

Key Reading

1. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(9):4133–60. https://doi.org/10.1210/jc.2009-2631.
2. Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, Bachega TA, et al. Guidelines for the Development of Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol. 2010;2010:275213. https://doi.org/10.1155/2010/275213.
3. Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2013;98(7):2645–55. https://doi.org/10.1210/jc.2013-1440.
4. Merke DP, Poppas DP. Management of adolescents with congenital adrenal hyperplasia. Lancet Diabet Endocrinol. 2013;1(4):341–52. https://doi.org/10.1016/S2213-8587(13)70138-4.
5. Kruse B, Riepe FG, Krone N, Bosinski HA, Kloehn S, Partsch CJ, et al. Congenital adrenal hyperplasia—how to improve the transition from adolescence to adult life. Exp Clin Endocrinol Diabet. 2004;112(7):343–55. https://doi.org/10.1055/s-2004-821013.

36 Adrenal Tumours: Adrenocortical Functioning Adenomas, Pheochromocytomas, Incidentalomas, and Adrenocortical Cancer

Andrew P. Demidowich, Miriam Asia, and Jérôme Bertherat

Contents

36.1 **Part A: Adrenocortical Functioning Adenomas and Adrenal Hyperplasia** 681
36.1.1 Introduction 681
36.1.2 Primary Aldosteronism 682
36.1.3 Cushing Syndrome 685
36.1.4 Adrenal Androgens 687

36.2 **Part B: Pheochromocytomas and Paragangliomas** 688
36.2.1 Anatomy and Physiology 688
36.2.2 Pheochromocytomas and Paragangliomas 688

36.3 **Part C: Adrenal Incidentaloma and Adrenocortical Cancer (ACC)** 693
36.3.1 Adrenal Incidentaloma 693
36.3.2 Adrenocortical Cancer (ACC) 698

36.4 **Conclusions** 701

References 701

A. P. Demidowich (✉)
National Institutes of Health, Bethesda, MD, USA
e-mail: andrew.demidowich@nih.gov

M. Asia
Department of Endocrinology, Birmingham University Hospital, Birmingham, UK
e-mail: Miriam.Asia@uhb.nhs.uk

J. Bertherat
Service d'Endocrinologie, Reference Center for Rare Adrenal Diseases, Hôpital Cochin, Paris, France
e-mail: jerome.bertherat@cch.ap-hop-paris.fr

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_36

Abstract

This chapter will discuss in detail the background, evaluation, and management of adrenal tumours, with an additional focus on the role of endocrine nursing in the care of these patients. It is divided into three parts, each providing a comprehensive outline of: A) Adrenocortical functioning adenomas and adrenal hyperplasia, B) Pheochromocytomas and Paragangliomas, and C) Adrenal incidentaloma and adrenocortical cancer (ACC).

Evaluation of adrenal tumours and adenomas requires a thorough history and physical examination. Family history is particularly important as adrenocortical disease can be caused by germline mutations passed down from generation to generation. More commonly, however, sporadic somatic mutations are the cause of spontaneous tumour formation and autonomous hormone secretion.

Adrenocortical adenomas, hyperplasia, and incidentalomas are non-cancerous "growths" or proliferation of cells in the adrenal cortex. Adenomas are rare in childhood but become more frequent as humans age. Approximately 20% of adenomas are functional; that is, they produce hormones to some degree in an autonomous or dysregulated manner. Functional adenomas most commonly produce cortisol or aldosterone, whereas androgen-producing tumours are quite rare and may portend a cancerous aetiology. Co-secretion of more than one hormone from adenomas/hyperplasia is also possible.

The biochemical work-up, with screening as well as confirmatory testing, and relevant imaging will be discussed in detail. The treatment, management, and long-term monitoring are also discussed for each of the adrenal tumours, respectively. Discussion in this chapter is illustrated with a rich content of figures, box inserts, and case studies.

Keywords

Adrenal adenoma · Adrenal hyperplasia · Cushing syndrome · Primary aldosteronism · Cortisol · Aldosterone · Adrenocortical cancer · Pheochromocytomas and paraganglioma

Abbreviations

ACC	Adrenocortical cancer
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
APA	Aldosterone-producing adenoma
ARR	Aldosterone-to-renin ratio
AVS	Adrenal venous sampling
BMI	Body Mass Index
CAH	Congenital adrenal hyperplasia
CPA	Cortisol-producing adenoma
CRH	Corticotropin releasing hormone
DHEA	Dehydroepiandrosterone
GRA	Glucocorticoid-remediable aldosteronism
HNPGL	Head and neck paraganglioma
IV	Intravenous
L-DOPA	L-dihydroxyphenylalanine
MRA	Mineralocorticoid receptor antagonist
PA	Primary aldosteronism
PAC	Plasma aldosterone concentration
PCC	Pheochromocytomas
PCOS	Polycystic ovarian syndrome
PGL	Paraganglioma
PMNT	Phenylethanolamine *N*-methyltransferase
RAAS	Renin-angiotensin-aldosterone system
SDHx	Succinate dehydrogenase complex

Key Terms

- **Adrenocortical functioning adenomas:** hypersecreting tumors of the adrenal cortex
- **Adrenal hyperplasia:** enlargement of the adrenal glands
- **Adrenal incidentalomas:** incidentally found benign adenomas on evaluation of unrelated symptoms
- **Co-secretion:** more than one hormone secreted from adrenal adenomas/hyperplasia
- **Cushing Syndrome:** hypersecretion of cortisol from an adrenal adenoma
- **Catecholamines:** are produced in the adrenal medulla and are essential for the stress response
- **Pheochromocytomas:** are tumors arising from the adrenal medulla that produce excess catecholamines

- **Paraganglioma:** are also tumors that produce catecholamines, but they originate in paraganglia along the parasympathetic and sympathetic chains

Key Points

- List the most common hormones produced by adrenal functioning tumours/hyperplasia
- Describe common presenting signs and symptoms of primary aldosteronism, Cushing syndrome, adrenocortical cancer, pheochromocytoma, paraganglioma
- Explain the evaluation for suspected adrenal tumours/hyperplasia
- Discuss the possible treatment and management options for adrenal tumours
- Emphasize and describe the role of the endocrine nurse in the care of these patients

36.1 Part A: Adrenocortical Functioning Adenomas and Adrenal Hyperplasia

36.1.1 Introduction

As described in the anatomy and physiology chapter of this section, the adrenal gland is comprised of two main layers: the cortex and the medulla. The medulla derives from neuroectodermal tissue in early fetal life and is mainly composed of chromaffin cells. The cortex develops from the mesoderm and is organized into three layers: the zona glomerulosa, zona fasciculata, and zona reticularis, responsible for producing the hormones aldosterone, cortisol, and androgens, respectively (Avisse et al. 2000). Part A of this chapter focuses on functional benign adrenal tumours and hyperplasia of the cortex; Part B covers pheochromocytomas and paragangliomas; and Part C covers adrenal incidentalomas and adrenocortical cancer (ACC). Congenital adrenal hyperplasia is covered in a separate chapter in this section.

Tumours and hyperplasia can be thought of as two ends of the same spectrum. A tumour is a proliferation of cells derived from a single progenitor cell. Hyperplasia, in contrast, is a "tissue-wide" proliferation of cells. Patients can develop a single discreet nodule, multiple nodules (in one or both adrenals), or hyperplasia. Additionally, nodules can grow in the background of a hyperplastic gland (Fig. 36.1). Adrenal adenomas and hyperplasia can occur secondary to chronic hormonal stimulation (e.g. ACTH stimulation in CAH or Cushing disease), or due to a somatic or germline mutation (Hsiao et al. 2009).

The imaging characteristics of adrenal tumours and masses are discussed in greater detail in Part B. Briefly, most (~60–90%) benign adrenocortical adenomas are comprised mainly of lipids and are therefore commonly described as "lipid-rich". On CT imaging, they have a lower density than surrounding organs, such as the liver, kidneys, or spleen, and therefore appear darker. The Hounsfield Units (HU; a measure of density) of the adenoma on non-contrast CT is typically less than 10 HU. Additionally, these tumours have a relatively high "washout" of IV contrast, when examined 10–15 min after contrast injection (Zeiger et al. 2009a).

"Lipid poor" adrenal masses, on the other hand, have higher density on non-contrast CT and commonly have low washout. Benign adrenocortical tumours (either functional or non-functional) can be lipid poor; however, other types of diseases, such as pheochromocytomas, ACC, adrenal haemorrhage, or metastatic lesions from other organs, can also present as "lipid poor" masses on CT (Zeiger et al. 2009a).

Benign adrenal tumours are extremely rare in childhood, increase to a prevalence of about 3% by age 50, and 10% in elderly adults (Minnaar et al. 2013; Fassnacht et al. 2016). Although 80% of adenomas are non-functional (Zeiger et al. 2009b), the signs and symptoms of a functional adrenal adenoma can be subtle and easily missed for many years, so most adenomas should undergo evaluation for functional status upon initial discovery (Fassnacht et al. 2016; Zeiger et al. 2009b).

The region in which the functional tumour or hyperplasia is located typically determines the hormone produced. In other words, a functional tumour in the zona glomerulosa will typically cause primary aldosteronism, whereas a functional tumour in the zona fasciculata will lead to

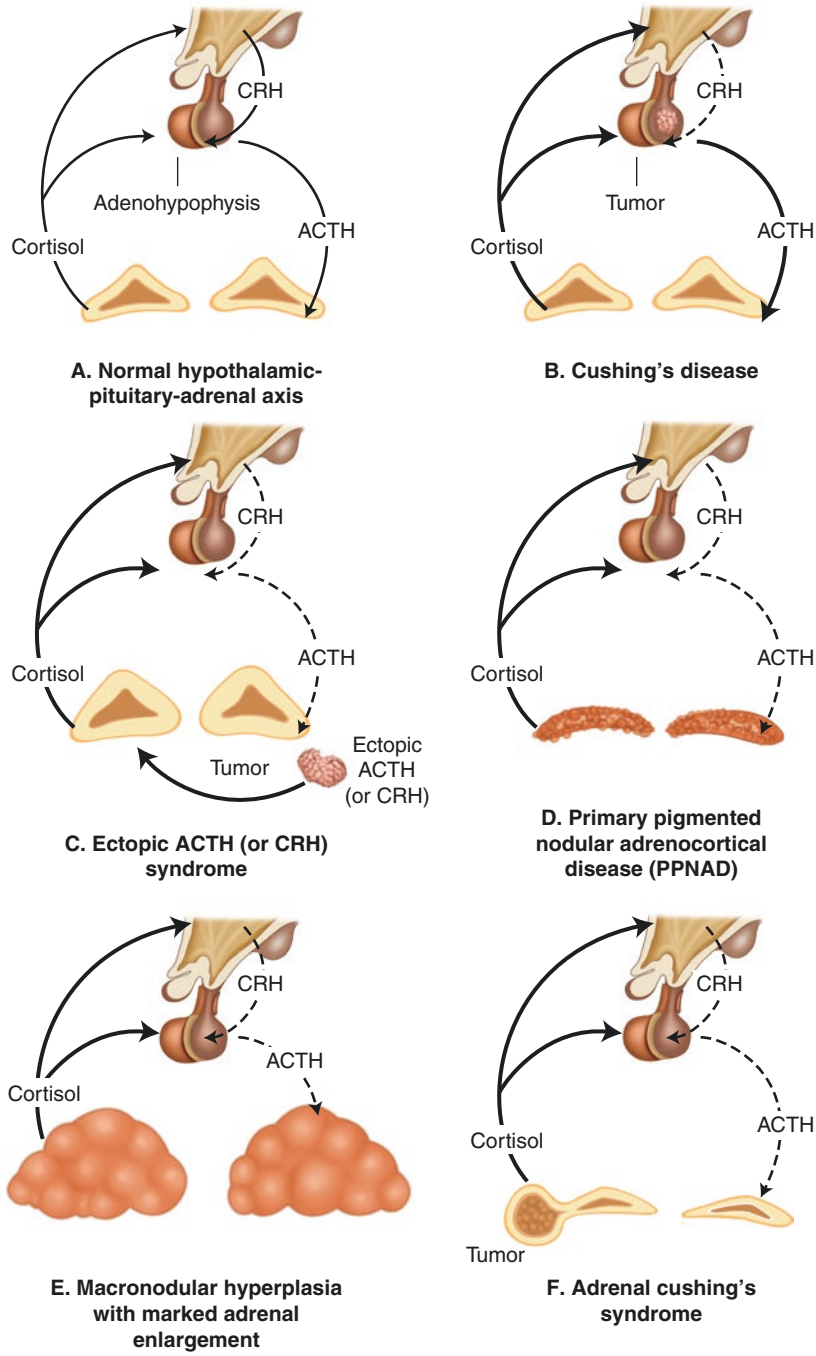


Fig. 36.1 Adrenal adenomas and hyperplasia

cortisol excess and Cushing syndrome. Functional tumours solely producing androgens are rare and often suggest a malignant, rather than benign, pathology. However, co-secretion of multiple hormones (e.g. cortisol and aldosterone) from benign tumours or hyperplasia can occur (Willenberg et al. 2010; Sakai et al. 1993).

36.1.2 Primary Aldosteronism

Aldosterone, a mineralocorticoid produced by the zona glomerulosa, is a major regulator of blood pressure and intravascular volume status. It exerts its effects primarily by acting on the distal convoluted tubule and collecting

duct in the kidney. By binding to its intracellular receptor, aldosterone stimulates production of the ENaC sodium channel, which enables increased sodium and water reabsorption from the urine. To counteract this cationic influx, potassium (and to a lesser degree hydrogen) ions are simultaneously excreted into urine.

Aldosterone synthesis is regulated by several mechanisms. The primary regulator is intravascular volume status via the renin-angiotensin-aldosterone system (RAAS), with hyperkalaemia also being a potent stimulus of aldosterone secretion (please see anatomy and physiology chapter in this section). Adrenocorticotropic hormone (ACTH) can also provoke aldosterone release but plays a minor role overall.

Primary aldosteronism (PA, a.k.a. Conn's syndrome) is the dysregulated hyperproduction of aldosterone from either one or both adrenal glands. Unilateral disease is seen in approximately two-thirds of cases (Mathur et al. 2010) and typically stems from an aldosterone-producing adenoma (APA, a.k.a. Conn's adenoma), frequently caused by a somatic mutation (e.g. *KCNJ5*, *ATP1A1*, *ATP2B3, CACNA1D,* or *CACNA1H*). In contrast, bilateral disease most commonly occurs as a result of bilateral adrenal hyperplasia. Heritable forms of PA make up less than 10% of cases; germline mutations include *KCNJ5, CLCN2, ARMC5,* or a chimeric *CYP11B1/CYP11B2* gene translocation (a.k.a. glucocorticoid-remediable aldosteronism or GRA) (Zilbermint et al. 2015; Dutta et al. 2016).

The most common presenting sign of PA is uncontrolled hypertension. In fact, PA is the leading secondary cause of hypertension, responsible for 5–10% of cases of "presumed" essential hypertension (Funder et al. 2016). Patients may commonly present with symptoms of recurring headache, chest pain, or oedema. More severe cardiovascular sequelae, such as myocardial infarctions, strokes, or congestive heart failure, may manifest at an early age (<40 years). Hypokalaemia is seen only in a minority (~30%) of patients with PA, but can be unmasked when loop diuretics are initiated (Funder et al. 2016).

36.1.2.1 Diagnosis and Treatment of Primary Aldosteronism

In recent years, it has become apparent that other comorbid conditions, including hyperparathyroidism, osteoporosis, nephrolithiasis, renal cysts (Petramala et al. 2014), obstructive sleep apnoea (Di Murro et al. 2010), and insulin resistance, are strongly associated with PA. Moreover, it is important to take a detailed family history, asking specifically about early-onset cardiovascular or cerebrovascular disease in first-degree relatives, as PA can be familial.

Patients should be screened for PA if they have (see Box 36.1 for more details):

1. Blood pressure greater than 150/100 mmHg on more than three occasions
2. Greater than 140/90 mmHg despite using three antihypertensive medications
3. Controlled blood pressure requiring four or more antihypertensive medications
4. Hypertension with adrenal incidentaloma on imaging
5. Hypertension with obstructive sleep apnoea
6. Hypertension with hypokalaemia (even if diuretic-induced)
7. Hypertension with first-degree relative with PA
8. Hypertension with first-degree relative with early-onset hypertension or stroke (age <40) (Funder et al. 2016)

Box 36.1 Principles of Good Clinical Practice for Screening for PA

It is important to follow below instructions when screening for PA, and this is a crucial aspect of the endocrine nurse role. The patient should be appropriately informed and educated about the procedure; supporting patient leaflets to reinforce this information are vital and should be written in an easy to understand language.

Screening consists of measuring a plasma aldosterone concentration (PAC) and plasma renin activity to calculate the

aldosterone-to-renin ratio (ARR). Ideally testing should be performed in the morning, after the subject has been out of bed for at least 2 h. Patients should be instructed to be on a liberal salt diet and be volume replete prior to testing. This will suppress the renin level, meaning that most of the circulating aldosterone is probably autonomously produced (i.e. dysregulated), rather than stimulated by the RAAS system. Patients **must** have stopped mineralocorticoid receptor antagonists (e.g. spironolactone, eplerenone) and potassium-wasting diuretics (e.g. furosemide, torsemide) for at least 4 weeks prior to ensure an accurate result. As hypokalaemia can impair aldosterone secretion, patients should also ideally be potassium replete ($[K^+]$ >4.0) prior to testing. Blood should be drawn with the patient in a seated position, rather than recumbent. It should be drawn slowly, ideally into a syringe rather than a vacutainer to avoid haemolysis, transported at room temperature (**not** on ice), and processed within 30 min of collection. An ARR ≥750 (SI units) or ≥30 (conventional units) with PAC ≥280 pmol/L (10 ng/dL) is strongly suggestive of PA (Funder et al. 2016).

Confirmatory testing should be performed, as no diagnosis should depend on a single lab result. Testing options include an oral salt loading test with 24-h urine collection of aldosterone (cut off >33 nmol/day, 12 μg/24 h), saline infusion test (cut off PAC ≥280 pmol/L, 10 ng/dL), captopril challenge test, and fludrocortisone suppression test (Funder et al. 2016).

Once confirmed, the patient should undergo CT imaging with IV contrast to better define the adrenal and associated venous anatomy. Because clinicians may be fooled by a non-functional adenoma on imaging, and the disease in fact may be on the contralateral gland or bilateral disease, it is often recommended that patients who are surgical candidates should subsequently undergo adrenal venous sampling (AVS), the current gold standard to confirm the laterality of disease. The rate of success of this technically demanding diagnostic procedure depends on the expertise of the interventional radiologist, so referral to high-volume centre is recommended. Patients younger than 35, with profound aldosterone concentrations (>830 pmol/L or 30 ng/dL), spontaneous hypokalaemia, and an obvious solitary lipid-rich nodule on imaging can forgo AVS and proceed directly to unilateral adrenalectomy (Funder et al. 2016).

Similarly, if AVS lateralizes to one side, it is recommended that the patient proceed to unilateral adrenalectomy (typically performed laparoscopically). Surgery will, in most cases, cure the patient of hypokalaemia and improve hypertension. Hypertension may not improve immediately but may continue to improve even up to 1 year post-operatively (see Box 36.2). Factors that portend a lower rate of hypertension cure include male sex, longer duration of PA (>6 years), multiple antihypertensive medications preoperatively, and overweight or obesity (BMI >25 kg/m^2) (Aronova et al. 2014).

Box 36.2 Important Message for Patients for Post-operative Care for PA

Advise your patient that hypertension may not improve immediately and can continue to improve even up to 1 year post-operatively. Lifestyle factors can influence this so encourage weight loss for your overweight patients.

If the disease is determined to be bilateral by AVS, however, surgery is typically not offered, and medical management with a mineralocorticoid receptor antagonist (MRA) is instituted. Spironolactone is typically cheap (as it is generic), may be the most potent MRA, and is commonly the first-line medication. However, it

can have mild off-target anti-androgenic effects leading to gynaecomastia or sexual dysfunction in males. Eplerenone, a newer and more specific MRA, does not cause these side effects and may be a better choice for male patients (Parthasarathy et al. 2011). However, it can also be significantly more costly if not covered by health insurance. If a single medication is unable to control the hypertension, additional agents, such as a calcium channel blocker, ACE inhibitor, or triamterene (ENaC channel blocker) may be added.

36.1.3 Cushing Syndrome

Cortisol, a glucocorticoid produced by the zona fasciculata, has many wide-ranging effects on the body, including regulation of blood pressure, glucose, immune function, metabolism, and bone turnover. Its synthesis and secretion are primarily regulated by ACTH, which is produced in the pituitary.

Among adrenal adenomas, between 5 and 25% have some degree of autonomous cortisol production (Rossi et al. 2000; Mantero et al. 2000). The vast majority of these cortisol-producing adenomas (CPA) do so in small quantities and rarely progress (<1%) to produce overt signs and symptoms typically associated with Cushing syndrome (prevalence 1 per million), such as moon-like face, plethora, dorsal buffalo hump, violaceous abdominal striae, thin skin, easy bruising, frequent infections, fragility fractures, or proximal muscle weakness (Fassnacht et al. 2016; Newell-Price et al. 2006) (Fig. 36.2). Thus, these CPAs have classically been denoted in the literature as causing "Subclinical" Cushing syndrome. In recent years, however, it has been realized that even subclinical Cushing syndrome may have subtle clinical signs such as obesity, acne, or hirsutism and is associated with an increased risk of hypertension, type 2 diabetes, hyperlipidaemia, and osteoporosis (Fassnacht et al. 2016; Rossi et al. 2000). Moreover, as this represents a degree of cortisol excess along a spectrum, the term "autonomous cortisol secretion" is preferred to subclinical Cushing syndrome.

36.1.3.1 Diagnosis of Cushing Syndrome

A thorough history needs to be taken, as effects of hypercortisolaemia may be subtle. Patients may have menstrual irregularities or low testosterone (in men), acanthosis nigricans or skin tags from insulin resistance, acid reflux or peptic ulcer disease from enhanced gastric acid production, and/or silent vertebral compression fractures. Mental disease may be a prominent feature and be very distressing to the patient, manifesting as anxiety, depression, insomnia, mood instability, anger outbursts, fatigue, forgetfulness, or even hallucinations (Rasmussen et al. 2015). Like primary aldosteronism, Cushing syndrome can result from germline (inherited) or somatic (sporadic) mutations (Lodish and Stratakis 2016); therefore, obtaining a good family history is also paramount.

Screening for hypercortisolaemia begins with a 1 mg overnight dexamethasone suppression test (Box. 36.3). Patients are instructed take 1 mg of dexamethasone, a synthetic glucocorticoid that is not recognized by the cortisol laboratory assay, between 11 pm and midnight, and a cortisol level is drawn at 8 am the following morning. Dexamethasone inhibits the hypothalamic production of corticotropin releasing hormone (CRH) and pituitary secretion of ACTH, thereby suppressing normal adrenal cortisol production. A morning cortisol >138 nmol/L (>5 μg/dL) is consistent with autonomous cortisol secretion, whereas a cortisol of ≤50 nmol/L (≤1.8 μg/dL) effectively rules out the disease. A cortisol between these two values is a grey zone and represents "possible" autonomous cortisol secretion (Fassnacht et al. 2016). It is important to note that women on oestrogen (e.g. oral contraceptives) may have a false-positive as oestrogen raises the circulating cortisol binding globulin. Also, some advocate to measure a dexamethasone level simultaneously with the morning cortisol to assess if a) the patient is a "hypermetabolizer" or b) if the patient did not actually take the medication, as both could lead to a false-positive result (Meikle 1982; Nieman et al. 2008).

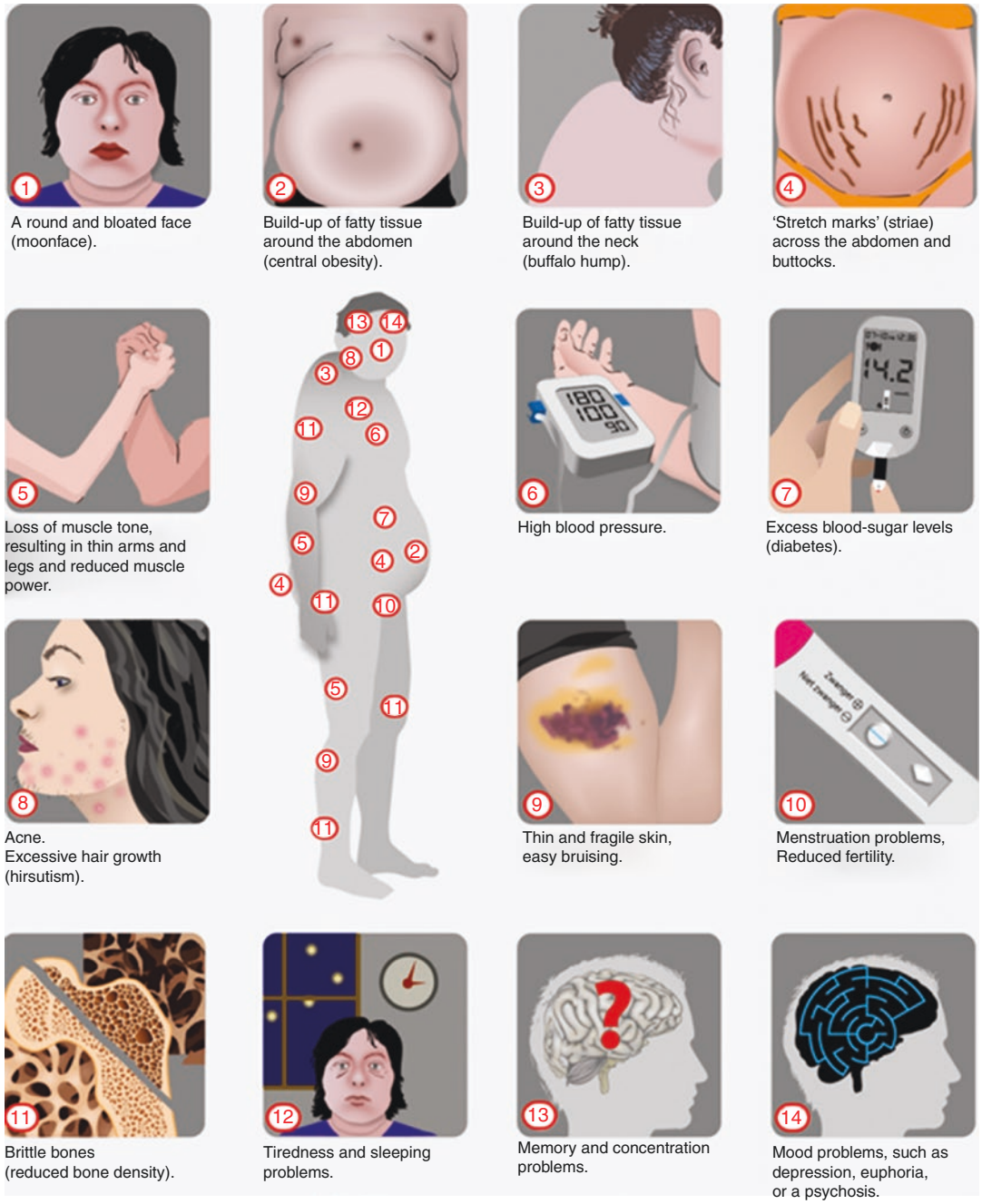


Fig. 36.2 Possible manifestations of cortisol excess (Cushing Syndrome). Used with permission from AdrenalNET and accessed via https://adrenals.eu/infographics/cushings-syndrome-infographic/

Patients with signs consistent with overt Cushing syndrome should undergo other screening tests, such as a 24-h urine collection for free cortisol (repeated at least twice), a late-night salivary cortisol (repeated at least twice), or a 48-h low-dose dexamethasone suppression test. Two positive screening tests in the setting of overt signs is consistent with the diagnosis of Cushing syndrome.

Box 36.3 Principles of Good Clinical Practice for Overnight Dexamethasone Text

Provide the patient with detailed information on why and how to take dexamethasone. Confirm that the patient has taken the tablet at the required time in order to interpret results accurately. Confirm the patient is not taking oestrogen or oral contraceptive pill (OCP) by asking "are you on the contraceptive pill?" rather than just "do you take other medication?". Patients often don't view the OCP as medication.

It is important to remember that ACTH excess (e.g. functional pituitary adenoma) can cause adrenal hyperplasia ± nodules. A suppressed ACTH level (<1.1 pmol/L, <5 pg/mL) is consistent with an adrenal, rather than an ACTH-dependent (e.g. pituitary or ectopic) source; however, unsuppressed ACTH levels (<3.3 pmol/L, 15 pg/mL) can be seen with adrenal disease as well (Newell-Price et al. 2006). In this case, an 8 mg overnight dexamethasone suppression test or CRH stimulation test may be helpful to distinguish between the two aetiologies.

36.1.3.2 Treatment of CPA Causing Cushing Syndrome

CPA causing Cushing syndrome should be surgically removed, if possible, via laparoscopic resection. If bilateral disease is seen on imaging, the surgical strategy should be thoroughly discussed with the patient. In the past, frequently both adrenal glands were excised leaving the patient cured, but with permanent adrenal insufficiency, requiring lifelong glucocorticoid (e.g. hydrocortisone) and mineralocorticoid (e.g. fludrocortisone) replacement. Recent studies have suggested that simply removing the larger gland on CT/MRI, or the more hypermetabolic gland on FDG PET, may lead to successful remission (Patel et al. 2016; Debillon et al. 2015).

The evidence regarding surgical intervention for autonomous cortisol secretion is less clear. Limited studies suggest that adrenalectomy for individuals who are surgical candidates and who also have related comorbid conditions, such as obesity, hypertension, type 2 diabetes, hypertension, or osteoporosis, may derive benefit (Fassnacht et al. 2016). For non-surgical candidates, medical therapy such as ketoconazole, metyrapone, mitotane, pasireotide, and/or mifepristone can be considered (Sharma and Committee 2017).

36.1.4 Adrenal Androgens

Androgens produced from the zona reticularis include dihydroepiandrostenone (DHEA), DHEA-sulphate (DHEAS), and androstenedione. Regulation of adrenal androgens is a complex system, partially under the control of ACTH. However, numerous other hormones may play a part in regulating the zona reticularis as well, including growth hormone, gonadotropins, oestrogens, and insulin (Parker 1991).

Females suspected of androgen overproduction may present with mild symptoms, such as hirsutism, acne, and menstrual irregularities. These patients should be assessed for non-classical congenital adrenal hyperplasia (see Chap. 35) and PCOS (see Chap. 39). Unlike in NCCAH, PCOS classically has been thought to result from dysregulated ovarian androgen synthesis. However, it has been recently suggested that a subgroup of PCOS patients suffer from mildly hyperactive adrenocortical function and adrenal hyperplasia (Gourgari et al. 2016). Benign androgen-producing adrenal adenomas have been previously described but are exceedingly rare (Ghayee et al. 2011; Goodarzi et al. 2003).

More rapid presentation and severe signs/symptoms of virilization, including deepening of the voice and male-pattern baldness, may signify an androgen-secreting adrenocortical cancer. For this reason, paediatric or female patients with confirmed hyperandrogenism, and particularly those with aggressive disease, should undergo imaging of the adrenals to help establish the aetiology. In instances of ACC or a benign functional adrenal adenoma, surgery is warranted.

Individuals with PCOS may benefit from spironolactone due to its anti-androgenic properties.

36.2 Part B: Pheochromocytomas and Paragangliomas

36.2.1 Anatomy and Physiology

The adrenal medulla is responsible for producing catecholamines (the hormones dopamine, norepinephrine, and epinephrine), which are essential for the stress response, otherwise known as the "fight or flight" response. The catecholamine pathway begins with the conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase, the rate limiting step. L-DOPA is then converted to dopamine by DOPA decarboxylase, and subsequently to norepinephrine (a.k.a. noradrenaline) by dopamine hydroxylase. The final step is catalysed by phenylethanolamine *N*-methyltransferase (PMNT) to form epinephrine (a.k.a. adrenaline) (Flatmark 2000).

Norepinephrine and epinephrine have potent cardiovascular effects. They can both bind to α1, α2, β1, and β3 adrenergic receptors. α1 binding mediates smooth muscle contraction and increases vascular tone; α2 binding leads to a negative feedback reduction of catecholamine production, decreased gastrointestinal motility, among numerous other actions; β1 binding causes increased heart rate and cardiac contractility; and β3 binding stimulates increased brown adipose tissue thermogenesis. Epinephrine has much greater affinity for the β2 adrenergic receptor than does norepinephrine, leading to increased smooth muscle relaxation in pulmonary bronchi and decreased gastrointestinal motility (Insel 1996, 1989; Sagrada et al. 1987).

For the most part, these hormones are stored in vesicles rather than directly released into circulation. Only upon stimulation do the vesicles fuse with the plasma membrane, thereby releasing the catecholamines in appreciable quantities. In contrast, metabolites of catecholamines (e.g. normetanephrine and metanephrine) are continuously excreted into circulation and are useful for diagnostic purposes (Lenders et al. 2014).

36.2.2 Pheochromocytomas and Paragangliomas

Tumours arising from the adrenal medulla are termed pheochromocytomas (PCC). Paraganglioma (PGL) are similar to PCC in that they can also produce catecholamines, but they originate in paraganglia along the parasympathetic and sympathetic chains. Sympathetic paraganglia are derived from chromaffin cells, are commonly located in the para-axial region from the neck to the pelvis, and secrete catecholamines in response to sympathetic stimulation. Parasympathetic ganglia, on the other hand, are not derived from chromaffin cells and are often found in the head and neck or close to their target organ, such as the carotid body, jugulotympanic ganglion, or along the vagus nerve (Fig. 36.3) (McNichol 2001). Thus, the location of a PGL can clue a clinician to its hormone secretory status; namely, paravertebral PGL often are biochemically active, whereas head and neck PGL (HNPGL) are commonly either non-functional (silent) or only dopamine producing.

PCC/PGL are rare, with an estimated incidence of 1 in 2000–5000 individuals. PCC make up about 80–85% of these cases, with PGL being less common. Sporadic PCC typically presents between ages 40 and 50 although 2–10% of cases are diagnosed in paediatric patients. Both sexes are affected equally (Wyszynska et al. 1992; Lenders et al. 2005; McNeil et al. 2000; Martucci and Pacak 2014).

PCC/PGL classically present with paroxysms of sympathetic excess, including episodic headache/migraines, sweating, and tachycardia. Both blood pressure spikes or sustained hypertension can be seen with PCC/PGL. Hypertensive crises caused by catecholamine surges can present with or lead to heart attacks, strokes, or death (Mazza et al. 2014; Whitelaw et al. 2014). Conversely, patients with predominantly epinephrine-producing PCC can present with orthostatic hypotension or even shock (Bergland 1989; Streeten and Anderson Jr. 1996). Other symptoms can include flushing or facial pallor, palpitations, diz-

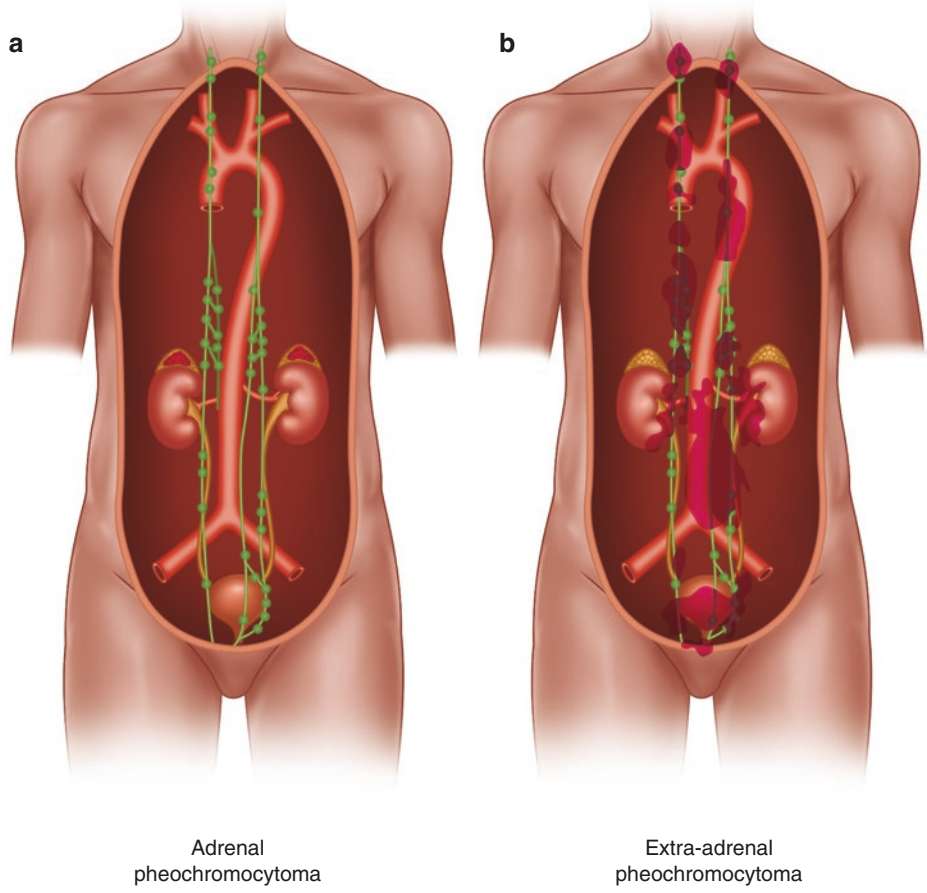


Fig. 36.3 The paraganglial system and sites of shown in red on the adrenals and extra-adrenal

ziness, visual disturbances, and feelings of anxiety or impending doom. Nausea and vomiting can present, particularly after exercise (Martucci and Pacak 2014). Constipation, commonly overlooked, can be severe and significantly impact patient quality of life (Thosani et al. 2015). Lastly, fasting hyperglycaemia or frank diabetes is a rare manifestation of PCC/PGL, particularly in younger patients without other diabetes risk factors (La Batide-Alanore et al. 2003).

The symptoms may occur spontaneously or may be brought on by stimuli, including the ingestion of certain tyramine-containing foods, micturition (in the cases of urinary bladder PCC), or certain medications or illicit drugs (Hodin et al. 2014). Anaesthesia or manipulation of a PCC/PGL during surgery can also lead to a catecholamine surge. PCC/PGL can also be discovered incidentally on imaging. Indeed, up to 5% of adrenal incidentalomas are found to be PCC (Mantero et al. 2000).

36.2.2.1 Diagnostic Testing

The initial diagnostic test of choice for PCC/PGL is either plasma-free metanephrines or 24-h urine fractionated metanephrines, which have greater than 90% sensitivity and specificity. The plasma or urine metanephrines are typically elevated more than threefold above the upper limit of normal for the reference range. Urine collections should also be measured for creatinine to ensure proper collection (Box. 36.4). These tests have demonstrated superior sensitivity and specificity over plasma or urine catecholamines or vanillylmandelic acid (VMA) (Lenders et al. 2002, 2014). HNPGL tend to be biochemically silent, or only secrete methoxytyramine, a dopamine metabolite,

for which commercial biochemical testing is not yet widely available (Rao et al. 2017).

Box 36.4 Principles of Good Clinical Practice for Testing for Pheochromocytomas

It is important to consider the conditions under which the samples are obtained, as they may affect the reliability of the results. Patients should have an indwelling intravenous catheter and be supine for at least 30 min prior to sampling. Phlebotomy performed with a butterfly needle or in the seated position can increase the likelihood for false-positive results (Lenders et al. 2014). Ideally, caffeine, nicotine, and alcohol should be avoided for at least 12 h prior to the test. Medications can also falsely elevate metanephrines, including acetaminophen, labetalol, phenoxybenzamine, tricyclic antidepressants (TCAs), decongestants, and buspirone (Lenders et al. 2014). Patients with chronic kidney disease will have decreased clearance of metanephrines, and therefore may have false-elevations (Martucci and Pacak 2014). Lastly, evaluation of PCC/PGL should not occur in the setting of an acute physical stress (e.g. acute myocardial infarction, infection) as increases in catecholamine production is a normal physiological response in such states.

Because up to 20% of metanephrine measurements may be false-positives (Yu and Wei 2010), equivocal results (e.g. metanephrine or normetanephrine elevation 1–3× the upper limit of normal) should be repeated, removing any possible offending medications. Patients with persistently equivocal tests or unclear diagnosis can also undergo a clonidine suppression test. The alpha receptor blocker clonidine specifically blocks norepinephrine released from neurons but does not block its release from the adrenal medulla or from PCC tumours. In individuals with PCC, plasma metanephrine levels do not suppress (<40% decrease) at 3 h after clonidine administration. This test has a specificity of 100% with sensitivity of 97%, but has not been validated prospectively. Importantly, the clonidine may cause significant hypotension, so patients should be monitored during this test (Lenders et al. 2014).

Once a diagnosis is established, patients should undergo imaging to locate the PCC/PGL. Typically, a CT of the abdomen and pelvis is pursued since most PCC/PGL are located in the abdomen. Because PCC are typically dense, a lesion with >10 Hounsfield units (HU) on non-contrast CT increases the likelihood, whereas a lesion with <5 HU almost definitively rules out the culprit lesion. To obtain washout values, contrast is injected, and the patient undergoes scanning one and 15 min later. The absolute washout $((HU_{1\,min} - HU_{15\,min})/(HU_{1\,min} - HU_{baseline}))$ is often less than 60% in PCC/PGL, reflecting their vascular and hypermetabolic nature, and therefore retaining (not "washing out") the IV contrast (Blake et al. 2010; McCarthy et al. 2016).

MRI imaging can be pursued instead, particularly in the paediatric population or in pregnant individuals, as it also has excellent sensitivity. On T1-weighted imaging, PCC/PGL have a signal intensity similar to liver, kidney, and muscle, which distinguishes them from the more common and benign cortical adenomas, which appear bright. Additionally, PCC/PGL do not have "signal drop out" between the in- and out-of-phase images. On T2-weighted images, PCC/PGL have a hyperintense appearance, sometimes nicknamed the "lightbulb" sign (Fig. 36.4) (Blake et al. 2010; McCarthy et al. 2016; Elsayes et al. 2005).

Ultrasound has much poorer sensitivity than CT or MRI, and therefore is not often used in the diagnosis of PCC/PGL, except when bladder PGL or liver metastases are suspected.

If a tumour is not localized on CT/MRI or metastatic disease is suspected, functional imag-

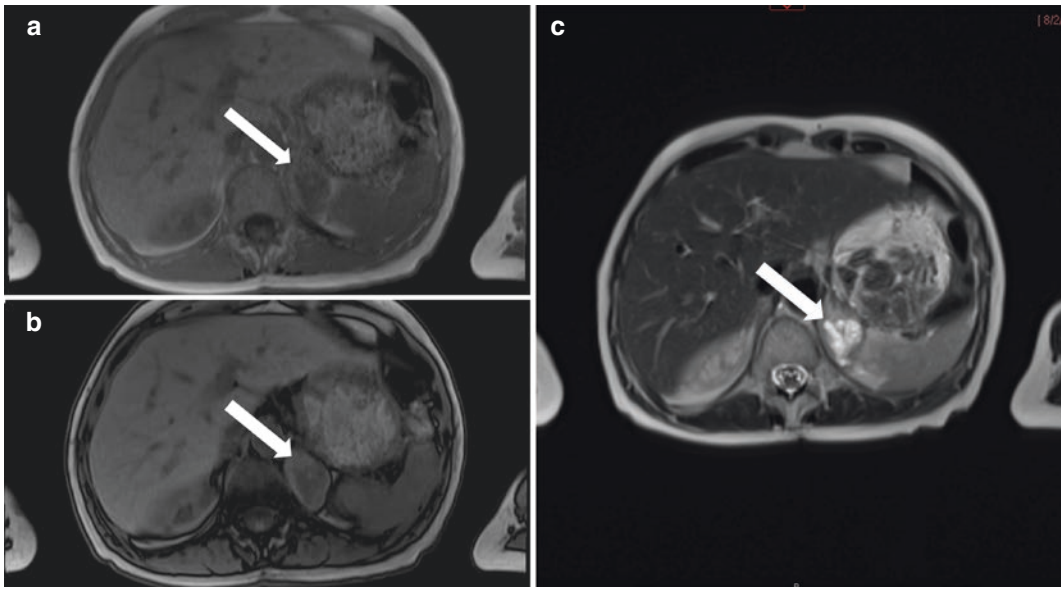


Fig. 36.4 MRI images of a pheochromocytoma (white arrows). Key: (**a**) T1 weighted MRI of the Abdomen In-phase with arrow pointing to pheochromocytoma at the left adrenal gland; (**b**) T1 weighted MRI of the Abdomen Out-phase with arrow pointing to pheochromocytoma at the left adrenal gland; (**c**) T2 weighted MRI of the Abdomen with arrow pointing to a bright pheochromocytoma lesion at the left adrenal gland. **Image provided by and used with permission from Dr Mayank Patel, MD, Special Volunteer, Section on Medical Neuroendocrinology, NICHD/NIH**

ing should be pursued. MIBG is available at many institutions and has classically been the first-line functional imaging test, as MIBG has high affinity for norepinephrine transporters. ^{131}I-MIBG is less sensitive and emits greater γ radiation than ^{123}I-MIBG and is no longer recommended. However, up to 50% of normal adrenal glands can demonstrate uptake, and false-positivity of MIBG is a significant problem. Conversely, MIBG has poor sensitivity for the detection of malignant, bilateral, or extra-adrenal PCC/PGL, or those related to certain germline PCC/PGL-driver mutations (e.g. *RET*, *VHL*, or *SDHx*) (Lenders et al. 2014; Timmers et al. 2012).

PET imaging is superior to MIBG with respect to PGLs or metastatic disease and is more commonly being used over MIBG in the evaluation of PCC/PGL. ^{18}F-dihydroxyphenylalanine (FDOPA) has been shown to have excellent sensitivity (>90%) and specificity in metastatic disease but is not commonly available. ^{18}F-fluorodeoxyglucose (FDG) PET is most frequently used and has excellent sensitivity due to the increased metabolic demand PCC/PGL. However, inflammation, infection, benign adrenal adenomas, and other tumours/cancers may also demonstrate positive FDG-PET uptake. Also, if the patient has hyperglycaemia or uncontrolled diabetes mellitus, the elevated circulating glucose may compete with the FDG tracer for uptake, thereby resulting in a false-negative scan (Timmers et al. 2012; Taieb and Pacak 2018).

Lastly, ^{68}Ga-DOTATATE has been shown great promise as a functional imaging modality, particularly in *SDHB* metastatic disease and HNPGL, and has exceptional sensitivity and specificity in abdominal and thoracic PGLs as well (Taieb and Pacak 2018; Janssen et al. 2015, 2016).

As 30–40% of PCC/PGL may arise as part of an inherited syndrome, genetic testing should be offered to all patients diagnosed with PCC/PGL. With improvements and cost reduction in genetic sequencing a plethora of new genes have been linked with PCC/PGL formation, including over 10 major driver genes and 20 minor or rare driver genes (Dahia 2014; Curras-Freixes et al. 2017). Mutations in the succinate dehydrogenase complex (SDHx), a multimer of different protein subunits involved in the electron transport chain, are the most commonly inherited PCC/PGL-driver gene mutations, with *SDHB* and *SDHD* representing 10% and 9% of cases, respectively. Genetic testing is important as it can give prognostic information (e.g. *SDHB* frequently cause metastatic disease), may help with preconception planning or screening of family members, and may guide biochemical and radiologic testing.

36.2.2.2 Treatment for Pheochromocytoma and Paraganglioma

For biochemically active tumours, patients should be started on alpha-blockade immediately (Box. 36.5). For tumours which are very symptomatic (e.g. frequent hypertensive crises, uncontrolled blood pressure) or have very elevated metanephrines, phenoxybenzamine, a powerful non-selective irreversible alpha-blocker, is recommended. Less active tumours may do well with a selective α1-antagonist (e.g. terazosin, doxazosin, prazosin) (Hodin et al. 2014).

Box 36.5 Nursing Considerations for Patients on Alpha-Blockers

The role of the endocrine nurse is crucial in monitoring blood pressure and pulse and titrating alpha-blockers medications. It is important to educate patient about the side effects of these medications and that these can cause postural hypotension. The patient is advised to avoid sudden change of position, i.e. abrupt standing whilst sitting or lying. The patient is advised to increase fluid intake as blood volume is diminished because of excess adrenaline.

Beta-blockers, such as atenolol or metoprolol, can be started at least 3 days after alpha-blockade initiation to help control tachycardia. Beta-blockade prior to alpha-blockade can cause unopposed alpha stimulation and precipitate a pheochromocytoma crisis. Additionally, beta-blockers with both alpha- and beta-adrenergic blocking ability (e.g. labetalol) should be avoided as single or first-line therapy, as the beta-blockade is much more potent than the alpha-blockade and may precipitate a crisis (Lenders et al. 2014). Calcium channel blockers may be used in addition to or instead of alpha-blockers, particularly in those with mild disease or who are intolerant of alpha-blockade (Hodin et al. 2014).

Metyrosine, a tyrosine hydroxylase inhibitor, prevents catecholamine synthesis and can be used in refractory patients. However, it is expensive, difficult to obtain, and poorly tolerated with significant side effects, including depression, fatigue, nausea, and somnolence. Therefore, it should be used as an adjunctive treatment to the above mentioned medications in selected patients (Hodin et al. 2014).

Once medically controlled, most patients should be referred to surgery. Because patients with inherited forms of PCC/PGL may have recurrences and/or bilateral disease, partial cortical-sparing adrenalectomies are preferred when possible to avoid lifelong glucocorticoid and mineralocorticoid replacement. Most surgeries can be performed laparoscopically; however, for large (e.g. >5 cm), invasive, or metastatic tumours, open laparotomies may be required (Lenders et al. 2014). Patients should have intravenous fluids initiated in the immediate preoperative period to ensure adequate intravascular fluid repletion and to help prevent cardiogenic shock from the rapid decline of catecholamine levels post-operatively (Parenti et al. 2012). Patients should be followed up for at least 10 years post-operatively for surveillance (Box. 36.6). Of note, recurrences occur more frequently for patients with familial forms of PCC/PGL or extra-adrenal disease (Lenders et al. 2005).

Tumours greater than 5 cm, *SDHB* carriers, extra-adrenal location, and high Ki-67 on pathology are prognostic markers placing individuals at increased risk for developing metastatic disease. Select patients with malignant PCC/PGL still can be referred to surgery. Although not generally

Box 36.6 Important Message for Patients for Post-operative Care for PCC/PGL

Advise your patient that follow-up for at least 10 years post-operatively for surveillance is necessary even if they feel well due to the risk of recurrence for pheochromocytoma and paraganglioma. Recurrences occur more frequently for patients with familial forms of PCC/PGL or extra-adrenal disease.

curative, debulking or rending a patient with no evidence of disease may reduce time to recurrence, improve symptoms and quality of life, and may possibly improve response to chemotherapy (Parenti et al. 2012). Radiofrequency ablation may provide benefit for liver or bone metastases. For MIBG-positive tumours, ^{131}I-MIBG therapy may be attempted, although this is rarely curative (Martucci and Pacak 2014). A combination of cyclophosphamide, vincristine, and dacarbazine (CVD) is often used for unresectable metastatic disease (Parenti et al. 2012). Somatostatin analogues (e.g. octreotide, a.k.a "cold" somatostatin) have shown the ability to slow tumour progression in several case reports or small case series although this has not been well studied (van Hulsteijn et al. 2013; Duet et al. 2005). Several new targeted therapies, including radiolabelled DOTA peptides (e.g. ^{177}Lu-DOTATATE) and tyrosine kinase inhibitors, are currently under study (Martucci and Pacak 2014). Patient advocacy groups such as Pheo Para Alliance (USA) (Box. 36.7) provide great support and valuable resources for patients and clinicians and the reader is encouraged to refer to their website.

Box 36.7 Case Study and Resources Provided by the Pheo Para Alliance (USA) (Published with Consent)

Often called the "Great Mimic", pheochromocytoma and paraganglioma mimic stress-related disorders with symptoms ranging from high blood pressure, flushing, and headaches, to anxiety and panic attacks. Often written off as being overly anxious, it takes the average patient six frustrating years to receive an accurate diagnosis. In some cases, such as mine, a family member makes the diagnosis based on "family history" due to the strong genetic disposition of the disease. My father-in-law had the disease, as do my husband, his siblings, our three adult children, and now two of my young grandchildren have tested positive for the genetic mutation.

Pheochromocytoma and paraganglioma are extremely rare neuroendocrine tumours. Patients with these tumours suffer from the initial challenge of a complicated diagnosis and the difficulty of finding healthcare providers that understand proper diagnosis and treatment. The ***Pheo Para Alliance*** provides educational support and resources from the time of initial diagnosis through treatment and a lifetime of monitoring. Patients may never meet another patient with their same diagnosis, which is one of the many reasons that the Alliance is so vital to the pheo/para community. We provide an opportunity for members of our community to meet, if not in person, virtually with others who understand what they're going through. Additionally, with a greater understanding of the strong genetic component of the disease, we're helping educate patients and their healthcare providers about the importance of genetic testing for patients and their family members. With the increase in genetic testing, patients are being diagnosed at a younger age, with a lifetime of looking for tumours ahead of them.

36.3 Part C: Adrenal Incidentaloma and Adrenocortical Cancer (ACC)

36.3.1 Adrenal Incidentaloma

Adrenal incidentaloma refers to a mass of the adrenal area discovered fortuitously on a medi-

Founded in 2007, the Pheo Para Alliance is the longest standing internationally recognized leader in advocacy for and awareness of pheochromocytoma and paraganglioma. Since our inception, the Pheo Para Alliance has dedicated more than $2 million towards research, diagnosis, education, advocacy, and finding a cure for this disease. In August 2017, we consolidated our power and influence by merging with our partner group, the ***Pheo Para Troopers***, a true alliance of forces working with a common mission: investing in research to accelerate treatments and cures whilst empowering patients, their families and medical professional through advocacy, education, and a global community of support.

Community support is provided through the following services:

- Website with educational articles and videos for patients and healthcare providers
- Monthly Pheo Para Alliance newsletter with articles on the latest research, educational opportunities, and patients' stories
- Patient forum: An online opportunity for patients and caregivers to reach out for information and support
- Educational brochures provided to medical centres for newly diagnosed patients
- Facebook page
- Annual Pheochromocytoma and Paraganglioma Patient Conference
- Support for patients and families to attend regional patient education forums
- Funding grants for research
- Doctor tracker: The Alliance assists patients from all over the world in finding healthcare providers and facilities equipped to handle their unique requirements
- Pheo Para Alliance medical advisors are on three continents, helping us keep patients advised of medical treatments that are available in their part of the world.

Once referred to the Pheo Para Alliance, patients are able to connect with a global community that understands the unique healthcare challenges they face. Advocacy, education, research, and a community of support form the core of the Alliance's work on behalf of those with these rare neuroendocrine cancers.

Emily Collins
President, Pheo Para Alliance
Pheo Para Alliance
9721 Whitley Park Place
Bethesda MD 20814
Website: www.pheopara.org
E-mail: pheoalliance@gmail.com

cal imaging indicated initially to explore a "non-adrenal" disease or symptom (Fassnacht et al. 2016; Grumbach et al. 2003; NIH 2002; Terzolo et al. 2011; Tabarin et al. 2008). The frequency of these masses of more than one centimetre varies from 1 to 8.7% on autopsy series. In the radiological series, the prevalence is between 0.3 and 4.4% and increases with age to reach 7% from 60 years. Five to ten percent of adrenal incidentaloma are bilateral. The etiologies are multiple and summarized in Table 36.1. Among these lesions some must be operated (primary malignant tumours of the adrenal or secreting tumours), others treated medically

Table 36.1 Adrenal incidentalomas—frequency of the different causes [adapted from Fassnacht et al. (2016)]

Type of adrenal mass	Median % (range %)
Benign adenomas	80
Non-functioning	75 (71–84)
Autonomously cortisol-secreting	12 (1.0–29)
Aldosterone-secreting	2.5 (1.6–3.3)
Pheochromocytoma	7.0 (1.5–14)
Adrenocortical cancer	8.0 (1.2–11)
Metastasis	5.0 (0–18)

(lymphoma) and most simply monitored (non-secreting benign adenoma).

36.3.1.1 Diagnostic Testing

In fact, most incidentalomas are benign non-secreting adenomas, but it is important to rule out first other diagnosis. This highlights the importance of a rigorous diagnostic approach to define the management of an incidentaloma (Box. 36.8). This approach is based on the analysis of imagery and biological investigations. Several consensus conferences or guidelines, the most recent being released by the European Society of Endocrinology, have defined this diagnostic procedure and patients management (Fassnacht et al. 2016).

Box 36.8 Important Message for Patients Diagnosed with Adrenal Incidentaloma

Advise your patient that most adrenal masses cause no health problems and usually are asymptomatic (there are no symptoms or signs of the disease). The majority are non-functioning, benign tumours but a small number can cause serious disease. Consult and prepare the patient that they may have to undergo several investigations to set the diagnosis and to define the management of an incidentaloma.

Radiological investigations are by definition the initial step. It gives essential data and must focus on providing a certain amount of information to clarify the nature of the lesion and its risk of malignancy. This sometimes requires to repeat the initial imaging to have a specific and rigorous analysis of the adrenal mass. CT-scan or MRI are the methods of choice for this initial investigation. Some lesions (pure cysts, myelolipomas, haematoma) have specific imaging characteristics that allow an accurate diagnosis. In addition to these particular situations, the first step is to define whether the lesion can be formally classified as a benign adenoma (the most common case) or not (leaving the possibility of a malignant tumour). CT-scan with spontaneous density measurement can provide very reliable parameters (Figs. 36.5 and 36.6). A spontaneous density of less than 10 HU is specific of a benign adenoma (Hamrahian et al. 2005). The washout after injection of the contrast medium with a signal drop of more than 50% is also a very specific element for a benign adenoma. The MRI study with chemical shift analysis can be used as an alternative or in addition to CT-scan for the diagnosis of benign adenoma. In practice, a well-conducted CT-scan may be sufficient for imaging of an incidentaloma if it classifies it as a benign adenoma. When the mass cannot be classified with this imaging, MRI and eventually FDG-PET scan can be done.

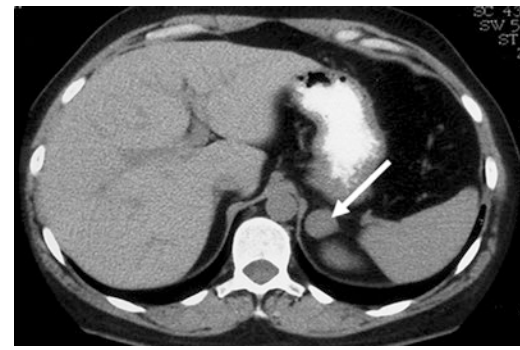


Fig. 36.5 CT-scan of a left adrenal adenoma (white arrow) incidentally discovered

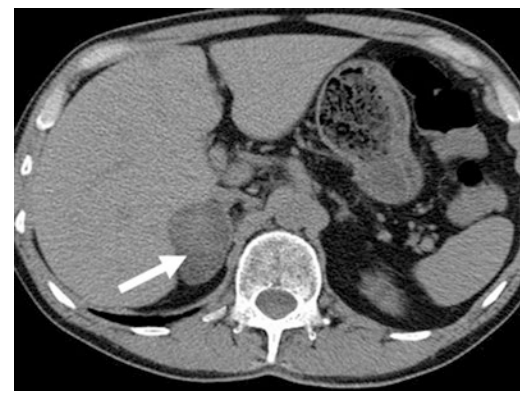


Fig. 36.6 CT-scan of a right adrenocortical cancer (white arrow) incidentally discovered

Adrenal tumours found in the investigation of an adrenal incidentaloma can cause excess secretion of steroid or catecholamine. It is important to identify the lesions responsible for hypersecretion that may warrant therapeutic intervention. The detection of a hormonal alteration is also an important step in the initial investigation for the diagnosis of an incidentaloma. Secreting tumours can be diagnosed after hormonal investigations in patients whose clinical signs are absent, modest, or non-specific, justifying a minimal systematic biological search whatever the clinical presentation. Bilateral lesions caused by infiltrative process or metastatic tumours can cause adrenal insufficiency, which should also be investigated by systematic biological investigations (Tabarin et al. 2008). Hormonal investigations will therefore be more complete in the context of bilateral lesions to explore this possibility. The initial reading stage of the imagery and the clinical data can obviously guide the hormonal work-up; however, a systematic minimal hormonal investigation is recommended by most consensus or guidelines (Fassnacht et al. 2016; Grumbach et al. 2003; NIH 2002; Terzolo et al. 2011; Tabarin et al. 2008).

It is recommended to systematically search hypersecretion of catecholamine and cortisol to look for hypokalaemia and hyperglycaemia. The systematic search for a pheochromocytoma is justified by the frequency of this tumour in the operated incidentalomas (about 10%), and the potential risk represented by hypersecretion of catecholamine, mostly cardiovascular complications. Screening for pheochromocytoma can be done on 24-h urine metanephrine derivatives with simultaneous measurement of urinary creatinine or on plasma assay when available. Urinary assays have a very good sensitivity and acceptable specificity and have been most often used in published series. The chromogranin A assay, by its lack of sensitivity and specificity, is not recommended systematically in the incidentaloma. The investigation of a potential hypersecretion of cortisol should detect tumours of the adrenal cortex responsible for Cushing syndrome.

A significant part of the incidentalomas is represented by the benign adenomas responsible for a more modest hypersecretion of cortisol, called "subclinical" or "autonomous cortisol secretion". Although the consequences of this cortisol excess are still a matter of debate, it is admitted that it should be screened systematically as 10–20% of patients with adrenal incidentaloma might have benign adenoma responsible for autonomous cortisol secretion. The biological investigations used for the diagnosis of clinical Cushing syndrome (cortisoluria, midnight cortisol) have a good specificity but are not sensitive enough in this situation. The 1 mg dexamethasone suppression test is more sensitive (Box. 36.9), using a stringent cut-off (Fassnacht et al. 2016).

Box 36.9 The 1 mg Dexamethasone Suppression Test

It is recommended to detect cortisol autonomous secretion by an overnight 1 mg dexamethasone suppression test with a threshold of cortisolaemia at 18 ng/mL (50 nmol/L) (Fassnacht et al. 2016). It is important to remember that this is a very sensitive threshold (>98%), but not very specific (<80%). For this reason, a patient with a cortisol level above this threshold should be further investigated and the test might have to be repeated few months later. In this situation, cortisoluria, blood or salivary midnight cortisol, and ACTH can be added to the diagnostic work-up.

Screening for aldosterone excess will be done in patients with hypertension and/or hypokalaemia. It is then suggested to carry out as a first screening blood assay of aldosterone and renin (or renin activity) (Fassnacht et al. 2016; Tabarin et al. 2008). The assay of androgens (testosterone, DHA or SDHA) or precursors (17 hydroxyprogesterone, compound S, DOC) will not be systematic but may be performed according to the radiological or clinical data, or preoperatively in a suspected adrenocortical cancer.

In the bilateral incidentalomas, an ACTH-stimulation test (250 μg) with 9 am cortisol and 17-hydroxyprogestrone assays, as well as an ACTH measurement will be added to this hormonal workout. This aim at the screening of

adrenal insufficiency requiring substitutive steroid treatment and it is also interesting for the etiological diagnosis. The purpose of the 17-hydroxyprogesterone assay is to search for 21-hydroxylase deficiency (congenital adrenal hyperplasia). The aim of the ACTH assay is to demonstrate the primary origin of the adrenal failure when present. Conversely, in situations of bilateral adrenocortical lesions such as macronodular hyperplasia, which is nowadays more often diagnosed in patients with incidentaloma causing cortisol autonomous secretion, the dosage of ACTH can help to refine the assessment of adrenal autonomy; ACTH being suppressed in this cause of Cushing syndrome.

36.3.1.2 Monitoring and Treatment of Adrenal Incidentalomas

The majority of adrenal incidentalomas are benign adenomas. If the hormonal investigations exclude cortisol autonomy, a simple monitoring will be offered. In the case of hypersecretion of steroids or catecholamine surgery is the rule. In patients with a "subclinical" Cushing due to a benign adenoma surgery will be discussed on an individual basis depending on potential complications of cortisol excess (diabetes, hypertension, obesity, osteoporosis). When imaging investigations suggest malignancy or if there is a remaining doubt about a malignant lesion, surgical removal is indicated (Fig. 36.7).

36.3.1.3 Nursing Role in the Diagnosis of Adrenal Incidentalomas

During the diagnostic phase, the endocrine nurse meets the patient for review to get a complete history, organize, and coordinate baseline adrenal biochemistry work-up to be completed and to ensure the patient understand the rationale of the tests. More specifically, the nurse will consult the patient in the following diagnostic aspects of the work-up:

1. *Metanephrine levels*
   Plasma normetanephrine and metanephrine test can have false-positive results, and it is important to consult the patient appropriately. Antidepressants, caffeine, and nicotine could potentially induce an elevation in the results. The endocrine nurse may organize for a fasting supine plasma metanephrines to ensure that there's no interference with the results.
2. *Overnight dexamethasone suppression test with 24 h urinary-free cortisol collection*
   Overnight dexamethasone involves taking a 1 mg of dexamethasone tablet between 11 pm

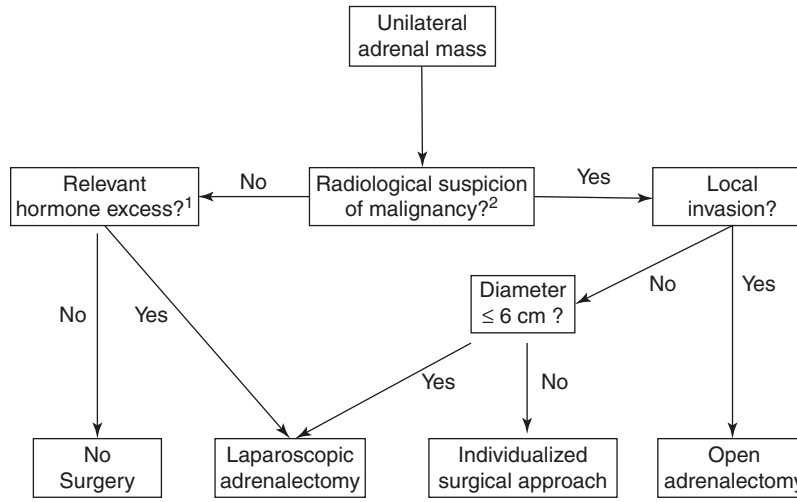


Fig. 36.7 Management of adrenal masses considered for surgery [reproduced from Fassnacht et al. (2016)]

[1] Autonomous cortisol secretion is not automatically judged as clinically relevant

[2] In tumors with benign radiological features and a tumor size >4 cm, surgery might also be individually considered

and 12 mn, the cortisol level the following morning by 9 am should be suppressed in patients who do NOT secrete excess steroids.

The 24 h urinary-free cortisol collection involves a collection of urine in a plain bottle for 24 h, usually starts in the morning with the first void discarded to ensure that the bladder is empty thereby ensuring an accurate collection, then collects all urine for the next 24 h including the first void the next morning. This test will determine the total cortisol excretion within a 24 h period which is usually <130 nmL/24 h.

It is important to advise the patient the importance of proper timing of the test and the rationale behind the test, i.e. to complete the urine collection first before the dexamethasone test. The patient does not need to fast and can take their usual medications as prescribed. However, there are factors that need to be considered which can cause false-positive and false-negative results.

False-positive can occur in female patients taking oestrogen which increases the cortisol binding globulin leading to increase in total cortisol. The patient should be advised to discontinue oestrogen for 6 weeks before testing. Patients on medications that induce the enzyme CYP3A4 (e.g. antiepileptic, rifampicin, alcohol) can increase hepatic clearance of dexamethasone.

False-negative can occur on patients with renal failure because of the drop in albumin and cortisol binding globulin, patients with liver failure and patients on medication that inhibits the enzyme CYP3A4 (e.g. fluoxetine, cimetidine) decreasing hepatic clearance.

If required, salivary cortisol can be completed. This involves the patient to chew a salivette (swab) for at least 2–3 min, ensuring that the swab is saturated with saliva. The salivette comes in a plastic container to put the sample back after. The patient is advised not to eat, drink, or brush teeth for at least 30 min before collection. The patient can rinse mouth with water at least 15 min before collection. The sample needs to be put in the fridge if not delivered within 2–3 days.

3. *Plasma aldosterone and renin levels*
   It is very important to identify any medications that can interfere with the renin-angiotensin system (e.g. angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)) before performing the tests. The endocrine nurse will review the medication history of the patient and identify and replace medications that can interfere. Once initial blood test suggests hyperaldosteronism, a saline suppression test is performed. The patient should be advised that test will require a day admission for minimum of 5 h. The patient will receive saline infusion of 500 mL/h for 4 h whilst the patient is lying in bed. Aldosterone and renin will be checked before and after the procedure. The patient needs to be potassium replete. Normal response shows a suppressed aldosterone as a response to the high plasma sodium. Failure to suppress suggests hormone aldosterone excess secretion.

36.3.2 Adrenocortical Cancer (ACC)

Cancer of the adrenal cortex (adrenocortical cancer, ACC) is a rare tumour, the annual incidence being estimated between 1 and 2 per million. In the USA, the Surveillance, Epidemiology and End-Results Study (SEER) studying deaths from 1975 to 1992 estimates the incidence of ACC at 1.8 cases/million/year. The Norwegian cancer registry from 1970 to 1980 reports a rather similar incidence of 1.5 cases/million/year. In children, ACC is considered ten times rarer than in adults. In southern Brazil, however, the incidence of ACC is very high in children, close to that of adults. Children's ACC in Brazil are due in almost all cases to the existence of a specific germline mutation of the *TP53* tumour suppressor gene (R337H) (Else et al. 2014; Libe et al. 2007; Fassnacht et al. 2009).

36.3.2.1 Diagnosing ACC

ACC can cause adrenal steroid excess in about three quarter of the cases. Signs of hypersecretion are mainly related to androgens in women and cortisol in both sexes (Libe et al. 2007). Androgen excess causes hirsutism, acne, and menstrual disorders (spaniomenorrhoea or amenorrhoea). In man, a tumour-secreting oestrogen can lead to the development of gynaecomastia. Excess glucocorticoid causes all the clinical signs of Cushing syndrome. When the tumour secretes aldosterone or steroid precursors with mineralocorticoid activity, arterial hypertension with hypokalaemia and oedema can be observed. When referred to an endocrine clinic, most patients are diagnosed by the presence of these endocrine signs and clinical symptoms. In some patients, ACC is diagnosed in the presence of clinical symptoms due to tumour mass or growth. It is primarily pain, more rarely venous thrombosis. In recent years, it is becoming more evident that some ACCs, previously considered as non-secreting, in fact secrete some urine steroid metabolites and recently urine steroid metabolomic analysis have been introduced in routine use (Arlt et al. 2011).

Adrenal incidentaloma has become an increasingly common mode of discovery. This mode of discovery often reveals a localized tumour whose prognosis after surgery is much better. Although the frequency of the adrenal cortex among the incidentalomas is low (3–10% of the operated tumours), this diagnosis must obviously be systematically considered. Recent advances in the survival of patients with adrenocortical carcinomas are certainly largely related to this earlier mode of diagnosis, allowing resection at a stage where the probability of complete remission is better (Libe et al. 2007; Fassnacht et al. 2009).

36.3.2.2 Management of ACC

The management of ACC requires a multidisciplinary expertise, which can be difficult to assemble in the case of a rare tumour. Complete surgical excision is without any discussion currently the best treatment of ACC (Gaujoux and Brennan 2012). If it is possible in stages 1 and 2 that are localized to the adrenal, it remains difficult in stages 3 (loco-regional extension), sometimes justifying sacrifice of adjacent organs. Half a century after its first use, mitotane (O, p'-DDD) remains to date the first-line medical treatment (De Francia et al. 2012). Although the place of mitotane is recognized by most teams in non-operable ACC (stage 4 mainly as seen in Fig. 36.8), there is currently no consensus on its place in adjuvant treatment after complete surgical resection. The side effects of mitotane are mostly digestive (nausea, vomiting) but also neurologic (confusion, somnolence, ataxia). By its adrenolytic action, mitotane also induces adrenal insufficiency requiring a steroid coverage, whose dosage adjustment is not always simple.

The assay of mitotane blood level is a valuable indicator to adjust the treatment. In fact, the severe adverse effects, in particular neurologic signs, are most often observed for mitotane blood levels higher than 20 mg/L. Different studies have showed that mitotane is more effective on tumour progression when its blood levels are higher than 14 mg/L. The therapeutic range (14–20 mg/L) is therefore narrow, which requires regular monitoring and frequent dose adjustment. In patients whose tumour disease progresses after surgery and under mitotane, various cytotoxic chemotherapies have been used (Berruti et al. 2012). Cisplatin is the most consistently successful drug. The first international randomized trial (FIRM-ACT) has established the association of Cisplatin, Etoposide, and Doxorubicin (Fassnacht et al. 2012) as the first-line cytotoxic chemotherapy in progressive ACC.

36.3.2.3 Nursing Role Considerations for Mitotane Treatment of ACC

Mitotane treatment should be performed only after the patient has received detailed information on the expected toxicity and its treatment. The main role of the endocrine nurse once patient is on adjuvant mitotane therapy is to counsel the patient about the medication, its mode of action, side effects and how to lessen its side effects, follow-up, and monitoring of the mitotane level. Patients are at risk of adrenal insufficiency and should be initiated on hydrocortisone replace-

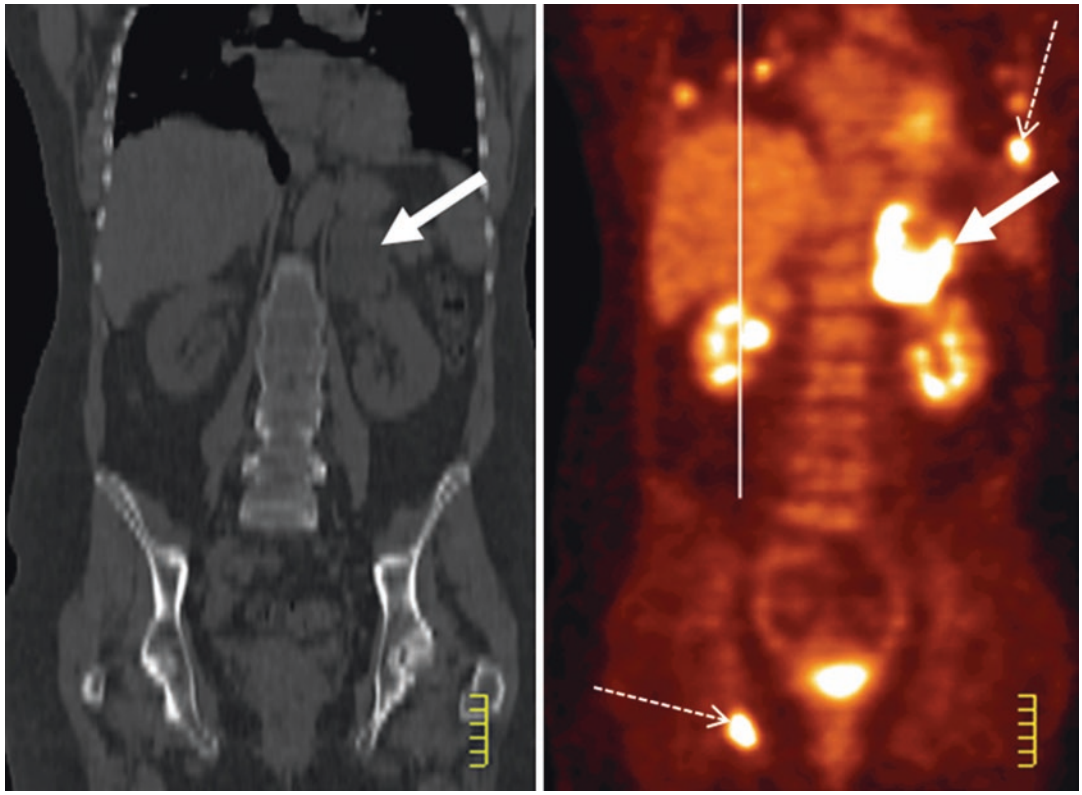


Fig. 36.8 FDG-PET scan of a left stage 4 adrenocortical cancer (white arrow) with distant metastasis (dotted thin arrows) (right image: CT-scan; left: FDG-scintigraphy)

ment concurrently with mitotane treatment to avoid potential adrenal crisis. High doses of hydrocortisone are needed (e.g. 20-10-10 mg or 20 mg three times daily) due to a substantial, mitotane-induced increase in cortisol binding globulin.

Patients should be consulted and be provided with comprehensive advice and education on management of adrenal insufficiency, sick day rules and prevention of adrenal crisis (please refer to Chaps. 37 and 62 for details). The endocrine nurse plays a vital role in this aspect.

Mitotane is lipophilic, accumulates in adipose tissue, from where it is slowly released back in to the blood stream. This means that plasma mitotane levels may substantially increase during ongoing treatment with the same dose. Thus, doses easily tolerated at the beginning may later cause significant side effects. The endocrine nurse should make patients aware of this potential adverse event and emphasize the need for regular follow-ups and monitoring of plasma mitotane levels.

Patient Case Study and Key Learning Points

A 46-year-old male patient, with no previous medical history or health issues, was diagnosed with hypertension in 2011. In the second half of 2012, he complained of being increasingly unwell, abdominal bloating, discomfort, and dyspepsia and was diagnosed with type 2 diabetes. A CT abdomen was done in December 2012 and showed a large adrenal mass. The patient was referred to his local hospital and was reviewed by the surgeons who subsequently referred him to the GI surgeons at the local tertiary specialist hospital. He was reviewed at the sarcoma MDT and as protocol; all patients with retroperitoneal masses, undergo biopsy. The patient was scheduled for CT-guided adrenal biopsy after a 24-h urine collection for catechol-

amines was sent for analysis. Prior to receiving the results, the patient was admitted for a CT-guided adrenal biopsy and had a large venous bleed as a result.

Key Learning Points:

- Biopsy should not be done for adrenal masses without prior confirmation of ALL these distinct criteria: history of malignancy, CT pre-contrast tumour density >20 HU, exclusion of pheochromocytoma with plasma metanephrines. Outcome of these test will dictate the therapeutic strategy.
- The cells obtained by a needle biopsy of an adrenal tumour cannot confirm whether the tumour is a benign adrenal mass or a rare adrenal carcinoma. It will only help in determining a primary adrenal tumour versus metastatic tumour. Most commonly, a biopsy is done if there is evidence of cancer outside the adrenal gland, or a patient with a known cancer has a suspicious adrenal mass. It is important to exclude a pheochromocytoma with biochemical testing prior to a biopsy.

36.4 Conclusions

The role of the endocrine nurse in the patient's journey following the incidental finding of an adrenal adenoma starts from diagnosis to follow-up. It involves coordinating the tests accurately and in timely manner, support in the diagnosis and management in close collaboration with the core members of the adrenal multidisciplinary team, education and training, follow-up of patients, and counselling. During this time, it is also important to take into consideration the possible psychological impact of the diagnosis to the patient and their families.

Acknowledgments With special thanks to Diane Silverman, Interim Executive Director, and Emily Collins, President, of the Pheo Para Alliance (Pheochromocytoma and Paraganglioma) www.pheopara.org for their contribution to this chapter with a case study and information on the Patient Advocacy Group. Also special thanks to Dr. Mayank Patel, MD, Special Volunteer, Section on Medical Neuroendocrinology, NICHD/NIH for providing the MRI image on pheochromocytoma.

References

Arlt W, Biehl M, Taylor AE, Hahner S, Libe R, Hughes BA, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab. 2011;96(12):3775–84.

Aronova A, Gordon BL, Finnerty BM, Zarnegar R, Fahey TJ 3rd. Aldosteronoma resolution score predicts long-term resolution of hypertension. Surgery. 2014;156(6):1387–92; discussion 92–3.

Avisse C, Marcus C, Patey M, Ladam-Marcus V, Delattre JF, Flament JB. Surgical anatomy and embryology of the adrenal glands. Surg Clin North Am. 2000;80(1):403–15.

Bergland BE. Pheochromocytoma presenting as shock. Am J Emerg Med. 1989;7(1):44–8.

Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii131–8.

Blake MA, Cronin CG, Boland GW. Adrenal imaging. AJR Am J Roentgenol. 2010;194(6):1450–60.

Curras-Freixes M, Pineiro-Yanez E, Montero-Conde C, Apellaniz-Ruiz M, Calsina B, Mancikova V, et al. PheoSeq: a targeted next-generation sequencing assay for pheochromocytoma and paraganglioma diagnostics. J Mol Diagn. 2017;19(4):575–88.

Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer. 2014;14(2):108–19.

De Francia S, Ardito A, Daffara F, Zaggia B, Germano A, Berruti A, et al. Mitotane treatment for adrenocortical carcinoma: an overview. Minerva Endocrinol. 2012;37(1):9–23.

Debillon E, Velayoudom-Cephise FL, Salenave S, Caron P, Chaffanjon P, Wagner T, et al. Unilateral adrenalectomy as a first-line treatment of Cushing's syndrome in patients with primary bilateral macronodular adrenal hyperplasia. J Clin Endocrinol Metab. 2015;100(12):4417–24.

Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, et al. Renin-angiotensin-aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. J Renin-Angiotensin-Aldosterone Syst. 2010;11(3):165–72.

Duet M, Guichard JP, Rizzo N, Boudiaf M, Herman P, Tran Ba Huy P. Are somatostatin analogs therapeutic alternatives in the management of head and neck paragangliomas? Laryngoscope. 2005;115(8):1381–4.

Dutta RK, Soderkvist P, Gimm O. Genetics of primary hyperaldosteronism. Endocr Relat Cancer. 2016;23(10):R437–54.

Elsayes KM, Narra VR, Leyendecker JR, Francis IR, Lewis JS Jr, Brown JJ. MRI of adrenal and extraadrenal pheochromocytoma. AJR Am J Roentgenol. 2005;184(3):860–7.

Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM, et al. Adrenocortical carcinoma. Endocr Rev. 2014;35(2):282–326.

Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a revised TNM classification. Cancer. 2009;115(2):243–50.

Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366(23):2189–97.

Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1–g34.

Flatmark T. Catecholamine biosynthesis and physiological regulation in neuroendocrine cells. Acta Physiol Scand. 2000;168(1):1–17.

Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(5):1889–916.

Gaujoux S, Brennan MF. Recommendation for standardized surgical management of primary adrenocortical carcinoma. Surgery. 2012;152(1):123–32.

Ghayee HK, Rege J, Watumull LM, Nwariaku FE, Carrick KS, Rainey WE, et al. Clinical, biochemical, and molecular characterization of macronodular adrenocortical hyperplasia of the zona reticularis: a new syndrome. J Clin Endocrinol Metab. 2011;96(2):E243–50.

Goodarzi MO, Dawson DW, Li X, Lei Z, Shintaku P, Rao CV, et al. Virilization in bilateral macronodular adrenal hyperplasia controlled by luteinizing hormone. J Clin Endocrinol Metab. 2003;88(1):73–7.

Gourgari E, Lodish M, Keil M, Sinaii N, Turkbey E, Lyssikatos C, et al. Bilateral adrenal hyperplasia as a possible mechanism for hyperandrogenism in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2016;101(9):3353–60.

Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med. 2003;138(5):424–9.

Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez G, Bogabathina H, Levin HS, et al. Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab. 2005;90(2):871–7.

Hodin R, Lubitz C, Phitayakorn R, Stephen A. Diagnosis and management of pheochromocytoma. Curr Probl Surg. 2014;51(4):151–87.

Hsiao HP, Kirschner LS, Bourdeau I, Keil MF, Boikos SA, Verma S, et al. Clinical and genetic heterogeneity, overlap with other tumor syndromes, and atypical glucocorticoid hormone secretion in adrenocorticotropin-independent macronodular adrenal hyperplasia compared with other adrenocortical tumors. J Clin Endocrinol Metab. 2009;94(8):2930–7.

Insel PA. Adrenergic receptors. Evolving concepts on structure and function. Am J Hypertens. 1989;2(3 Pt 2):112S–8S.

Insel PA. Seminars in medicine of the Beth Israel Hospital, Boston. Adrenergic receptors—evolving concepts and clinical implications. N Engl J Med. 1996;334(9):580–5.

Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. Clin Cancer Res. 2015;21(17):3888–95.

Janssen I, Chen CC, Taieb D, Patronas NJ, Millo CM, Adams KT, et al. 68Ga-DOTATATE PET/CT in the localization of head and neck paragangliomas compared with other functional imaging modalities and CT/MRI. J Nucl Med. 2016;57(2):186–91.

La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens. 2003;21(9):1703–7.

Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287(11):1427–34.

Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet (London, England). 2005;366(9486):665–75.

Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–42.

Libe R, Fratticci A, Bertherat J. Adrenocortical cancer: pathophysiology and clinical management. Endocr Relat Cancer. 2007;14(1):13–28.

Lodish M, Stratakis CA. A genetic and molecular update on adrenocortical causes of Cushing syndrome. Nat Rev Endocrinol. 2016;12(5):255–62.

Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Ali A, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab. 2000;85(2):637–44.

Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. Curr Probl Cancer. 2014;38(1):7–41.

Mathur A, Kemp CD, Dutta U, Baid S, Ayala A, Chang RE, et al. Consequences of adrenal venous sampling in primary hyperaldosteronism and predictors of unilateral adrenal disease. J Am Coll Surg. 2010;211(3):384–90.

Mazza A, Armigliato M, Marzola MC, Schiavon L, Montemurro D, Vescovo G, et al. Anti-hypertensive treatment in pheochromocytoma and paragangli-

oma: current management and therapeutic features. Endocrine. 2014;45(3):469–78.
McCarthy CJ, McDermott S, Blake MA. Adrenal imaging: magnetic resonance imaging and computed tomography. Front Horm Res. 2016;45:55–69.
McNeil AR, Blok BH, Koelmeyer TD, Burke MP, Hilton JM. Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland. Aust NZ J Med. 2000;30(6):648–52.
McNichol AM. Differential diagnosis of pheochromocytomas and paragangliomas. Endocr Pathol. 2001;12(4):407–15.
Meikle AW. Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone. Clin Endocrinol. 1982;16(4):401–8.
Minnaar EM, Human KE, Henneman D, Nio CY, Bisschop PH, Nieveen van Dijkum EJ. An adrenal incidentaloma: how often is it detected and what are the consequences? ISRN Radiol. 2013;2013:871959.
Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet (London, England). 2006;367(9522):1605–17.
Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40.
NIH. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). NIH Consens State Sci Statements. 2002;19(2):1–25.
Parenti G, Zampetti B, Rapizzi E, Ercolino T, Giache V, Mannelli M. Updated and new perspectives on diagnosis, prognosis, and therapy of malignant pheochromocytoma/paraganglioma. J Oncol. 2012;2012:872713.
Parker LN. Control of adrenal androgen secretion. Endocrinol Metab Clin N Am. 1991;20(2):401–21.
Parthasarathy HK, Menard J, White WB, Young WF Jr, Williams GH, Williams B, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens. 2011;29(5):980–90.
Patel D, Gara SK, Ellis RJ, Boufraqech M, Nilubol N, Millo C, et al. FDG PET/CT scan and functional adrenal tumors: a pilot study for lateralization. World J Surg. 2016;40(3):683–9.
Petramala L, Zinnamosca L, Settevendemmie A, Marinelli C, Nardi M, Concistre A, et al. Bone and mineral metabolism in patients with primary aldosteronism. Int J Endocrinol. 2014;2014:836529.
Rao D, Peitzsch M, Prejbisz A, Hanus K, Fassnacht M, Beuschlein F, et al. Plasma methoxytyramine: clinical utility with metanephrines for diagnosis of pheochromocytoma and paraganglioma. Eur J Endocrinol. 2017;177(2):103–13.
Rasmussen SA, Rosebush PI, Smyth HS, Mazurek MF. Cushing disease presenting as primary psychiatric illness: a case report and literature review. J Psychiatr Pract. 2015;21(6):449–57.
Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, et al. Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab. 2000;85(4):1440–8.
Sagrada A, Fargeas MJ, Bueno L. Involvement of alpha-1 and alpha-2 adrenoceptors in the postlaparotomy intestinal motor disturbances in the rat. Gut. 1987;28(8):955–9.
Sakai Y, Yanase T, Takayanagi R, Nakao R, Nishi Y, Haji M, et al. High expression of cytochrome b5 in adrenocortical adenomas from patients with Cushing's syndrome associated with high secretion of adrenal androgens. J Clin Endocrinol Metab. 1993;76(5):1286–90.
Sharma ST, Committee AAS. An Individualized approach to the evaluation of cushing syndrome. Endocr Pract. 2017;23(6):726–37.
Streeten DH, Anderson GH Jr. Mechanisms of orthostatic hypotension and tachycardia in patients with pheochromocytoma. Am J Hypertens. 1996;9(8):760–9.
Tabarin A, Bardet S, Bertherat J, Dupas B, Chabre O, Hamoir E, et al. Exploration and management of adrenal incidentalomas. French Society of Endocrinology Consensus. Ann Endocrinol. 2008;69(6):487–500.
Taieb D, Pacak K. Molecular imaging and theranostic approaches in pheochromocytoma and paraganglioma. Cell Tissue Res. 2018;372(2):393–401.
Terzolo M, Stigliano A, Chiodini I, Loli P, Furlani L, Arnaldi G, et al. AME position statement on adrenal incidentaloma. Eur J Endocrinol. 2011;164(6):851–70.
Thosani S, Ayala-Ramirez M, Roman-Gonzalez A, Zhou S, Thosani N, Bisanz A, et al. Constipation: an overlooked, unmanaged symptom of patients with pheochromocytoma and sympathetic paraganglioma. Eur J Endocrinol. 2015;173(3):377–87.
Timmers HJ, Taieb D, Pacak K. Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. Horm Metab Res. 2012;44(5):367–72.
van Hulsteijn LT, van Duinen N, Verbist BM, Jansen JC, van der Klaauw AA, Smit JW, et al. Effects of octreotide therapy in progressive head and neck paragangliomas: case series. Head Neck. 2013;35(12):E391–6.
Whitelaw BC, Prague JK, Mustafa OG, Schulte KM, Hopkins PA, Gilbert JA, et al. Phaeochromocytoma [corrected] crisis. Clin Endocrinol. 2014;80(1):13–22.
Willenberg HS, Spath M, Maser-Gluth C, Engers R, Anlauf M, Dekomien G, et al. Sporadic solitary aldosterone- and cortisol-co-secreting adenomas: endocrine, histological and genetic findings in a subtype of primary aldosteronism. Hypertens Res. 2010;33(5):467–72.
Wyszynska T, Cichocka E, Wieteska-Klimczak A, Jobs K, Januszewicz P. A single pediatric center experience with 1025 children with hypertension. Acta Paediatr. 1992;81(3):244–6.
Yu R, Wei M. False positive test results for pheochromocytoma from 2000 to 2008. Exp Clin Endocrinol Diabetes. 2010;118(9):577–85.

Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009a;15(Suppl 1):1–20.

Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas: executive summary of recommendations. Endocr Pract. 2009b;15(5):450–3.

Zilbermint M, Xekouki P, Faucz FR, Berthon A, Gkourogianni A, Schernthaner-Reiter MH, et al. Primary Aldosteronism and ARMC5 Variants. J Clin Endocrinol Metab. 2015;100(6):E900–9.

Key Reading

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1–g34.
2. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(5):1889–916.
3. NIH. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). NIH Consens State Sci Statements. 2002;19(2):1–25.
4. Sharma ST, Committee AAS. An individualized approach to the evaluation of cushing syndrome. Endocr Pract. 2017;23(6):726–37.
5. Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15(Suppl 1):1–20.

37 Diagnosis and Management of Adrenal Insufficiency in Children and Adults

Sofia Llahana, Irene Mitchelhill, Phillip Yeoh, and Marcus Quinkler

Contents

37.1 **Introduction** 707

37.2 **Causes and Clinical Presentation of Adrenal Insufficiency in Children and Adults** 708
37.2.1 Primary Adrenal Insufficiency 708
37.2.2 Secondary Adrenal Insufficiency 708
37.2.3 Iatrogenic Adrenal Insufficiency 708

37.3 **Clinical Presentation of Adrenal Insufficiency in Adults** 710
37.3.1 Clinical Presentation of Adrenal Insufficiency in Children 711

37.4 **Diagnosis of Adrenal Insufficiency in Adults** 712
37.4.1 Diagnosis of Adrenal Insufficiency in Children 714

37.5 **Treatment of Adrenal Insufficiency** 716
37.5.1 Mineralocorticoid Replacement Therapy 716
37.5.2 Adrenal Androgen Replacement Therapy in Women 717
37.5.3 Glucocorticoid Replacement Therapy in Adult Patients with AI 717
37.5.4 Treatment of AI and GC Adjustment for Intercurrent Illness in Children 722

S. Llahana (✉)
School of Health Sciences,
City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

I. Mitchehill
Department of Endocrinology, Sydney Children's Hospital (SCHN), Randwick, NSW, Australia
e-mail: Irene.mitchelhill@health.nsw.gov.au

P. Yeoh
The London Clinic, London, UK
e-mail: p.yeoh@thelondonclinic.co.uk

M. Quinkler
Endocrinology in Charlottenburg Stuttgarter Platz 1,
Berlin, Germany

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_37

37.6 **The Importance of Patient Education in AI** 723
37.7 **Role of Adherence to Medication in Optimising GC Replacement** 723
37.7.1 Evidence of Nonadherence to GC Replacement 724
37.7.2 How to Identify and Address Nonadherence to GC Replacement 724
37.8 **Glucocorticoid Replacement in Special Therapeutic Situations** 725
37.8.1 Fertility and Pregnancy 725
37.8.2 Thyroid Dysfunction 726
37.8.3 Growth Hormone Deficiency in Adults 726
37.8.4 Increased Physical and Emotional Stress 726
37.8.5 Prolonged Fasting or Shift Working 726
37.8.6 Medications and Food Interactions with Glucocorticoids 727
37.9 **Morbidity and Mortality Related to Glucocorticoid Replacement Therapy** 727
37.9.1 Mortality and Risk of Adrenal Crisis 727
37.9.2 Bone Metabolism 728
37.9.3 Blood Pressure, Glucose/Lipid Metabolism, and Body Composition 729
37.9.4 Quality of Life (QoL) and Subjective Well-Being 729
37.10 **Long-Term Monitoring of Patients with AI** 730
37.11 **The Role of Patient Advocacy Groups in Improving Patient Care and Education** 732
37.11.1 The Australian Addison's Disease Association Inc (AADAI) 732
37.12 **Conclusions** 732
References 733

Abstract

Adrenal insufficiency (AI) is a common life-threatening endocrine condition. It is caused by the inability of the adrenal glands to produce cortisol, a hormone essential for life, either due to failure of the adrenals (primary AI), or due to diseases affecting the hypothalamus or the pituitary which control the adrenals (secondary AI). Patients with AI require lifelong glucocorticoid (GC) replacement therapy and increased GC doses during periods of intercurrent illness or other major psychological and physical stress to mimic the normal increase in physiological cortisol response to such situations. Inadequate GC replacement for daily maintenance and increased doses during illness, can precipitate an adrenal crisis (AC) an adrenal crisis which can be fatal if the immediate administration of parenteral hydrocortisone is delayed.

The prevalence of primary AI is 93–140 patients/million population and of secondary AI is 150–280/per million. Standard mortality rate for patients with AI is more than twofold compared to the general population according to retrospective hospital data. AI has significant impact on patients' quality of life, and suboptimal GC replacement (over- or under-replacement) can lead to acute and long term complications such as osteoporosis and type 2 diabetes.

AI encompasses a wide variety of medical diagnoses and can be an unrecognised underlying condition masked by another diagnosis in both paediatrics and adults. There should be a heightened sense of suspicion in the presentation of any seriously unwell neonate, child or adult where an unexplained presentation, deterioration of an intercurrent illness or other stress (e.g. surgery or significant trauma) may have precipitate an AC.

The diagnosis of AI brings many challenges for children, parents, adult patients and their families with the impact of a multiple daily medication routine, and the need for sick day surveillance and management, and for vigilance to detect potential illness and possible events which may be life threatening. Health professionals need to provide adequate ongoing psychological support and education for patients and families long term as they adapt to their health needs of their condition and incorporate treatment plans into their daily lives. Understanding of the education process is crucial and one of the most one important aspects of the role of the endocrine nurse.

Keywords
Adrenal insufficiency · Adrenal crisis · Hydrocortisone · Glucocorticoids · Fludrocortisone · Patient education · Primary adrenal insufficiency · Secondary adrenal insufficiency · Quality of life

Abbreviations

AC	Adrenal crisis
ACTH	Adrenocorticotropic hormone
AD	Addison's disease
AI	Adrenal insufficiency
CA	Cortisone acetate
CAH	Congenital adrenal hyperplasia
CRH	Corticotropin-releasing hormone
CSHI	Continuous subcutaneous hydrocortisone infusion
DHEA	Dehydroepiandrosterone
GC	Glucocorticoids
HPA	Hypothalamic-pituitary-adrenal axis
ITT	Insulin tolerance test
PAI	Primary adrenal insufficiency
QoL	Quality of life
SAI	Secondary adrenal insufficiency
SST	Short synacthen test

Key Terms

- Adrenocorticotropic hormone (ACTH) is the hormone responsible for stimulating cortisol production from the adrenal glands, which is essential for life.
- Adrenal insufficiency (AI) refers to the failure or impairment of the adrenal glands which can be primary adrenal insufficiency (PAI) most commonly autoimmune or Addison's disease, or secondary adrenal insufficiency (SAI) due to hypothalamic-pituitary diseases, resulting in cortisol deficiency.
- ACTH stimulation test is a diagnostic test to assess the adrenal steroid production after the administration of the synthetic ACTH analogue Tetracosactide.
- Adrenal crisis is life-threatening emergency caused by inadequate production of the adrenal hormone cortisol in situations of stress.

Key Points

- Patients with adrenal insufficiency need to have adequate steroid replacement in order to have a better outcome in quality of life, reduce their risk of adrenal crisis, and preventable hospital admissions and fatalities.
- GC replacement needs to take in account a patient's needs, the daily dosage variation and timing, and consideration of the most effective delivery options for effective absorption in order to maximise the benefit of therapy.
- Endocrine nurses play a key role in the care of patients with adrenal insufficiency. They provide education and support in order to engage with these patients life-long to ensure they achieve positive health outcomes for life.

37.1 Introduction

Adrenal insufficiency (AI) is a common life-threatening endocrine condition. It refers to the failure or impairment of the adrenal glands which can be primary adrenal insufficiency (PAI) most commonly autoimmune or Addison's disease, or secondary adrenal insufficiency (SAI) due to hypothalamic-pituitary diseases. In children, the most common cause is Congenital Adrenal Hyperplasia (see Chap. 35). Long-term corticosteroid treatment which can lead to adrenal gland atrophy can also result in AI, and is often referred to as tertiary adrenal insufficiency. The adrenal glands produce glucocorticoids (GC) (cortisol in humans, but e.g. corticosterone in rats), mineralocorticoids (aldosterone), and androgens. Cortisol secretion exhibits a distinct circadian rhythm reaching peak levels in the early morning prior to awakening and low levels in the evening with lowest levels at midnight (Arlt 2017). In the case of neonates, their circadian rhythm is not established until later in their first year of life (Miller et al. 2008; Mendoza-Cruz et al. 2013); hence cortisol levels are difficult to interpret and can be confusing. Please read Chap. 34 for more details on anatomy and physiology of adrenal glands. It is important to have a clear understanding of the circadian rhythm as it plays a crucial role in the planning of GC replacement therapy.

The prevalence of primary AI is 93–140 patients/million population and of secondary AI is 150–280/per million (Arlt and Allolio 2003). AI arising from prolonged administration of corticosteroid treatment leading to suppression of the hypothalamic-pituitary-adrenal axis (HPA) is much more common, occurring in 0.5–2% of the population in developed countries (Arlt 2017); in the UK for example an average of 0.75% of the population was prescribed long-term oral corticosteroid therapy (e.g. prednisolone, dexamethasone) at any time point (Fardet et al. 2011).

37.2 Causes and Clinical Presentation of Adrenal Insufficiency in Children and Adults

Primary adrenal insufficiency (PAI) refers to glucocorticoid deficiency in the context of adrenal failure or disease in the gland itself, whereas secondary adrenal insufficiency (SAI) arises because of ACTH deficiency due to causes affecting the hypothalamic or pituitary function (Fig. 37.1). A major distinction between PAI and SAI is that PAI is invariably accompanied by deficiency of mineralocorticoids which are regulated by the renin-angiotensin-aldosterone (RAA) system (please see chap. 34 for anatomy and physiology of the adrenal gland); this does not occur in SAI because only ACTH is deficient, and the RAA system is intact (Arlt and Allolio 2003; Stewart 2008). A summary of the most common causes and associated features of AI is presented in Table 37.1 (Arlt 2017; Arlt and Allolio 2003; Stewart 2008; Barthel et al. 2016; Bancos et al. 2015).

37.2.1 Primary Adrenal Insufficiency

Thomas Addison was the first physician to describe the clinical phenotype of PAI in 1855 hence the name Addison's disease. PAI is most commonly caused by autoimmune-mediated adrenalitis accounting for 68–94% of cases in adults. It can occur in isolation (30–40% of cases) or in combination with other autoimmune diseases as part of the autoimmune polyglandular syndrome type 1 (APS1) in 10–15% of cases, and type 2 (APS2) in 50–60% of cases (Table 37.1). In children, most frequent monogenic cause of AI is congenital adrenal hyperplasia (CAH) which is caused by mutations in enzymes involved in steroid hormone synthesis, most commonly mutations in CYP21A2 encoding 21-hydroxylase, with an incidence of 1 in 12,000–15,000 people (Arlt and Allolio 2003; Bancos et al. 2015) (please see Chap. 35). Worldwide, infectious diseases such as tuberculosis fungal infections, HIV and cytomegalovirus, are common causes of AI (Stewart 2008).

37.2.2 Secondary Adrenal Insufficiency

SAI is the consequence of the dysfunction of the HPA axis. The most frequent causes of SAI are tumours involving the hypothalamic-pituitary region associated with ACTH deficiency caused by tumour growth leading to suppression of the pituitary function, or treatment with surgery or radiotherapy resulting in hypopituitarism (Table 37.1) (please see chapters in Section 3, the Pituitary Gland). In children, SAI is due to mal-development of the hypothalamus and pituitary gland: aplasia, hypoplasia or ectopic placement of the pituitary are most common and lead to multiple pituitary hormone deficiency (MPHD). In neonates and infants, birth trauma, and in childhood head injury and brain tumours are other causes of SAI (Migeon and Lanes 2009; Miller et al. 2008).

37.2.3 Iatrogenic Adrenal Insufficiency

An underestimated and significant cause of AI is the suppression of the HPA axis by exogenous long-term GC treatment leading to atrophy of adrenal cortex. This becomes apparent when patients cease treatment and HPA axis is not restored for endogenous production of ACTH and hence cortisol. Two recent systematic reviews demonstrated that the risk of AI after cessation of GC therapy varied significantly and there is no administration form, dosing, treatment duration, or underlying disease for which AI can be excluded with certainty (Joseph et al. 2016; Broersen et al. 2015). This risk increases with a

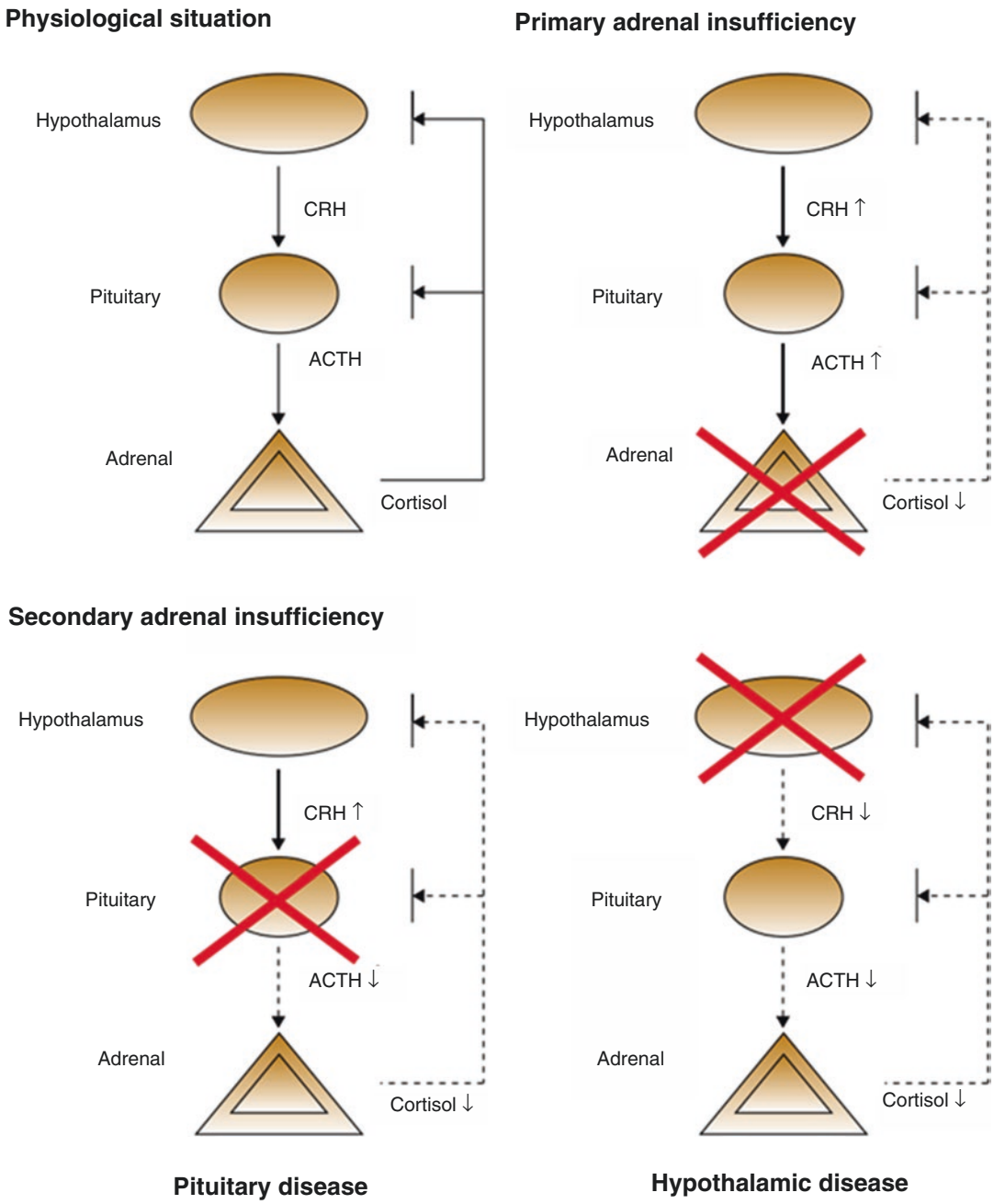


Fig. 37.1 Differentiation between primary and secondary adrenal insufficiency. Key: *ACTH* adrenocorticotropic hormone, *CRH* corticotropin-releasing hormone. Used with permission from Arlt, W. & Allolio, B. 2003. Adrenal insufficiency. *Lancet,* 361, 1881–93

dose equivalent of 5 mg of prednisolone or higher for longer than 4 weeks, irrespective of route of administration, i.e. topical, inhaled, oral, or injected (Bancos et al. 2015; Joseph et al. 2016). The risk of AI is difficult to predict hence all patients must be generally considered at risk of developing AI and consulted regarding prevention and management of adrenal crisis (Joseph et al. 2016; Broersen et al. 2015; Quinkler et al. 2013) (see Chap. 62). Administration of exogenous opioids, e.g. in pain therapy, may also cause suppression of plasma ACTH and serum cortisol, leading to AI, particularly in susceptible individuals (Policola et al. 2014; Lee and Twigg 2015).

Table 37.1 Common causes and associated features of adrenal insufficiency [adapted from Arlt (2017), Arlt and Allolio (2003), Stewart (2008), Barthel et al. (2016), and Bancos et al. (2015)]

Primary Adrenal Insufficiency (PAI)
Autoimmune adrenalitis (Addison's disease)
Isolated autoimmune adrenalitis
Adrenalitis as part of autoimmune polyglandular syndrome
Type 1 (APS1 or APECED): hypoparathyroidism, chronic mucocutaneous, candidiasis, other autoimmune disorders
Type 2 (APS2): thyroid disease, type 1 diabetes mellitus, other autoimmune diseases
Type 4 (APS4): Other autoimmune diseases, excluding thyroid disease or diabetes
Adrenalitis caused by infections
Tuberculosis, HIV, systemic fungal infections occurring mostly in immunosuppressed patients (histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis), cytomegalovirus
Genetic disorders leading to adrenal insufficiency
Adrenoleukodystrophy, adrenomyeloneuropathy
Demyelination of CNS (cerebral adrenoleukodystrophy), spinal cord, or peripheral nerves (adrenomyeloneuropathy)
Congenital adrenal hyperplasia (see Chap. 35)
Ambiguous genitalia, salt wasting
ACTH insensitivity syndromes (familial glucocorticoid deficiency)
Glucocorticoid deficiency, but no impairment of mineralocorticoid synthesis
Triple A syndrome (Allgrove's syndrome)
Alacrima achalasia, neurological impairment, deafness, mental retardation, hyperkeratosis
Bilateral adrenal haemorrhage
Meningococcal sepsis, primary antiphospholipid syndrome
Adrenal infiltration
Amyloidosis, hemochromatosis, adrenal metastasis, lymphomas, sarcoidosis
Bilateral adrenalectomy
For management of Cushing's or other adrenal disease, after bilateral nephrectomy
Drug-induced adrenal insufficiency
Treatment with mitotane, aminoglutethimide, etomidate, abiraterone, trilostane, ketoconazole, suramin, mifepristone
Secondary Adrenal Insufficiency (SAI)
Pituitary adenomas (see Part III)
Adrenal insufficiency caused by ACTH deficiency from tumour growth or post-surgery or radiotherapy.
Idiopathic hypopituitarism (see Chap. 25) or isolated idiopathic ACTH deficiency
Other tumours of the hypothalamic-pituitary region
Craniopharyngioma, meningioma, ependymoma, and intrasellar or suprasellar metastases
Pituitary irradiation for tumours outside the hypothalamic-pituitary axis, e.g. leukaemia
Lymphocytic hypophysitis
Autoimmune hypophysitis
Often associated with pregnancy; may present with isolated ACTH deficiency or panhypopituitarism; can also be associated with autoimmune thyroid disease, vitiligo, premature ovarian failure, type 1 diabetes, pernicious anaemia
Pituitary apoplexy or Sheehan's syndrome (see Chap. 64)
Pituitary infiltration or granulomatous disease
Tuberculosis, actinomycosis, sarcoidosis, histiocytosis X, Wegener's granulomatosis
Head trauma
Iatrogenic Adrenal Insufficiency
Prolonged treatment with exogenous glucocorticoids
Treatment with opioids leading to ACTH suppression

37.3 Clinical Presentation of Adrenal Insufficiency in Adults

Table 37.2 presents a summary of the clinical manifestations of AI (Arlt 2017; Arlt and Allolio 2003; Stewart 2008; Bornstein et al. 2016). Presenting symptoms of AI are often non-specific such as fatigue, loss of energy, loss of appetite, nausea, or weight loss which often result in a delayed or missed diagnosis, for example, depression or anorexia (Arlt 2017; Bancos et al. 2015). In a study by Bleicken et al., less than 30% of women and 50% of men with AI were diagnosed within the first 6 months after onset of symptoms

Table 37.2 Clinical manifestations of adrenal insufficiency [adapted from Arlt (2017), Arlt and Allolio (2003), Stewart (2008), and Bornstein et al. (2016)]

Common sign and symptoms in PAI and SAI (caused by glucocorticoid and androgen deficiency)
Fatigue, lack of energy or stamina, reduced strength
Anorexia, weight loss (in children failure to thrive)
Gastric pain, nausea, vomiting (more frequent in PAI)
Myalgia, joint pain
Dizziness
Fever
Low blood pressure, postural hypotension, and dizziness (pronounced in PAI)
Hyponatraemia (more common in PAI)
Hypoglycaemia
Symptoms specific to adrenal androgen deficiency
In women: dry and itchy skin, impaired libido loss of axillary or pubic hair
In girls: absence of adrenarche or pubarche
Sign and symptoms specific in PAI (caused by mineralocorticoid deficiency)
Salt craving
Skin hyperpigmentation
Raised serum creatinine
Hypercalcaemia
Hyperkalaemia
Increased thyroid stimulating hormone
Additional sign and symptoms in SAI
Related to pituitary adenomas, such as acromegaly, Cushing's, prolactinoma (see relevant chapters in Part III), hormone deficiencies in hypopituitarism (see Chap. 25), and visual-field impairment from compression of the optic chiasm.

and 20% suffered for longer than 5 years before being diagnosed. Almost 70% of patients were given a false diagnosis and had consulted at least three physicians in the process (Bleicken et al. 2010a). This is more common in PAI as a history of pituitary conditions affecting the HPA axis with an increased risk of SAI prompts for further investigations to confirm ACTH deficiency. Hypothalamic-pituitary conditions can also manifest with other symptoms such as visual impairment caused by chiasmal compression suggesting a possible pituitary or brain tumour. It is important to remember that AI resulting from cessation of exogenous GC therapy can present with all the symptoms associated with GC deficiency even though these patients appear clinically Cushingoid from previous long-term exposure to GC therapy (Arlt 2017).

The most obvious clinical feature that distinguishes PAI from SAI, which is often present in PAI, is skin pigmentation caused by excess POMC stimulation, the precursor peptide of ACTH and melanocortin-1, the latter stimulating melanocytes. This is mostly seen in sun-exposed areas, pressure points, axillae, nipples, genitalia, and mucous membranes. Vitiligo and other autoimmune endocrinopathies (hypothyroidism) can often present in patients with autoimmune Addison's disease (Stewart 2008) (Fig. 37.2). A high biochemical measure of ACTH will also distinguish between PAI (being excessively raised) from SAI where the level will be low.

The clinical features of PAI in adults (Addison's disease) result from the loss of both glucocorticoid and mineralocorticoid and tend to be more acute in the onset. Hyponatraemia and hyperkalaemia are found in 80% and 40%, respectively, of patients with PAI at diagnosis. Acute AI presents with postural hypotension which can progress to hypovolaemic shock; it can also present with acute gastrointestinal symptoms of abdominal tenderness, nausea vomiting, and fever. Symptoms can often be mistaken as episodes of isolated gastroenteritis or appendicitis and if misdiagnosed can lead to a potentially life threatening AC. Autoimmune causes are rare in childhood, but the occurrence increases in the second decade of life into adolescence and onto adulthood (Arlt 2017; Kwok et al. 2005; Rushworth et al. 2017).

37.3.1 Clinical Presentation of Adrenal Insufficiency in Children

Similar to adults, undiagnosed AI in children can often be overlooked when another more significant diagnosis arises with symptoms often masking the underlying cortisol deficiency and which can mislead or confuse the diagnostic process. A new diagnosis of AI can reveal itself with either an acute presentation or have a prolonged insidious onset with a history of evolving features and concerns by parents with failure to thrive, poor weight gain and growth failure, and prolonged recovery from illnesses. An acute presentation occurs with the presentation of a infant or child in a state of systemic collapse, often precipitated by a significant intercurrent illness, when their adrenal function is no longer adequate to support their

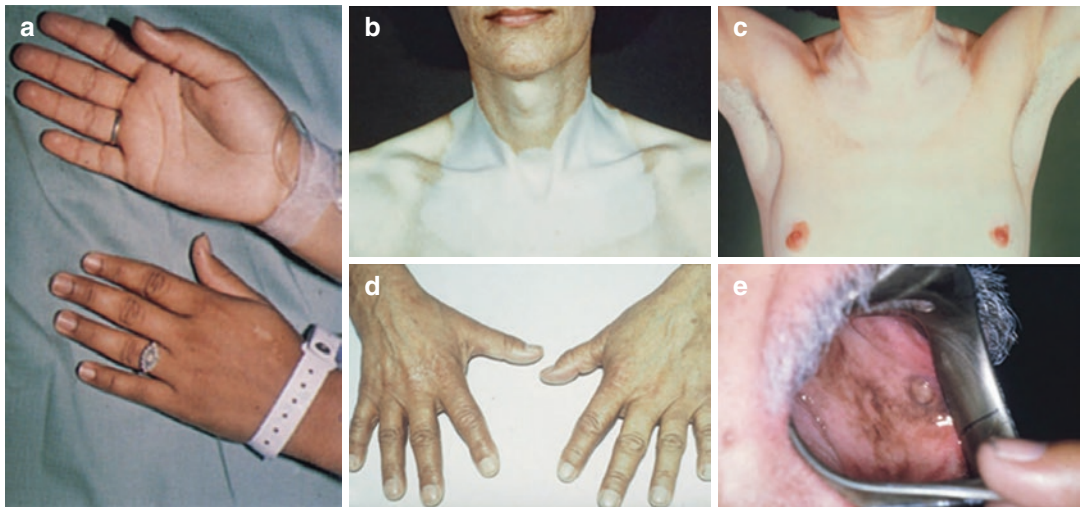


Fig. 37.2 Skin pigmentation and vitiligo in Addison's disease. Key: (**a**) hands of an 18-year-old woman with autoimmune polyendocrine syndrome and Addison's disease. (**b**) Pigmentation and vitiligo in a patient before and (**c**) after treatment with hydrocortisone and fludrocortisone. (**d**) Change in skin pigmentation of the hands of a 60-year-old man with tuberculous PAI before and after GC replacement, and (**e**) buccal pigmentation in the same man before treatment. Used with permission from Stewart P.M. (2008) The adrenal cortex, Chapter 14. In: Kronemberg H.M., Melmed S., Polonsky K.S. and Larsen P.R. (Eds) Williams Textbook of Endocrinology, 11th Edition. Saunders Elsevier, Philadelphia, pages: 445–503

metabolic needs in response to stressful situation (Migeon and Lanes 2009; Miller et al. 2008).

37.3.1.1 Acute Clinical Presentation of AI in Children and Neonates

In acute presentation of AI, examination will reveal a pale and lethargic child, with progressive signs of deterioration of a listless and floppy demeanour and a reduced level of consciousness due to hypoglycaemia. The child will be cool to touch and has hypothermia due to, hypovolaemia and peripheral shutdown (evident with poor skin turgor, delayed capillary return), dry mucous membranes and a history of minimal urine output indicating significant dehydration. Background history may reveal a period of intercurrent illness, poor oral intake, maybe a period of persistent diarrhoea and/or vomiting. Observations reveal tachycardia, dyspnoea, hypotension, and hypoglycaemia. A blood gas and peripheral blood is needed to confirm or rule out any biochemical cause, and a septic workup to determine a bacterial or viral cause for the presentation (Migeon and Lanes 2009; Miller et al. 2008).

An acute presentation in a neonate or infant is life threatening. It may occur following a history of persistently poor feeding, excessive sleepiness, persistent jaundice, and failure to regain birth weight, with significant weight loss of >10% of their total body weight. Acute episodes of AI require to be managed immediately, guided by standard emergency protocol guidelines, to prevent otherwise a fatal outcome due to AC (see Chap. 62 for more details).

37.4 Diagnosis of Adrenal Insufficiency in Adults

The diagnosis of AI is based on the patient's medical history, clinical sign and symptoms suggestive of AI, adrenal and/or pituitary imaging, and diagnostic biochemistry provocative tests. Figure 37.3 presents the diagnostic algorithm for adults with clinical sign and symptoms suggestive of AI and diagnostic test which can set the differential diagnosis (Bancos et al. 2015).

The diagnosis of AI is established by the ACTH stimulation test, also known as the short

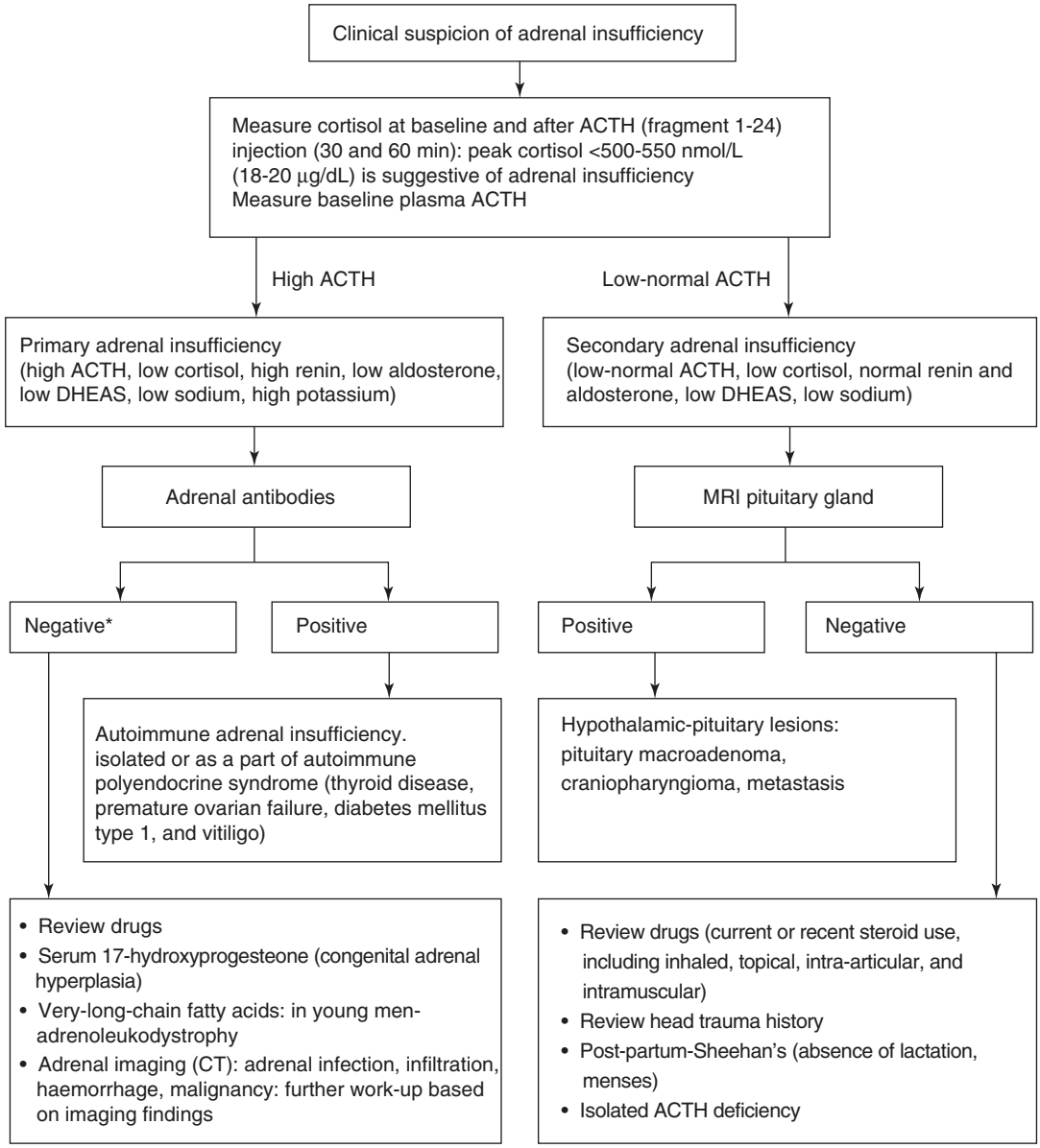


Fig. 37.3 Diagnostic algorithm for adults with clinical signs and symptoms suggestive of adrenal insufficiency. Key: *ACTH* adrenocorticotropic hormone, *DHEAS* dehydroepiandrosterone. Important to remember: Diagnostic measures must never delay the start of hydrocortisone treatment in suspected adrenal crisis and should be done when the patient is better. Cut-off values to exclude AI vary depending on the assay uses; always check local reference ranges. Used with permission from Bancos, I., Hahner, S., Tomlinson, J. & Arlt, W. 2015. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol,* 3, 216–26

cosyntropin or short synacthen test (SST), through assessment of cortisol at baseline, 30 min and 60 min post administration of synthetic ACTH hormone of 250 μg for adults and children ≥2 years of age, 125 μg for children <2 years of age, and 15 μg/kg for infants (Bornstein et al. 2016). Cortisol response tends to be slightly higher at 60 min but there are no documented advantages in specificity and sensitivity for either time point (Bancos et al. 2015).

The cut-off values for cortisol for exclusion of AI are recommended at 500 nmol/L (18 μg/dL) (Bornstein et al. 2016), but this may vary according to the assay used. For example, a study reported that the low reference limit for cortisol 30 min after ACTH stimulation ranged from 420 to 574 nmol/L (15.2–20.8 μg) depending on the assay used (El-Farhan et al. 2013); cut-off values for cortisol may differ significantly between measurements using immunoassays or mass spectrometry assays and therefore specific local reference ranges must always be confirmed before setting the diagnosis.

The ACTH stimulation test is a test of adrenal function and therefore should not be used to diagnose SAI before adrenal gland atrophy has occurred, which takes approx. 3–4 months. Therefore, testing with the SST for SAI, for example, within a month after a pituitary insult and suspected ACTH deficiency, may not detect SAI. It has also been suggested that ACTH stimulation testing could lack sensitivity in chronic SAI due to the 250 μg supraphysiological dose and the 1 μg was advocated as an alternative (Dorin et al. 2003). However, later evidence found that significant proportion of patients fail the 1 μg test using the agreed cut-off cortisol limit, and this could lead to unnecessary lifelong GC replacement (Neary and Nieman 2010); therefore, it is not recommended to use as a diagnostic test. In addition, diluting a 250 mg ampoule in 1 mg portions is not recommended. The insulin tolerance test (ITT) is an alternative, but it is more invasive and contraindicated in patients with a history of seizures, cardiovascular disease, untreated hypothyroidism, and elderly patients, and in particular it is contraindicated in children owing to the dangers of significant hypoglycaemia and risk of an AC (Miller et al. 2008). (please refer to Chap. 15, in Part III for more details on provocative diagnostic testing). In addition, ITT should be avoided in SAI when random morning cortisol concentrations are lower than 80 nmol/L (3 mg/dL) which are strongly predictive of AI (Bancos et al. 2015). Suspected AI presenting with acute AC must be treated promptly with parenteral hydrocortisone (Bancos et al. 2015; Bornstein et al. 2016; Wass and Arlt 2012) (Box 37.1). In the paediatric population the IV synacthen test has been useful in determining suspected cortisol deficiency and utilised in determining recovery of the adrenal gland function following adrenal suppression following iatrogenic use of steroids (Mendoza-Cruz et al. 2013).

Box 37.1 *Treat first, diagnose later*! Management of Acute AI

For patients admitted with adrenal crisis where AI is suspected, hydrocortisone must be given without delay along with intravenous fluid resuscitation. Blood samples for paired cortisol and ACTH should be taken if there is an opportunity but it is crucially important to promptly treat the AC and undertake diagnostic investigations later when the patient is better (please see Chap. 62 for more details on management of AC).

It is also important to remember that oral oestrogen preparations increase total cortisol concentration (which is measured in current assays) by increasing circulating cortisol-binding globulin (CBG) and therefore should be discontinued for at least 6 weeks prior to evaluating cortisol levels although one study showed that these effects were not seen in patients using transdermal oestrogen replacement (Qureshi et al. 2007).

37.4.1 Diagnosis of Adrenal Insufficiency in Children

Specific considerations need to be given making the diagnosis of AI in children and neonates in addition to those discussed earlier in the diagnosis of adults with AI. In addition to clinical manifestations of AI described earlier, observations confirm **hypothermia** (temperature less than 36 °C), **hypoglycaemia** (<2.6 mmol/L) via peripheral blood glucose analysis or blood gas, and **hypotension** with unmeasurable blood pressure. Table 37.3 presents a summary of the relevant biochemistry and microcytic investigations

Table 37.3 Investigations in the differential diagnosis of AI in children

Investigation	Biochemical features and results
Venous blood gas	Immediate assessment of BGL, EUC metabolic status/acidosis
EUC	Hyponatraemia and high serum potasium indicating aldosterone deficiency
Urea and creatinine	Assess for dehydration Elevated levels confirm dehydration
Blood glucose	Confirms hypoglycaemia Lack of glucocorticoid and gluconeogenesis (fasting and vomiting)
Insulin	Normal insulin level in presence of hypoglycaemia rules out hyperinsulinism as cause of low BGL
Cortisol, growth hormone	Low levels in view of hypoglycaemia, confirms—multiple pituitary hormone deficiency (MPHD) and cortisol deficiency
Thyroid function tests	Low TSH/T4 confirms MPHD
17 OHP, androgen profile	Raised levels indicate possible CAH
ACTH	Raised level ++ Indicates—primary adrenal insufficiency
Lactate/pyruvate, free fatty acid, ammonia, carnitine	Assess metabolic acidosis as cause of hypoglycaemia—rule out metabolic diagnosis Rule out deficiency—causes hypoketotic hypoglycaemia
Aldosterone and renin	Low levels of aldosterone with high levels of renin indicate PAI, e.g. salt losing CAH—deficiency
Urinary keto-steroids	Positive levels determine CAH Minimise multiple blood tests requiring large amounts of blood (not done if acutely unwell)
Blood culture	Rule out sepsis
Urine culture	Rule out urinary tract infection

undertaken in the differential diagnosis of AI in children.

The most common cause of AI in childhood is Congenital Adrenal Hyperplasia (PAI) with mineralocorticoid deficiency or associated with multiple pituitary hormone deficiency (SAI). The distinguishing feature between PAI and SAI is the presence or absence of a significantly raised ACTH, 17OHP level and significant electrolyte imbalance in PAI. The synacthen test and a urine steroid profile (Miller et al. 2008; Koyama et al. 2014) are useful in diagnosing PAI. In SAI, determining diurnal variations in serum cortisol (8 am and 4 pm) and understanding normal secretion rates in neonates, infants and childhood can be helpful in interpreting the results (Migeon and Lanes 2009; Miller et al. 2008; Koyama et al. 2014). Other investigations for SAI include a closely monitored brief fasting study in a neonate or infant to measure the response of counter-regulatory hormones (cortisol & growth hormone) along with insulin to rule out hyperinsulinism in response to hypoglycaemia. A glucagon stimulation test (GST) can be useful in place of an ITT (contraindicated in childhood) to determine a child's cortisol response to hypoglycaemia along with possible growth hormone deficiency in children (Miller et al. 2008).

37.4.1.1 Psychological Impact of Diagnosis of AI on Children and Parents

The diagnosis of AI in the child can have a significant psychological impact on the parents. The parental role to nurture and protect is challenged by a medical condition which has life-long implications. The distress and shock following the diagnosis impacts greatly on the parents' ability to rationalize the situation which is out of their control. As such the effectiveness of information which the medical and nursing staff impart can be diminished (Betman 2006). As health professionals, we have no control over this process, other than to provide emotional support and explanation in a timely manner in an initial and ongoing process. The significance of a potentially life-threatening condition, challenges parental strengths and weaknesses and puts many relationships under extreme pressure. They need to grieve for the loss of their expected healthy child and fear the limitations such a diagnosis will have on their child's future life. Eventually, rationalising their fears and worries about the future will see subsequent resolution with final acceptance to move forward and manage the care required for their child. The endocrine nurse needs to understand the grief process that parents experience following a significant diagnosis in

order to provide the support they need to move forward with their child's journey in life (Betman 2006).

37.5 Treatment of Adrenal Insufficiency

Treatment of AI is multifaceted and, although it is primarily focused on replacement therapy, it should not be considered in isolation from the self-management and psychological well-being of patients and their families. A holistic overview of the patient's psychosocial environment, quality of life (QoL), well-being, other health needs and comorbidities, as well as their priorities, beliefs on and expectations from their treatment, is necessary. In addition, patient/family empowerment and shared decision-making are crucial in achieving an individualised treatment regimen and improved patient adherence. The objectives for treatment in AI are summarised in Box 37.2 [summarised from Arlt and Allolio (2003), Barthel et al. (2016), Bancos et al. (2015), Bornstein et al. (2016), Fleseriu et al. (2016), Grossman (2010), and Chapman et al. (2016)].

37.5.1 Mineralocorticoid Replacement Therapy

Mineralocorticoids are vital for maintaining water and electrolyte homeostasis, and thereby blood pressure. Only patients with PAI have mineralocorticoid deficiency as this is controlled by the RAA system and not the HPA axis. Fludrocortisone is a synthetic mineralocorticoid used to replace aldosterone in patients with PAI. It is recommended that all patients with confirmed aldosterone deficiency should be on fludrocortisone replacement starting at 50–100 μg and taken on waking up together with GC. In childhood, fludocortisone doses may be required

Box 37.2 Objectives for Treatment Optimisation in Adrenal Insufficiency

The following objectives should be taken into consideration when planning and monitoring the treatment regimen for patients with AI:

- To provide optimal replacement for GC, androgens and, specifically for patients with PAI, mineralocorticoids
- To involve patients and families in planning a treatment regimen which is tailored to each patient's individual needs in order to minimise or avoid where possible complications and symptoms from over- or under-replacement
- To restore normal well-being, quality of life, sexual function, weight balance, normal growth for children, and social, family, and professional activity
- To ensure patients and families are well informed of their condition and can recognise the symptoms of over- or under-replacement
- To ensure patients and families receive support and education on their treatment so they can self-manage their daily replacement, adjust GC appropriately during intercurrent illness, and know how to prevent an adrenal crisis
- To ensure that the education provided translates to behavioural change for patients and families; any potential detrimental medication behaviours need to be identified and patients should be supported to address these factors
- To develop an infrastructure and health service that supports the needs of patients with AI and ensures prompt management of AC to minimise or avoid hospitalisations and to eradicate preventable deaths from AC

twice daily in the first few years of life, owing to mineralocorticoid pathway resistance. The addition of salt supplements is essential in neonates and infants as dietary sodium is inadequate in this age group (Migeon and Lanes 2009; Miller et al. 2008). Fludrocortisone is primarily monitored based on clinical assessment of salt cravings, postural hypotension, or presence of peripheral oedema alongside blood pressure, blood electrolytes (sodium and potassium) and renin (Quinkler et al. 2015); salt intake should not be restricted (Bornstein et al. 2016). For patients who develop hypertension, a reduction in the dose of fludrocortisone is recommended alongside monitoring of electrolytes but antihypertensive treatment can be initiated whilst continuing fludrocortisone if blood pressure remains uncontrolled (see also Box 37.3). During pregnancy fludrocortisone doses often need to be increased due to the antimineralocorticoid effect of progesterone (Quinkler et al. 2015). Also during episodes with hot weather fludrocortisone dose increases of 50 mg/day often lead to better physical performance. Hydrocortisone also exerts a mineralocorticoid activity and a 20 mg dose is equivalent of 50 μg of fludrocortisone (Arlt 2017; Bornstein et al. 2016) hence with increasing the dose of hydrocortisone during illness or managment of an AC, there is no need to increase the dose of fludrocortisone.

Box 37.3 Key Points in the Assessment of Mineralocorticoid Replacement

Does your patient crave salt, feel lightheaded, have low blood pressure, postural hypotension, low blood sodium, high potasium and reports a general feeling of being unwell? If the answer is YES, replacement is inadequate, and the dose of fludrocortisone should be increased. Advise your patient that temporary dose increments of fludrocortisone by 50–100% or increase in salt intake are also needed in a hot climate or situations that promote excessive sweating.

37.5.2 Adrenal Androgen Replacement Therapy in Women

Dehydroepiandrosterone (DHEA) is the main source of androgen production in women and plays important role in maintaining sexual function, energy, and libido. DHEA replacement in women with AI also leads to development or restoration of pubic hair and may therefore have a role in pubertal females (Neary and Nieman 2010). DHEA replacement at 25–50 mg as a single dose should be considered for women with PAI complaining of low libido, depressive symptoms, dry skin, and fatigue when GC and mineralocorticoids are optimised (Bornstein et al. 2016). This can be on a 6-month trial and can be discontinued if there is no benefit. Women should be monitored for possible androgenic side effects of hirsutism or hair thinning. Small studies found that patients with SAI also reported improvement in psychological well-being on DHEA replacement (Brooke et al. 2006). However, evidence in this patient group population is controversial regarding QoL outcomes and recent guidelines recommend against routine use of androgens for women with SAI (Fleseriu et al. 2016).

37.5.3 Glucocorticoid Replacement Therapy in Adult Patients with AI

As already discussed, cortisol secretion exhibits a circadian rhythm and the objective for GC replacement therapy is to mimic this rhythm in an as closest as possible manner although this has so far been a challenge. A crucial step to understand is the regulation of cortisol metabolism by interconversion of cortisol to cortisone, governed by the intracellular 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes; type 1 (11β-HSD1) modulates local tissue cortisol levels by converting cortisone (*inactive* GC) to cortisol (*active* GC) and type 2 (11β-HSD2) converts cortisol to cortisone which functions as a systemic glucocorticoid reservoir (Oksnes et al. 2015; Aulinas et al. 2013). Box 37.4 lists the three aspects which should be considered for optimal GC replacement.

Box 37.4 The Three Important Aspects of Optimal GC Replacement Therapy

Consult and educate the patient and their families on the following three aspects of GC replacement therapy:

1. **Circadian rhythm daily dosing for oral GC**

   Objective: to optimise well-being, improve adherence and minimise or avoid negative effects of over- or under-replacement

   Action plan:
   - work with patient and family to select an individualised treatment regime and the correct dose and type of GC
   - advise patient of special situations such as travelling, shift working, extreme physical or emotional stress
2. **GC replacement during intercurrent illness—"sick day rules"**

   Objective: to support the patient and aid recovery from illness by increasing GC dose as needed

   Action plan:
   - advise your patient and family on the different situations which require "sick day rules" and how to adjust the dose of their GC
   - patients are often on different GC regimens so a blanket rule of "double or triple" dose will not be applicable to everyone
   - provide supporting information, e.g. leaflets, emergency ID card, and an emergency GC injection kit, smartphone applications, as well as education on how to recognise and prevent AC
3. **Prevention and management of adrenal crisis**

Objective: recognise and manage AC in a timely manner to avoid hospitalisation

Action plan:
- ensure patients and their families are aware of the symptoms of AC and able to take immediate action
- check that patents wear emergency ID card and have access to GC injection which can be administered promptly
- advise patients on supporting services which they can call upon in case of AC, e.g. ambulance service, inform family and friends about risks of AC

There are several GC formulations used to treat AI (Table 37.4). The most commonly used GC is hydrocortisone (cortisol) given in two or three divided oral doses daily (total daily dose of 15–25 mg for patients with PAI (Bornstein et al. 2016) and 15–20 mg for patients with SAI (Fleseriu et al. 2016)). Cortisone acetate two to three times daily to a total of 20–35 mg is also used although not available in some countries such as the UK or Germany. Contrary to hydrocortisone, cortisone acetate (*inactive*) requires activation via hepatic 11β-HSD1 before it becomes biologically *active* cortisol. This may result in broader interindividual variability of cortisol which can make it difficult to obtain a precise profile. However, it has been suggested that the slower onset and offset of cortisol levels may be advantageous in smoothing fluctuations in levels (Grossman 2010), and this would be a good option for patients complaining of "energy dips" between doses.

The first and largest dose of hydrocortisone should be given on waking up on empty stomach, for faster absorption and as early in the morning as possible. The second dose is given at lunch time and the third dose, if required, given late afternoon but no more than 4–6 h before sleep (with a 5–6-h gap between doses). Generally, patients with PAI require higher and more frequent doses of hydrocortisone compared to patients with SAI who may have some residual cortisol reserve. Caution is required in patients

Table 37.4 Formulations, characteristics, and dose equivalent for GCs

GC name	Equivalent GC dose (mg)	Potency relative to hydrocortisone	Half-life plasma (min)	Duration of action (h)
Hydrocortisone	20	1	90	8–12
Cortisone acetate	25	0.8	30	8–12
Prednisone	4–5	4–5	60	12–36
Prednisolone	3–4	5–6	60	12–36
Dexamethasone	0.5	30–50	200	36–54

with SAI to avoid over-replacement (Grossman 2010). The general aim is to give the lowest possible dose of hydrocortisone without compromising the patient's well-being or put them at risk of AC. Two large studies including more than 1000 patients with AI, showed that most patients take hydrocortisone, i.e. 75% (Forss et al. 2012) and 87.4% (Murray et al. 2017), respectively, at either twice or thrice daily. The most common regimen of hydrocortisone was 10 mg on waking up, 5 mg at lunch time, and 5 mg late afternoon or evening (Murray et al. 2017), which is generally the most accepted regimens we use in clinical practice. Interestingly, both studies showed a large variation of daily regimens, regarding total daily dose and number of divided doses; Murray et al. reported that 25 different regimens were being used by patients to deliver a total daily hydrocortisone dose of 20 mg (Murray et al. 2017). This emphasises that requirements for GC replacement are individual to each patient's needs. Endocrine nurses have a pivotal role in identifying and addressing these needs to plan an optimal GC replacement regimen for patients. A small study concluded that hydrocortisone dosing and regimen should be adjusted according to the patient's weight (Mah et al. 2004), but there is no robust evidence to support this approach over current practice, and this would add to the already very complex regimen for patients with AI.

Prednisolone 3–5 mg once or twice daily, which is a long-acting GC, can be considered as an alternative treatment option for patients who continue to report impaired QoL or poor adherence to the twice or thrice daily regimen (Bornstein et al. 2016). It is however not a preferred choice, as it has been associated with an increased tendency to adverse metabolic complications including weight gain, dyslipidaemia, and type 2 diabetes (Filipsson et al. 2006; Quinkler et al. 2016), and osteoporosis (Frey et al. 2018). Dexamethasone should not be used as GC replacement in AI due to the Cushingoid side effects and difficulties in dose titration (Bornstein et al. 2016) although there is a rare indication for use in certain patients with CAH (please see Chap. 35).

The modified dual-release hydrocortisone (Plenadren®) is an alternative option for GC replacement. It comes in tablets of 20 mg and 5 mg taken once daily on waking up. It has an immediate release coating combined with an extended-release core and provides physiological levels and a smoother cortisol profile during the day when compared to immediate release thrice daily hydrocortisone (Aulinas et al. 2013; Johannsson et al. 2009) (Fig. 37.4). It is important to note that the bioavailability of Plenadren is 20% less than hydrocortisone which may require a dose adjustment. In addition, cortisol levels during the evening decrease by up to 58% (Johannsson et al. 2009) and some patients may experience fatigue in the last part of the day especially if they are active. Two randomised studies showed that after switching from conventional thrice daily to once daily modified-release hydrocortisone, patients have a more circadian-based cortisol profile during the day, improved QoL scores, and a reduction in body weight, blood pressure, and glucose metabolism over 12 and 24 weeks (Isidori et al. 2018; Johannsson et al. 2012).

Infacort® (licenced for use in children with AI and CAH) is an immediate-release, granule

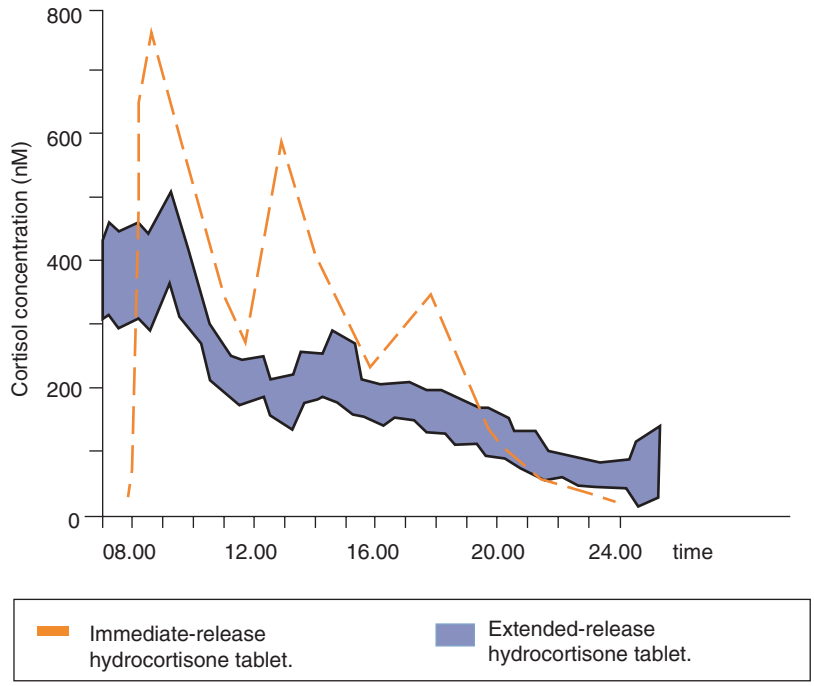


Fig. 37.4 Comparison of cortisol profiles between thrice daily immediate release and once daily modified-release hydrocortisone. Used with permission from: Aulinas, A., Casanueva, F., Goni, F., Monereo, S., Moreno, B., Pico, A., Puig-Domingo, M., Salvador, J., Tinahones, F. J. & Webb, S. M. 2013. Adrenal insufficiency and adrenal replacement therapy. Current status in Spain. *Endocrinol Nutr,* 60, 136–43

formulation of hydrocortisone with taste masking for a dose-appropriate formulation of hydrocortisone for children with adrenal insufficiency (Neumann et al. 2018; Uta et al. 2018). Chronocort® (developed for adults with CAH) is a modified-release hydrocortisone formulation based on a multi-layered multi-particulate technology where the sustained release and enteric coats are varied to provide differing release profiles (release of hydrocortisone 4–5 h after intake). Taken twice daily, 20 mg before sleep and 10 mg on waking up, it can mimic circadian rhythm of cortisol with a release of hydrocortisone in the early hours of the morning providing a pre-waking cortisol rise, which is not provided with other oral GCs (Whitaker et al. 2014).

Up to now, there has been no robust evidence to inform us whether one GC formulation is superior to the others regarding short term and long term goals (Grossman et al. 2013); therefore more research is needed in this area. It is important however to remember that every patient has different needs, and treatment should be individualised. The endocrine nurse has a crucial role in identifying and addressing these needs by adopting a holistic care approach.

37.5.3.1 Continuous Subcutaneous Hydrocortisone Infusion (CSHI)

Continuous subcutaneous hydrocortisone infusion (CSHI), using an insulin pump (Fig. 37.5), can mimic the physiological cortisol rhythm and is suggested as a potential alternative treatment option for patients with difficult to control AI and those in whom oral GC are not absorbed (Oksnes et al. 2015), as also demonstrated by our patient in the case study (Box 37.5). Preliminary evidence suggests that CSHI improves health-related QoL scores and improves fatigue in patients with AI (Oksnes et al. 2014) although it can be quite a cumbersome regimen for patients. Further studies are however needed to investigate long-term outcomes of CSHI treatment and to refine the infusion regimen.

37.5.3.2 GC Dose Adjustment During Intercurrent Illness in Adults

Patients with AI need to increase the dose of their GC replacement in order to mirror the physiological increase in serum cortisol levels during major stress and illness. This is normally referred to as “sick day rules”. There is no

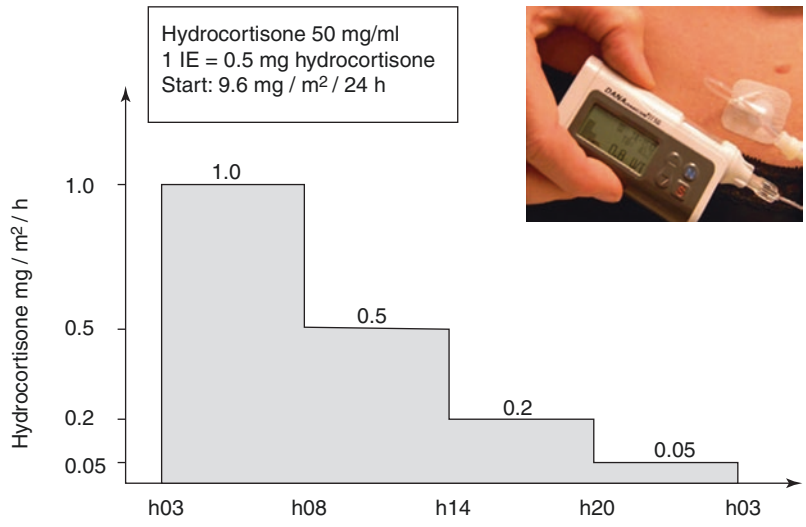


Fig. 37.5 Starting doses for continuous subcutaneous hydrocortisone infusion. The insulin pump reservoir is filled with hydrocortisone 50 mg/mL. Doses are adjusted to body surface area (BSA/m2). The daily dose is divided into four dosing intervals, with the highest dose during the last part of the night, half that dose during the first part of the day, and further decreasing doses in the afternoon and early part of the night. **Used with permission from:** Oksnes, M., Ross, R. & Lovas, K. 2015. Optimal glucocorticoid replacement in adrenal insufficiency. *Best Pract Res Clin Endocrinol Metab,* 29**,** 3–15. [Figure 4, page 11]

Box 37.5 Case Study of a Patient Using Continuous Subcutaneous Hydrocortisone Infusion (CSHI) for GC Replacement

What being on the CSHI Pump means to me

I was diagnosed with severe adrenal insufficiency in September 2016 even with oral hydrocortisone my blood cortisol levels were virtually non-existent.

I also have several pre-existing gastric issues—I have gastroparesis so reliably taking oral hydrocortisone was impossible as I was vomiting several times daily… Secondly, as I have Crohn's disease which is refractory and always active to some degree I was having diarrhoea several times daily so was burning through the hydrocortisone…

Between the end of March and beginning of May I had 6 back-to-back infections including a life-threatening sepsis and pneumonia. Since being on the pump I have been infection free…

I had heart palpitations due to tachycardia, constant terrible headaches which are so painful that I couldn't sleep, extreme fatigue—I had no energy and even sitting zapped me of my resources, every day I fainted up to five times daily as my blood pressure was persistently low… Since being on the pump I now have energy, my life is much more predictable and whilst I have a life-threatening condition I am much more in control of it rather than it controlling me. … my quality of life is exponentially better, and I no longer feel like death warmed up. The gastric and duodenal ulcers are now a thing of the past…

The other great thing is I am now on 21 mg of hydrocortisone daily… This means my chances of getting long-term side effects from excess steroid treatment, e.g. diabetes, heart disease, are drastically reduced … Some people may think being on a pump is restrictive but in all honesty most of the time I forget I am even wearing it…

(published with patient consent)

evidence on the optimal replacement during illness, but general consensus is to double or triple the dose of GC tablets for minor to moderate illness were oral intake is possible. For more severe illness and when the patient is unable to take oral tables in situations such as vomiting, diarrhoea or nil by mouth procedures, hydrocortisone needs to be administered immediately intramuscularly or intravenously at 50–100 mg starting dose followed by 50–100 mg every 6 h or 100–200 mg/24 h by continuous intravenous infusion (Arlt and Allolio 2003; Bornstein et al. 2016; Husebye et al. 2014). Patient education is crucial to ensure that patients and their families are familiar with the sick day rules. The endocrine nurse should take a detailed history of the patient's treatment, how and when they take their medication. A blanket rule of "double the dose" as reflected in the case study presented in Box 37.6, is not always applicable to every patient and patient education needs to take an individualised approach. Please read Chap. 62 for a comprehensive overview of the management of intercurrent illness and the diagnosis, prevention and timely management of AC. Chapter 62 also provides details on best approaches to patient education in AI.

Box 37.6 Case Study of GC Dose Adjustment During Intercurrent Illness

John is a 49-year-old man with SAI. He calls for an urgent consultation and is seen in the nurse-led clinic. He tells me he has not been feeling well and has had a lingering nasty cold for over 3 weeks, even though he doubled the dose of his hydrocortisone. His prescribed daily dose is 10 + 5 + 5 mg three times daily, but on further questioning, he tells me he has been taking 20 mg first thing in the morning. He also takes the double dose of 40 mg as single dose on waking up. Following an education session, John understands the rationale for thrice daily regimen based on his insulin tolerance test results. A blood test when we met, taken 9 h after 40 mg of hydrocortisone, also shows a very low level of cortisol 68 nmol/L. We discuss ways to help him remember his second and third doses. He calls me a month later to say he has recovered and energy levels have "picked up".

37.5.4 Treatment of AI and GC Adjustment for Intercurrent Illness in Children

The treatment objective in children is to find a balance between under- or over-replacement with GC, to minimise acute and long-term complications and to minimise the risk of AC with a dose that allows normal growth and pubertal development (Bornstein et al. 2016; Salprietro et al. 2014; Kwok et al. 2005). The Endocrine Society guidelines recommend treatment with hydrocortisone in three or four divided doses (starting daily dose of 6–8 mg/m^2 in children with SAI and 12–16 mg/m^2 in children with PAI. For its short acting properties, hydrocortisone is used in preference) over other GC replacement therapies in children (Migeon and Lanes 2009; Bornstein et al. 2016; Fleseriu et al. 2016). Children with PAI and confirmed aldosterone deficiency should be treated with fludrocortisone (starting dose of 100 μg daily); it does not require adjustment by body surface and generally remains the same throughout early life. However, in neonates and infants, mineralocorticoid pathway resistance requires higher fludrocortisone doses of 50–200 μg daily in order to maintain sodium levels in PAI (Migeon and Lanes 2009; Miller et al. 2008). Many of these patients also require sodium chloride supplementation of 1–2 g daily divided in several feedings (Bornstein et al. 2016).

Treatment of inter-current illness requires increasing the dose of oral hydrocortisone to at least 45–50 mgs/M2/day in divided doses 6 hourly until well again. In children with SAI, where there is a lower maintenance replacement

dose, doubling or tripling the daily dose maybe inadequate (Miller et al. 2008). Regular clinical review and monitoring of growth and development are essential long term. Blood tests and a yearly bone age X-ray are included in this process to ensure hormonal and biochemical parameters are stable. The endocrine nurse should support parents to manage their child's condition and treatment and ensure there is an understanding of the importance of adherence with medication administration and attendance for clinical reviews to monitor growth and development. Patient and parent education is a critical component in the care of these children as parents integrate managing their child's care into their daily lives and in the future empower their children to gain independence as adolescents and adults.

Understanding the importance of managing health issues with stress hydrocortisone is imperative. All patients need stress hydrocortisone along with consideration of a sweet drink to prevent hypoglycaemia. Children with PAI require the addition of a salt supplement when unwell because of the risk of possible hyponatraemia and failure or absorption of their oral medication. At home this may be administered using salt tablets/sachets in water, rock salt, or with high salt containing foods. Table 37.5 presents a summary of daily and stress treatment for children with AI. Please refer to Chap. 62 for more details on management of adrenal crisis.

Table 37.5 Maintenance and stress dosing for children with AI

Two different dosing plans for children with AI	
Primary Adrenal Insufficiency (PAI)	12–16 mgs/m^2/day hydrocortisone 0.05–0.2 mgs per day Fludrocortisone *(Note: in CAH patients doses need not only to replace but also to suppress excess androgen secretion to prevent virilisation)*
Secondary adrenal insufficiency (SAI)	6–8 mgs/m^2/day *(Exact replacement dosing)*
Stress doses for hydrocortisone doses are the same in PAI and SAI	
Stress dosing—oral *Moderate illness*	45–50 mgs/m^2/day divided into 4 doses 6-hourly
Stress dosing—Intramuscular injection or intravenous *Significant illness, vomiting, diarrhoea, reduced consciousness*	45–100 mgs/m^2 stat Followed by: 45–100 mg/m^2/day divided in 4 doses 6-hourly 6-hourly or Hydrocortisone infusion with 100–200 mg/24 h

37.6 The Importance of Patient Education in AI

Patient education is paramount in optimising replacement therapy and minimising complications of over- and under-replacement. Endocrine nurses play a crucial role in educating patients and their families on day-to-day self-management, intercurrent illness, or special situations and how to prevent AC. Their role is also vital in educating other healthcare professionals and raising awareness of the life-threatening nature of AI. This is especially important in the care of children as parents can be in a state of shock. Endocrine nurses begin their patient education by assessing parental grief, understanding and coping strategies in adapting to their child's diagnosis. It is important to instil confidence into parents' coping abilities and to reassure them that there is advice and support available to guide them through any difficulties they may encounter in managing the day-to-day care of their child. At each consultation, it is crucial to check the patient's knowledge on management of intercurrent illness and prevention of AC, and provide relevant education if gaps are identified. The process of patient education is described in more detail in Chap. 62.

37.7 Role of Adherence to Medication in Optimising GC Replacement

Current treatment options, although not yet perfected, can offer an individualised approach that can meet the needs of most patients with AI, especially with the new formulations developed recently. However, "*drugs don't work in patients*

who don't take them" (C.Everett Koop, MD, US Surgeon General, 1985). Nonadherence has been recognised as a significant challenge by the World Health Organisation suggesting that only 50% of patients with chronic conditions take their medications as recommended (Nunes et al. 2009). More specifically in AI, adherence to GC replacement encompasses the three aspects of appropriate dosing of daily GC to avoid over- or under-replacement, dose adjustment during intercurrent illness and prevention of adrenal crisis (AC).

Adherence to medication is defined as the extent to which a patient's behaviour matches agreed recommendations from their healthcare professional (Nunes et al. 2009). It is also important to understand that adherence to medication is not always in the patient's control. To understand this, Professor Robert Horne uses a simple analogy of "*patients don't want or cannot take their medications*" (quote from personal communication, November 2016). His *Perceptions and Practicalities Approach* provides a theoretical framework to understand the complex human behaviour nature of nonadherence (Horne et al. 2005; Horne 2006) which can be:

- Unintentional where the patient wants to adhere but is prevented from doing so by **practical barriers** or resources beyond their control (*ability*). These include barriers such as forgetfulness, complexity of regimen, difficulty with prescriptions, poor recall or lack of information about the medication, and side effects.
- Intentional where the patient decides not to follow the prescribed treatment regime whether this is conscious or subconscious. **Perceptual barriers** such as beliefs about medicines or fear of side effects can influence patient's *motivation* to start and continue treatment.

37.7.1 Evidence of Nonadherence to GC Replacement

Tailoring the GC dose to patients' needs and achieving optimal adherence are two of the main challenges reported by endocrine clinicians (Grossman et al. 2013). Forss et al. found that 23% of patients with AI (N = 1245) report dissatisfaction with treatment, 38% find multiple daily dosing problematic, over 50% perceive that GC interferes with life aspects such as work, travel, or sex life, and many missed tablets or took them before sleep which resulted in fatigue or insomnia (Forss et al. 2012). Chapman et al. found that 25% of patients took higher doses than advised (Chapman et al. 2016) which can lead to complications. Both studies found that over 50% of patients report concerns about side effects and long-term complications (Chapman et al. 2016; Forss et al. 2012); concerns were strongly associated with nonadherence (Chapman et al. 2016). About 1 in 25 patients reported prolonged treatment interruptions (Chapman et al. 2016); GC dose reduction or cessation was a significant factor to trigger AC for 3.9% (Smans et al. 2016) and 5.5% (Hahner et al. 2010) of patients with AI.

37.7.2 How to Identify and Address Nonadherence to GC Replacement

The endocrine nurse is the best placed person in the multidisciplinary team to identify nonadherence factors and to support patients, their families, and other healthcare professionals to improve adherence to GC replacement; Box 37.7 summarises the key steps in this process adapted from (Horne 2006).

Box 37.7 Key Steps in Improving Adherence to GC Replacement Therapy

1. **Provide a rationale for the need to take GC replacement and the various treatment adaptations**

   Provide patients and their families with a clear rationale for why they should take GC daily, emphasise the difference between a hormone replacement therapy and a steroid pharmacotherapy, and explain the need for dose adjustment in intercurrent illness and

prevention of adrenal crisis. Explain what diagnostic tests mean. Illustrations or other patient stories often help patients to understand and to recall the information received.

2. **Elicit and address concern about GC replacement and potential side effects**

   GC treatment in high doses is associated with a high prevalence of side effects, and these can affect patients' adherence as they increase their concerns and beliefs of harm from taking the medicine. Similarly, some patients may take more than the prescribed dose believing that more is better which can lead to adverse effects and treatment nonadherence. Advise patients of potential side effects from the start, how to recognise and deal with them. Emphasise that GC replacement is individualised and not a "one size fits all" treatment.

3. **Identify and address the practical barriers**

   Adopt a shared decision-making approach when planning GC replacement and develop an easy-to-follow managed care plan which can guide patients, their families, or parents of children with AI, on how to manage the daily GC regimen. Identify and address any barriers which may potentially prevent the patient from following this regimen, such as: Can they remember or are they able (external barriers) to take their tablets? What hours do they work? How do they get their prescriptions? Will the school teachers/nurses help? These are some of the factors that can inhibit adherence and are not always within the patient's control.

4. **Patient and family beliefs**

   Nonadherence may also be associated with concerns arising from more abstract beliefs about medications. They may come with preconceived misconceptions about steroid treatment. Some of my patients tell me they "*don't want to take hydrocortisone and get fat*". Adopt an empathetic and non-judgmental approach when eliciting and addressing these beliefs and emphasise that with appropriate monitoring and correct GC dose, complications can be minimised.

37.8 Glucocorticoid Replacement in Special Therapeutic Situations

37.8.1 Fertility and Pregnancy

Total cortisol concentrations start to rise in pregnancy and free cortisol also increases substantially in the third trimester from the 22nd week of gestation onwards. Hydrocortisone is recommended over cortisone acetate, prednisolone, or prednisone during pregnancy; dexamethasone should not be used because it is not inactivated in the placenta (Bornstein et al. 2016). Common AI symptoms (fatigue, nausea, hyponatraemia, vomiting) are difficult to differentiate in pregnancy, and it is recommended that hydrocortisone doses are increased based on individual patient assessment. It is also recommended that hydrocortisone dose should be increased by 50% in the third trimester (Arlt and Allolio 2003; Bancos et al. 2015; Bornstein et al. 2016).

In addition, the increased levels of serum progesterone in pregnancy exert an anti-mineralocorticoid action, but clinical assessment can be difficult due to overlapping unspecific symptoms of oedema and postural hypotension. Fludrocortisone should be adjusted if necessary according to blood pressure and serum sodium and potassium; while plasma renin is not accurate as it is physiologically increased during pregnancy. During delivery

(active phase of labour) parenteral hydrocortisone should be administered at doses similar to that used in major surgical stress (refer to Chap. 62 for more details) and after delivery hydrocortisone can be tapered back to pre-pregnancy doses within 2–4 days (Bancos et al. 2015; Bornstein et al. 2016).

37.8.2 Thyroid Dysfunction

Hyperthyroidism increases cortisol clearance and therefore in patients with AI and unresolved hyperthyroidism, GC doses should be doubled or tripled. In addition, thyroxine treatment should only be initiated once GC deficiency has been excluded or confirmed and GC replacement has been established (Arlt and Allolio 2003). Thyroxine can precipitate adrenal crisis in untreated hypocortisolism and the patient needs to be advised appropriately when reviewing their treatment regimen and adherence to medication.

37.8.3 Growth Hormone Deficiency in Adults

In growth hormone (GH) deficiency in adults, there is an increased 11β-HSD type 1 activity which results in increased cortisol tissue exposure (see Sect. 37.5.3). This is reduced after initiating GH treatment (high GH and IGF-1 levels enhance conversion of cortisol to cortisone, i.e. lower levels of active cortisol) which can unmask central hypoadrenalism and predispose the patient to AI and risk of AC. Therefore, the assessment of the HPA axis to confirm or exclude AI is mandatory prior to starting GH replacement (Filipsson and Johannsson 2009; Giavoli et al. 2004).

37.8.4 Increased Physical and Emotional Stress

In healthy subjects, in addition to the circadian profile, cortisol levels increase in response to stressful daily stimuli such extreme physical extortion or emotional distress. Patients with AI should take an extra dose of 5–10 mg prior to being exposed to the stressful situation (Grossman 2010; Quinkler and Hahner 2012). It is often difficult to define "stress" for individual patients and a detailed history would reveal fatigue, feeling unwell and light-headed, the same or the next day after exerting increased levels of stress. Examples include training and running a marathon, mountain biking, triathlon, moving to a new house, long flights, bereavement, or acute depression episodes. Short lasting stressor, such as exams, house work, or work-related meetings, do not normally require dose adaptation.

37.8.5 Prolonged Fasting or Shift Working

During the month of Ramadan, Muslims tend to fast, i.e. abstain from eating, drinking, and use of oral medication from predawn to sunset. This can put patients with AI at risk of dehydration, fainting, hypotension, or low glucose levels which can precipitate AC. A cross-sectional study of 180 patients with AI found that of the 91 patients who did fast, 67% developed complications such as asthenia, intense thirst, dehydration, and symptoms of hypoglycaemia; one patient was hospitalised with AC (Chihaoui et al. 2017). It is important that patients wanting to fast during Ramadan are well educated on the risks of fasting and given the option for alternative treatment. A longer acting formulations such as immediate-sustained release hydrocortisone (Plenadren® 20 mg) or prednisolone 4–5 mg at dawn before starting the fast is a preferred option during the fasting period.

Similarly, the cortisol circadian rhythm is misaligned in people who sleep outside a normal sleep cycle such as shift workers or during jet lag. Patients with AI who work shifts or travel between wide timezones should adapt their GC intake to their wake-sleep pattern (Quinkler and Hahner 2012), i.e. take first dose of hydrocortisone on waking up and the last dose no later than

5–6 h before sleep. Short acting hydrocortisone versus long-acting formulations is advisable to avoid exposure to cortisol during the sleep periods which can result in increased risk of glucose intolerance or impaired quality of sleep. The case study in Box 37.8 delineates the importance of adapting hydrocortisone intake during night working.

Box 37.8 Case Study of a Patient on Emergency Night Shifts

Richard is 54 and has SAI following pituitary surgery. He takes hydrocortisone 10 + 5 mg twice daily on waking up at 7 am and at 3 pm. He volunteers as coast guard and often is called on emergencies in the middle of the night. This can be quite stressful physically and emotionally. He described feeling exhausted the next day of such events and on one occasion he developed adrenal crisis for which he needed a hospital admission. We advised him to take 10 mg of hydrocortisone as soon as he is being called for duty and another 10 mg if he is out at sea for longer than 5 h. This helped him significantly to overcome fatigue post emergency duty he did not experience any further AC episodes.

37.8.6 Medications and Food Interactions with Glucocorticoids

Table 37.6 presents a list of drugs and food types that interact with GC and mineralocorticoids in AI (Arlt and Allolio 2003; Liu et al. 2013; Methlie et al. 2011). It is important to take a detailed history from patients on prescribed medication, including oral contraceptive pill, over the counter medications, supplements, herbal remedies, and foods that can decrease or increase concentrations of bioavailable cortisol.

37.9 Morbidity and Mortality Related to Glucocorticoid Replacement Therapy

AI was a fatal condition until cortisone was synthesised and used as life-saving treatment in 1949 by Kendall, Reichtein, and Sarrett (Arlt and Allolio 2003). Even though GC treatment has been available for over half a century, optimal replacement therapy in AI, negative acute and long-term health outcomes, including hospitalisations from AC, GC-induced morbidities, and impaired QoL, are still presenting major challenges.

37.9.1 Mortality and Risk of Adrenal Crisis

The standard mortality rate (SMR) for patients with AI is more than twofold compared to the general population (Tomlinson et al. 2001; Bergthorsdottir et al. 2006). AC is a factor that increases the mortality rate in patients with AI. SMR was significantly elevated in patients diagnosed before the age of 40 years; this was more pronounced in males with SMR 2.03 (CI 1.19–2.86) and younger patients were at higher risk of sudden death from AC (Erichsen et al. 2009). Approximately 1 in 100 patients with AI are expected to die from a potentially preventable AC (Hahner et al. 2015). One in 12 patients report at least one hospital admission per year related to AC (Forss et al. 2012; Hahner et al. 2015; White and Arlt 2010) and about 10% of patients with PAI who reported AC, had this on four or more occasions (Hahner et al. 2015) indicating that there is a subgroup of patients at high risk, and we need to identify and support them with relevant individualised treatment planning and education. AC is mainly precipitated by gastrointestinal infection and fever but also other stressful physical or emotional events (more details on AC mortality are discussed in Chap. 62).

Table 37.6 Common food and drug interactions with glucocorticoids

Interacting drug class (drug example) or food type	Interaction mechanisms (key: ↓-reduces; ↑-increases; GC-glucocorticoids)	Suggested management
Anticonvulsants (phenytoin, carbamazepine, phenobarbital)	Enhanced GC metabolism ↓ Efficacy of GC may persist for weeks following discontinuation of anticonvulsant	Monitor outcomes, may need GC dose adjustment (increase)
Anti-Tuberculosis (rifampicin, rifabutin)	Increases cortisol clearance ↓ Efficacy of GC which may persist for weeks following discontinuation of anti-tuberculosis drugs	Monitor outcomes, increase GC dose during rifampicin
Antifungal drugs (ketoconazole, itraconazole)	↑ GC bioavailability	May need antifungals or GC adjustment if show signs of GC overdose
Anticoagulants (warfarin)	May ↑ effects of anticoagulant and ↑ risk of GI bleeding	Monitor INR within 3–7 days, may need significant warfarin dose adjustment
Antibiotics (erythromycin, telithromycin, and clarithromycin)	May inhibit the metabolism of corticosteroids ↑ GC bioavailability	Monitor signs of GC over-replacement, may need to change antibacterial or adjust GC dose
Antidiabetic agents (insulins)	Antagonism of hypoglycaemic effect ↓ Efficacy of GC	↑ frequency of blood glucose monitoring adjust antidiabetic therapy
Antivirals (atazanavir, indinavir, ritonavir, saquinavir)	↑ GC bioavailability	Monitor signs of GC over-replacement
Oral oestrogen replacement and oral contraceptive pill	Increases circulating cortisol-binding globulin False high plasma cortisol levels	Oestrogen needs to be discontinued for diagnostic investigations
Mitotane	↓ concentration and increased metabolism and efficacy of bioavailable GC	Usual GC doses need to be at least doubled or tripled
Herbal remedies (St John's wort)	↑ GC bioavailability	Avoid or take at least 2–3 h later
Grapefruit, grapefruit juice, Liquorice	↑ GC bioavailability	Avoid or take at least 2–3 h later

37.9.2 Bone Metabolism

GCs affect the rate of bone remodelling; they impair the replication, differentiation, and function of osteoblasts, induce the apoptosis of mature osteoblasts and osteocytes, and increase osteoclastogenesis. Supraphysiological doses of GC are associated with a decrease in markers for bone formation and resorption, leading to osteoporosis (Canalis et al. 2007). Several studies found that patients with AI on GC replacement have lower bone mineral density (BMD) scores compared to the average population and that BMD decreases with increasing doses of hydrocortisone over 30 mg daily (Zelissen et al. 1994; Lovas et al. 2009; Schulz et al. 2016; Bjornsdottir et al. 2011). A population-based cohort study identified hip fractures in 6.9% of patients with PAI compared with 2.7% of controls although authors did not investigate association of fractures with GC dose (Bjornsdottir et al. 2011). Schulz et al. found that by reducing the total daily dose of hydrocortisone equivalent to 20–25 mg from 30 to 35 mg, values of BMD significantly improved 2 years later, and the risk of AC did not increase (Schulz et al. 2016). It is therefore important to remember that high doses of GCs have a detrimental effect on bone health (Johannsson et al. 2015) and replacement doses of hydrocortisone should be maintained generally to a total daily dose below 20–25 mg, where indicated. Patients should be reassured that the risk of AC will not increase if they adjust GC doses appropriately during increased stress and illness.

37.9.3 Blood Pressure, Glucose/Lipid Metabolism, and Body Composition

The physiologic circadian rhythm of cortisol affects fluctuations in glucose tolerance throughout the day. Abnormal glucose tolerance is therefore more common in patients with AI. This is especially important to keep in mind for patients with PAI and concomitant type 1 diabetes as insulin requirements, especially in the afternoon, are higher compared to patients with type 1 diabetes alone (Johannsson et al. 2015).

Patients with hypopituitarism and SAI are at higher risk of developing metabolic syndrome with a combination of hypertension, dyslipidaemia, central obesity, and insulin insensitivity (Johannsson et al. 2015). A large pharmacovigilance study of patients with hypopituitarism (N = 2424) treated with growth hormone, compared patients with and without ACTH deficiency. Patients with ACTH deficiency treated with a total daily dose of hydrocortisone-equivalent of 20 mg or more had an unfavourable metabolic profile with greater body mass index, waist circumference, serum levels of total cholesterol, triglycerides, and low-density lipoprotein; this was not observed in patients taking doses lower than 20 mg (Filipsson et al. 2006). Changes in body weight and blood pressure may also be a contributing risk factor to the increased prevalence of premature cardiovascular deaths in patients with AI (Tomlinson et al. 2001; Bergthorsdottir et al. 2006). Detrimental effects of over-replacement can be more significant in patients with SAI as there is often residual cortisol production and it is very important to plan for an individualised GC replacement regimen. The modified-release hydrocortisone also has a favourable profile with regard to body weight, glucose metabolism, and insulin insensitivity at equivalent total daily doses of hydrocortisone (Muller and Quinkler 2018; Johannsson et al. 2012).

37.9.4 Quality of Life (QoL) and Subjective Well-Being

AI has significant impact on patients' lives with 64% of them reporting impaired QoL, 40% absence from work/school every 3 months, and 38% at least one hospital admission annually (Forss et al. 2012). Almost a quarter of patients with AI receive disability pension compared to 4–10% of the general population (Lovas et al. 2002; Hahner et al. 2007). Delay in the diagnosis of AI has a negative impact on QoL; Bleicken found that patients who received a correct diagnosis within 3 months reported significantly better subjective health status compared to those for whom diagnosis was delayed (Bleicken et al. 2010b). Higher GC replacement doses are associated with a negative effect on the patient's QoL, although it is unclear if the increased dose itself diminishes QoL, or if the dose was increased by the clinician due to an impaired QoL. Two studies found that QoL decreased with increasing dose of GC and the worst QoL was reported by patients who took hydrocortisone-equivalent doses of more than 25 mg daily (Filipsson et al. 2006) and 30 mg daily (Bleicken et al. 2010a), respectively. This was more significant in patients with SAI. Additional hormone deficiencies in SAI may also impact on QoL and often patients increase the dose of GC to compensate for impaired QoL and fatigue caused by unoptimised concomitant deficiencies.

It is also important to remember that current conventional GC replacement therapy in patients with PAI does not restore the unphysiologically low cortisol levels in the night, particularly the last part of the night, which may reduce early morning glucose levels (Oksnes et al. 2015). Patients may complain of impaired quality of sleep and waking up with nausea, dizziness fatigue, and headaches, and it is important to discuss a GC therapy regimen that can combat these symptoms.

Validated questionnaires are useful in clinical practice to assess patient's QoL and agree on a

relevant care plan to respond to individualised needs. In addition, they can be used to track improvement or deterioration of QoL over time or post changes in the management of patient's care. The AddiQoL is a validated Likert scale questionnaire of 36 items with high internal validity and psychometric properties which make it a useful tool for use in clinical practice (Lovas et al. 2010).

37.10 Long-Term Monitoring of Patients with AI

The goal of treatment and follow-up for patients with AI is to restore normal well-being by optimising replacement therapy, to minimise or avoid complications from over- or under-replacement, and to minimise episodes of AC and avoid hospital admissions due to AC. Monitoring of replacement is mainly based on clinical symptoms but cortisol day curve may be useful and indicated when symptoms persist or when malabsorption of hydrocortisone is suspected (see case study in Box 37.5). Similarly, random cortisol levels are helpful to obtain evidence of adequate cortisol uptake (Bornstein et al. 2016) and to establish peak and trough levels, but they must only be interpreted with an accurate history of timing and dose of hydrocortisone and are not needed routinely.

Routine laboratory analyses and imaging are requested depending on diagnosis and cause of AI; these should include blood serum sodium and potassium levels for patients with PAI. In addition, surveillance for other autoimmune disorders, such as thyroid disease or type 1 diabetes, is necessary in patients with PAI given the increased prevalence of concomitant autoimmune disorders; genetic counselling should also be provided to patients with PAI due to monogenic disorders (Bornstein et al. 2016). Patients should be made aware and educated on possible symptoms related to other autoimmune disorders.

It is recommended that adults and children with PAI are seen by an endocrinologist or a healthcare provider, including nurses, with expertise in endocrinology at least annually. Infants should be seen at least every 3–4 months (Bornstein et al. 2016). There is no consensus regarding frequency of monitoring for patients with SAI as this depends on other concomitant comorbidities, but patients should be seen at a minimum 6–12 monthly (Fleseriu et al. 2016).

Patients should be examined and asked questions to evaluate physical and psychological (QoL, subjective health status) condition in relation to possible over-replacement or under-replacement and adverse effects from the GC therapy. A UK-wide study of patients with asthma showed a dissociation between patient-reported concerns and side effects about corticosteroid treatment and those perceived by physicians (Cooper et al. 2015). Medication side effects are strongly associated with nonadherence and treatment discontinuation. It is therefore important to take a detailed history of any possible side effects to the AI medication and address them accordingly; this should also include possible interactions with other concomitant medications, food and over-the-counter supplements and hormone deficiencies.

A holistic assessment will identify and support patients with medical but also psychosocial and educational needs. It is crucial to ensure that patients are familiar with and are provided with education on management of intercurrent illness and prevention of AC. Exploring and addressing all potential needs in a single consultation can however be time consuming for the nurse. It is also difficult to remember all relevant points relating to AI and GC treatment which need addressing, particularly if patients have other comorbidities or treatments. Consultation checklists are often useful toolkits which nurses can use to ensure a productive and effective consultation. On the other hand, there is a risk of "information overload" for patients or repeating what they already know to the detriment of missing out on information which patients really need.

It is useful to advise patients to come with a list of questions and concerns which can be addressed during each consultation and are pertinent to each individual's needs. There is however evidence to suggest that patients often do not know what to ask, believe that concerns are

not relevant to their condition or treatment, feel there is too little time to address everything, or feel embarrassed to disclose information such as nonadherence to medication or sexual dysfunction (Henselmans et al. 2015). To facilitate the process of consultations and to provide support for self-management, our research team developed a one-page questionnaire based on behavioural medicine, which can help patients identify concerns about their AI and GC replacement therapy (Box 37.9), adopting this way an individualised approach to patient care and treatment planning. The questionnaire is accompanied by a comprehensive patient information booklet designed to address the concerns identified in the questionnaire which patients can read before attending clinic. This is also used as an aid to stimulate further questions or help the patient to identify more needs. An online survey involving 100 patients with AI, members of the Pituitary Foundation in the UK, showed good acceptability of this consultation aid and booklet as a resource to support self-management in AI (Llahana et al. 2016).

Box 37.9 A Questionnaire to Identify and Address Individualised Patient Needs in the Treatment and Management of AI

This questionnaire was developed specifically to help with the management of cortisol replacement therapy for patients with adrenal insufficiency (AI). The questionnaire aims to get you thinking about the things that matter most to you about your AI and your cortisol replacement therapy. You may also be taking additional medications for AI and other conditions. However, please ONLY take into account your cortisol replacement therapy when answering these questions.

There are no right or wrong answers—simply answer the questions by ticking the relevant box if it applies to you. Use the answers to guide you to the most relevant sections of the accompanying booklet, specific to you and your needs. You can also use this questionnaire during your consultation with your doctor or nurse to focus your discussion on areas which you identified as a concern.

Section A: Managing Adrenal Insufficiency			
A1	I know how to adjust my cortisol replacement dose during illness	**Yes**	**No**
A2	I need help in managing an adrenal crisis	**Yes**	**No**
A3	I often feel tired during the day	**Yes**	**No**
A4	The quality of my sleep is impaired (I don't sleep well)	**Yes**	**No**
Section B: Medication (managing cortisol replacement therapy)			
B1	I am not sure why I need to take cortisol replacement therapy every day	**Yes**	**No**
B2	I am concerned about the side effects of my cortisol replacement therapy	**Yes**	**No**
B3	Having to take cortisol replacement therapy affects aspects of my life:		
	Travel	**Yes**	**No**
	Physical activities	**Yes**	**No**
	Family	**Yes**	**No**
	Social	**Yes**	**No**
	Work	**Yes**	**No**
	Other—please specify	**Yes**	**No**
B4	Having to take more than one dose every day is an inconvenience for me	**Yes**	**No**
Section C: Your way of taking cortisol replacement therapy			
C1	I sometimes/often miss my doses for a day or more	**Yes**	**No**
C2	I sometimes/often miss my second or third dose	**Yes**	**No**
C3	I sometimes/often take an extra dose just to feel better	**Yes**	**No**
C4	I don't take extra doses when I'm ill or have "sick days"	**Yes**	**No**
C5	I don't always take my dose(s) at the recommended times	**Yes**	**No**
Please include any additional information here			

Original version of the questionnaire and the patient booklet are available by request from Spoonful of Sugar, a behaviour-change consultancy in London, http://sos-adherence.co.uk/

37.11 The Role of Patient Advocacy Groups in Improving Patient Care and Education

Patient advocacy groups (PAGs) are a highly valuable resource for patients and their families, not just as a clinical and supportive tool, but by also enabling empowerment and enriching the relationship between patients, families, and their healthcare providers. The advent of social media, with websites and online support groups can add to this, and patients have a reliable and trusted resource for peer support. Most PAGs work very closely with clinical teams to develop evidence-based information and support clinical research. As seen in the example below, PAGs can form a useful resource and can reach patients and healthcare teams across the globe especially for rare conditions such as AI.

37.11.1 The Australian Addison's Disease Association Inc (AADAI)

Through an amazing amount of volunteer work by people across the nation, the Association has grown from just a handful of members to over 300 spread across this vast country. The goal of the AADAI is to:

- Educate the medical profession and the general public to have a higher awareness of Addison's disease and AI
- Supply up-to-date information to people living with Addison's disease/AI
- Create a caring network to give support for people with Addison's disease/AI

To provide the best possible information and support to people living with adrenal insufficiency, the association works closely with healthcare professionals, especially endocrine nurses and endocrinologists. All our online and print educational and resource materials are thoroughly reviewed before publication by our medical advisor; seminars are presented each year for people living with AI and these are strongly supported by key healthcare professionals.

Our quarterly member newsletter focuses on a range of support and medical information issues. These are written by people with medical expertise including our medical advisor and our pharmacy advisor. The website provides detailed information about materials we produce. These include new member packs: online and print information material and the regular newsletter. A telephone support service to help members find specific information is also offered by the AADAI President and the Secretary. To find out more about the AADAI, please visit our website at http://addisons.org.au.

37.12 Conclusions

AI is a life-threatening condition if not managed appropriately but with correct and individualised replacement therapy and adequate support and education, patients can lead a normal life. This is a chronic condition and the initial diagnosis will have a significant impact on how the condition is perceived by the patient and their families and especially for parents and their young children. Patients and their families require sensible day-to-day management plans, careful dosing regimens, and an action plan for times of illness, injury, or procedures. The endocrine nurse is a key person in supporting patients and families in the process of acceptance, understanding, and confidence to manage situations as they arise.

AI is a condition where mortality rate is high and a team approach and interdisciplinary collaboration in key to offering the best treatment options to improve patients' health outcomes and QoL. Patients with AI and their families need to gain an understanding about their condition and treatment, which can be very complex especially when dose titration is required during stress, intercurrent illness, and prevention of AC. Having an endocrine service with sound and knowledgeable endocrine nursing team can offer best treatment options in chronic disease condition such as AI. Endocrine nurses with advanced practice skills can utilise their specialist knowledge and excellent communication skills to tailor treatment options to meet individual needs of their patients.

Acknowledgments With special thanks to our patients for their case studies and to Grahame Collier from the Australian Addison's Disease Association Inc (http://addisons.org.au; email: secretary@addisons.org.au) for the information on their Patient Advocacy Group.

References

Arlt W. Chapter 8: Disorders of the adrenal cortex. In: Jameson JL, editor. Harrison's endocrinology. 4th ed. New York: McGraw Hill Education; 2017. p. 107–35.

Arlt W, Allolio B. Adrenal insufficiency. Lancet (London, England). 2003;361(9372):1881–93.

Aulinas A, Casanueva F, Goni F, Monereo S, Moreno B, Pico A, et al. Adrenal insufficiency and adrenal replacement therapy. Current status in Spain. Endocrinol Nutr. 2013;60(3):136–43.

Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216–26.

Barthel A, Willenberg HS, Gruber M, Bornstein SR. Chapter 102—Adrenal insufficiency. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, et al., editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: W.B. Saunders; 2016. p. 1763–74.e4.

Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab. 2006;91(12):4849–53.

Betman JEM. Parental grief when a child is diagnosed with a life threatening chronic illness: impact of gender, perceptions and coping strategies. University of Canterbury NZ. Thesis submitted for Doctor of Philosophy degree; 2006.

Bjornsdottir S, Saaf M, Bensing S, Kampe O, Michaelsson K, Ludvigsson JF. Risk of hip fracture in Addison's disease: a population-based cohort study. J Intern Med. 2011;270(2):187–95.

Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B, et al. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. Clin Endocrinol. 2010a;72(3):297–304.

Bleicken B, Hahner S, Ventz M, Quinkler M. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. Am J Med Sci. 2010b;339(6):525–31.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.

Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metabol. 2015;100(6):2171–80.

Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hubner C, Maher KT, Walker DM, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. J Clin Endocrinol Metab. 2006;91(10):3773–9.

Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–28.

Chapman SC, Llahana S, Carroll P, Horne R. Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. Clin Endocrinol. 2016;84(5):664–71.

Chihaoui M, Chaker F, Yazidi M, Grira W, Ben Amor Z, Rejeb O, et al. Ramadan fasting in patients with adrenal insufficiency. Endocrine. 2017;55(1):289–95.

Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. NPJ Prim Care Res Med. 2015;25:15026.

Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med. 2003;139(3):194–204.

El-Farhan N, Pickett A, Ducroq D, Bailey C, Mitchem K, Morgan N, et al. Method-specific serum cortisol responses to the adrenocorticotrophin test: comparison of gas chromatography-mass spectrometry and five automated immunoassays. Clin Endocrinol. 2013;78(5):673–80.

Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol. 2009;160(2):233–7.

Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology (Oxford, England). 2011;50(11):1982–90.

Filipsson H, Johannsson G. GH replacement in adults: interactions with other pituitary hormone deficiencies and replacement therapies. Eur J Endocrinol. 2009;161(Suppl 1):S85–95.

Filipsson H, Monson JP, Koltowska-Haggstrom M, Mattsson A, Johannsson G. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. J Clin Endocrinol Metab. 2006;91(10):3954–61.

Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(11):3888–921.

Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency—a worldwide patient survey. BMC Endocr Disord. 2012;12:8.

Frey KR, Kienitz T, Schulz J, Ventz M, Zopf K, Quinkler M. Prednisolone is associated with a worse bone min-

eral density in primary adrenal insufficiency. Endocr Connect. 2018;7(6):811–8.
Giavoli C, Libé R, Corbetta S, Ferrante E, Lania A, Arosio M, et al. Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. J Clin Endocrinol Metabol. 2004;89(11):5397–401.
Grossman AB. Clinical review: the diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab. 2010;95(11):4855–63.
Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol. 2013;169(6):R165–75.
Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. J Clin Endocrinol Metab. 2007;92(10):3912–22.
Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010;162(3):597–602.
Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100(2):407–16.
Henselmans I, Heijmans M, Rademakers J, van Dulmen S. Participation of chronic patients in medical consultations: patients' perceived efficacy, barriers and interest in support. Health Expect. 2015;18(6):2375–88.
Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest J. 2006;130(Suppl 1):65S–72S.
Horne R, Weinman J, Barber N, Elliot R, Morgan M. Concordance, adherence and compliance in medicine taking: a conceptual map and research priorities. London: National Institute for Health Research (NIHR) Service Delivery and Organisation (SDO) Programme; 2005.
Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104–15.
Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V, et al. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. Lancet Diabetes Endocrinol. 2018;6(3):173–85.
Johannsson G, Bergthorsdottir R, Nilsson AG, Lennernas H, Hedner T, Skrtic S. Improving glucocorticoid replacement therapy using a novel modified-release hydrocortisone tablet: a pharmacokinetic study. Eur J Endocrinol. 2009;161(1):119–30.
Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metabol. 2012;97(2):473–81.
Johannsson G, Falorni A, Skrtic S, Lennernas H, Quinkler M, Monson JP, et al. Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy. Clin Endocrinol. 2015;82(1):2–11.
Joseph RM, Hunter AL, Ray DW, Dixon WG. Systemic glucocorticoid therapy and adrenal insufficiency in adults: a systematic review. Semin Arthritis Rheum. 2016;46(1):133–41.
Koyama Y, Homma K, Hasegawa T. Urinary steroid profiling: a powerful method for the diagnosis of abnormal steroidogenesis. Endocrinol Metab. 2014;9(3):273–82.
Kwok MY, Scanlon MC, Slyper AH. Atypical presentation of shock from acute adrenal insufficiency in an adolescent male. Paediatr Emerg Care. 2005;21(6):380–3.
Lee AS, Twigg SM. Opioid-induced secondary adrenal insufficiency presenting as hypercalcaemia. Endocrinol Diabetes Metab Case Rep. 2015;2015:150035.
Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.
Llahana S, Philips D, Webber J, Chapman S, Carroll P, McBride P, et al., editors. Development and evaluation of the acceptability of new materials to address individualised needs to support self-management for patients with adrenal insufficiency Society for Endocrinology. Brighton: BES; 2016.
Lovas K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol. 2002;56(5):581–8.
Lovas K, Gjesdal CG, Christensen M, Wolff AB, Almas B, Svartberg J, et al. Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. Eur J Endocrinol. 2009;160(6):993–1002.
Lovas K, Curran S, Oksnes M, Husebye ES, Huppert FA, Chatterjee VK. Development of a disease-specific quality of life questionnaire in Addison's disease. J Clin Endocrinol Metab. 2010;95(2):545–51.
Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, et al. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clin Endocrinol. 2004;61(3):367–75.
Mendoza-Cruz AC, Wargon O, Adams S, Tran H, Verge CF. HPA axis recovered within 6-12 weeks of infant prednisolone therapy. J Clin Endocrinol Metab. 2013;98(12):E1936–40. https://doi.org/10.1210/jc.2013-2649.
Methlie P, Husebye EE, Hustad S, Lien EA, Lovas K. Grapefruit juice and licorice increase cortisol availability in patients with Addison's disease. Eur J Endocrinol. 2011;165(5):761–9.

Migeon CJ, Lanes R. Adrenal cortex: hypofunction and hyperfunction (Chpater 8). In: Lifshitz F, editor. Pediatric endocrinology. Growth, adrenal, sexual, thyroid, calcium and fluid balance disorders, vol. 2. 5th ed. New York: Informa Healthcare; 2009.

Miller W, Achermann JC, Fluck CE. The adrenal cortex and its disorders (Chapter 12). In: Sperling MA, editor. Pediatric Endocrinology. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2008.

Muller L, Quinkler M. Adrenal disease: imitating the cortisol profile improves the immune system. Nat Rev Endocrinol. 2018;14(3):137–9.

Murray RD, Ekman B, Uddin S, Marelli C, Quinkler M, Zelissen PM. Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity—data from the EU-AIR. Clin Endocrinol. 2017;86(3):340–6.

Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):217–23.

Neumann U, Whitaker MJ, Wiegand S, Krude H, Porter J, Davies M, et al. Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency. Clin Endocrinol. 2018;88(1):21–9.

Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, et al. Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2009.

Oksnes M, Bjornsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM, et al. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of Addison's disease: a randomized clinical trial. J Clin Endocrinol Metab. 2014;99(5):1665–74.

Oksnes M, Ross R, Lovas K. Optimal glucocorticoid replacement in adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2015;29(1):3–15.

Policola C, Stokes V, Karavitaki N, Grossman A. Adrenal insufficiency in acute oral opiate therapy. Endocrinol Diabetes Metab Case Rep. 2014;2014:130071.

Quinkler M, Hahner S. What is the best long-term management strategy for patients with primary adrenal insufficiency? Clin Endocrinol. 2012;76(1):21–5.

Quinkler M, Beuschlein F, Hahner S, Meyer G, Schofl C, Stalla GK. Adrenal cortical insufficiency—a life threatening illness with multiple etiologies. Dtsch Arztebl Int. 2013;110(51–52):882–8.

Quinkler M, Oelkers W, Remde H, Allolio B. Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2015;29(1):17–24.

Quinkler M, Ekman B, Marelli C, Uddin S, Zelissen P, Murray RD, et al. Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency. Endocr Connect. 2016;6(1):1–8.

Qureshi AC, Bahri A, Breen LA, Barnes SC, Powrie JK, Thomas SM, et al. The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol. Clin Endocrinol. 2007;66(5):632–5.

Rushworth RL, Chrisp GL, Dean B, Falhammar H, Thorpy DJ. Hospitalisation in children with adrenal insufficiency and hypopituitarism: is there a differential burden between boys and girls and between age groups? Horm Res Paediatr. 2017;88(5):339–46. https://doi.org/10.1159/000479370.

Salprietro V, Polizzi A, Di Rosa G, Romeo AC, Dipasqualw V, Morabito P, Chirico V, Arrigo T, Ruffieri M. Adrenal disorders and the paediatric brain: pathophysiological considerations and clinical implications. Int J Endocrinol. 2014. https://doi.org/10.1155/2014/282489. 15 pages.

Schulz J, Frey KR, Cooper M, Zopf K, Ventz M, Diederich S, et al. Reduction in daily hydrocortisone dose improves bone health in primary adrenal insufficiency. Eur J Endocrinol. 2016;174(4):531–8. https://doi.org/10.1530/eje-15-1096.

Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. Clin Endocrinol. 2016;84(1):17–22.

Stewart PM. Chapter 14: The adrenal cortex. In: Kronemberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th ed. Philadelphia: Saunders Elsevier; 2008. p. 445–503.

Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al. Association between premature mortality and hypopituitarism. Lancet (London, England). 2001;357(9254):425–31.

Uta N, WM J, Susanna W, Heiko K, John P, Madhu D, et al. Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency. Clin Endocrinol. 2018;88(1):21–9.

Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. BMJ (Clin Res Ed). 2012;345:e6333.

Whitaker M, Digweed D, Huatan H, Eckland D, Spielmann S, Johnson T, et al. Infacort, oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency. Endocr Rev. 2014;35.

White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol. 2010;162(1):115–20.

Zelissen PM, Croughs RJ, van Rijk PP, Raymakers JA. Effect of glucocorticoid replacement therapy on bone mineral density in patients with Addison disease. Ann Intern Med. 1994;120(3):207–10.

Key Reading

1. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216–26.

2. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.
3. Grossman AB. Clinical review: the diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab. 2010;95(11):4855–63.
4. Migeon CJ, Lanes R. Adrenal cortex: hypofunction and hyperfunction (Chapter 8). In: Lifshitz F, editor. Pediatric endocrinology. Growth, adrenal, sexual, thyroid, calcium and fluid balance disorders, vol. 2. 5th ed. New York: Informa Healthcare; 2009.
5. Arlt W. Disorders of the adrenal cortex (Chapter 8). In: Jameson JL, editor. Harrison's endocrinology. 4th ed. New York: McGraw Hill Education; 2017. p. 107–35.
6. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361(9372):1881–93.

Part VI

Female Endocrinology and Reproduction

Sofia Llahana and Gerard S. Conway

38 Anatomy and Physiology of the Female Reproductive System

Artemis Vogazianou

Contents

38.1 **Introduction** 740

38.2 **Ovarian Follicular Development** 741

38.3 **Puberty** 742
38.3.1 Age of Onset of Puberty 743
38.3.2 The Physical Changes of Puberty 744

38.4 **The Menstrual Cycle** 745
38.4.1 Menstruation 747
38.4.2 The Proliferative Phase 747

38.5 **Pregnancy** 749

38.6 **Menopause** 751

38.7 **Conclusions** 752

References 752

Abstract

At birth, a female baby already has her lifetime supply of oocytes that will be released through ovulation when she is sexually matured, between menarche and menopause. Puberty initially starts with thelarche (breast budding) around the age of 11 and menarche usually starts at an average age of around 13. Initial cycles are anovulatory, but subsequently a single egg is released each cycle during a woman's fertile years. The menopause is the end of menstrual cycles. Puberty, menstrual cycles, and establishment of pregnancy are controlled by the hypothalamic, pituitary, and ovarian hormones. Following the menopause, the ovaries are no longer able to produce enough oestrogen and ovarian failure results in a rise in the gonadotropins.

A. Vogazianou (✉)
Department of Diabetes and Endocrinology,
University College Hospital, London, UK
e-mail: artemisvogazianou@nhs.net

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_38

Keywords
Female reproduction · Puberty · Menstrual cycle · Ovulation · Menopause · Pregnancy Menarche · Thelarche · Tanner Stages

Abbreviations

17-OHP	17-Hydroxyprogesterone
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
FSH	Follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
IGF-1	Insulin-like frowth factor-1
IHH	Idiopathic hypogonadotropic hypogonadism
IVF	In vitro fertilisation
KISS1	Kisspeptin
LDL	Low-density lipoprotein
LH	Luteinising hormone
LPD	Luteal phase deficiency
PCOS	Polycystic ovarian syndrome

Key Terms

- **Puberty:** the period of 2–3 years prior to menarche when secondary sexual characteristics begin to develop and the final and most substantial growth spurt occurs, with fusion of the epiphyseal plates.
- **Thelarche:** breast budding
- **Adrenarche:** the onset of androgen hormone release from the matured adrenals
- **Pubarche:** the development of pubic hair
- **Menarche:** first period
- **Climacteric:** the 6–7 years leading up to the menopause, when menstrual cycles tend to be irregular and anovulatory
- **Menopause:** last period

Key Points

- The female endocrine reproductive system relies on the relationship between the hypothalamus, pituitary, and ovaries.
- A female is born with a finite number of oocytes 300–400 of which will be released through ovulation during a woman's reproductive life.
- Puberty starts around the age of 11 with breast budding and it's complete around 2.5–3 years later with the onset of menarche (first period). Initial cycles are irregular and tend to be anovulatory.
- Pregnancy is maintained by hormones released by the corpus luteum and subsequently the placenta and have a wide range of functions, including immune suppression in the mother to prevent loss of the pregnancy through immune mediated response.
- Climacteric starts in the late 40s and lasts around 6–7 years. Menstrual cycles during this period are also irregular and tend to be anovulatory until the menopause (last period).

38.1 Introduction

The female reproductive system is controlled by hormones secreted by the hypothalamus, the anterior pituitary, and the ovaries, which interact with each other in a dynamic way. Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus in response to neuronal activity in the limbic region of the brain, which is predominantly influenced by emotional and sexual factors.

GnRH is a small polypeptide which regulates the release of gonadotropins: luteinising hormone (LH) and follicle-stimulating hormone (FSH), by the gonadotrope cells of the anterior pituitary gland. The gonadotropins are then released in short bursts every 1–4 h, stimulating cells in the ovaries to synthesise and secrete oestradiol and progesterone, which in turn promote and regulate menstruation and ovulation.

High concentrations of oestrogen and progesterone in the serum provide negative feedback to the hypothalamus and therefore inhibit further secretion of GnRH (Fig. 38.1). Please refer Chap. 12 in Part III for more details on the menstrual cycle regulation by FSH and LH and the hypothalamic-pituitary and gonadal feedback.

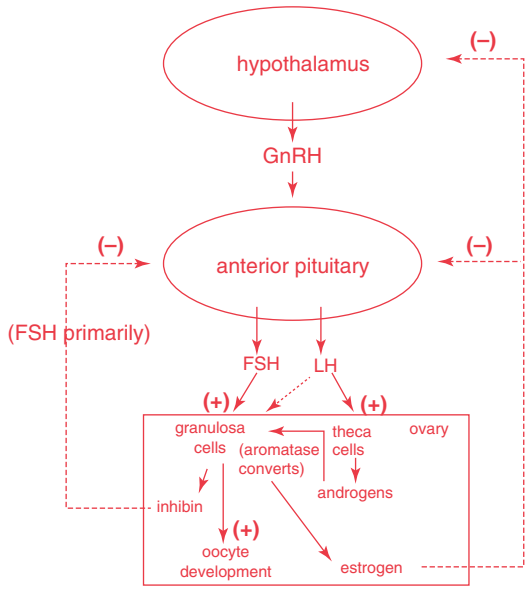


Fig. 38.1 The interplay between the hypothalamic, anterior pituitary, and ovarian hormones

GnRH released by the hypothalamus stimulates FSH and LH secretion by the anterior pituitary which in turn stimulates the secretion of oestrogen and progesterone by the ovaries.

FSH receptors only exist on the granulosa cell membranes of the ovaries and as the numbers of granulosa cells increase in late luteal phase, in parallel to increasing FSH levels, so does oestradiol secretion by granulosa cells, in response to FSH levels. The formation of LH receptors on the granulosa cells is stimulated by FSH, in the presence of oestradiol, facilitating these cells to also become responsive to LH and allowing secretion of small amounts of progesterone and 17-hydroxyprogesterone (17-OHP). These two hormones then have a positive feedback on the pituitary gland which has been primed by the high oestrogen levels to release LH.

FSH also stimulates the production of aromatase and 3β-hydroxysteroid dehydrogenase (3β-HSD). LH receptors are found on the theca cells of the ovaries, which produce androstenedione and small amounts of testosterone. Androstenedione is transported to the granulosa cells and converted into oestrone, by aromatase, and eventually converted to oestradiol by 17-β-hydroxysteroid dehydrogenase type I (17-β-HSD).

FSH also stimulates the secretion of inhibin from the granulosa cells, which suppresses FSH. There are two types of inhibin: *Inhibin B*, which reaches a peak in the early- to mid-follicular phase and has a second peak at ovulation and *Inhibin A*, which reaches its peak in the mid-luteal phase. Inhibin secretion is inhibited by GnRH and enhanced by insulin-like growth factor-1 (IGF-1).

Only unbound oestrogen and progesterone are biologically active, stimulating the target organs of the reproductive system (breasts, uterus, and vagina). However, most of the oestrogen and progesterone found in the bloodstream are bound to proteins. In general, oestrogen and progesterone inhibit the release of GnRH but around the time of ovulation stimulate gonadotropin secretion. Oestrogen and progesterone also have both direct and indirect effects on other major tissues including bone, skin, and muscle.

38.2 Ovarian Follicular Development

A female baby is born with a fixed number of germ cells (egg precursors). Germ cells begin as primordial oogonia that proliferate significantly by mitosis during the 3rd and 4th months of gestation of a female foetus. Around the same time, some oogonia begin to undergo meiosis, which halves the number of chromosomes to 23, resulting in the formation of haplotype primary oocytes. Beginning after the 4th month of gestation, oogonia and later oocytes are spontaneously lost by apoptosis, through a process called atresia. Eventually more than 99.9% of the original oogonia are lost by the time of birth.

The surviving germ cells (haplotype oocytes), become arrested in the meiotic prophase and are termed primary oocytes. By the 7th month of gestation, each viable primary oocyte develops a surrounding layer of granulosa cells, forming a primordial follicle. All primordial follicles, each containing its primary oocyte, potentially available for future reproduction during a woman's life are, therefore, present in the ovaries at birth. The so-called ovarian reserve is the number of oocytes or primordial follicles in a woman's ovaries at any given time, and this can be estimated by direct ultrasound visualisation or through measuring Mullerian hormone, with the latter being less reliable but often more widely used.

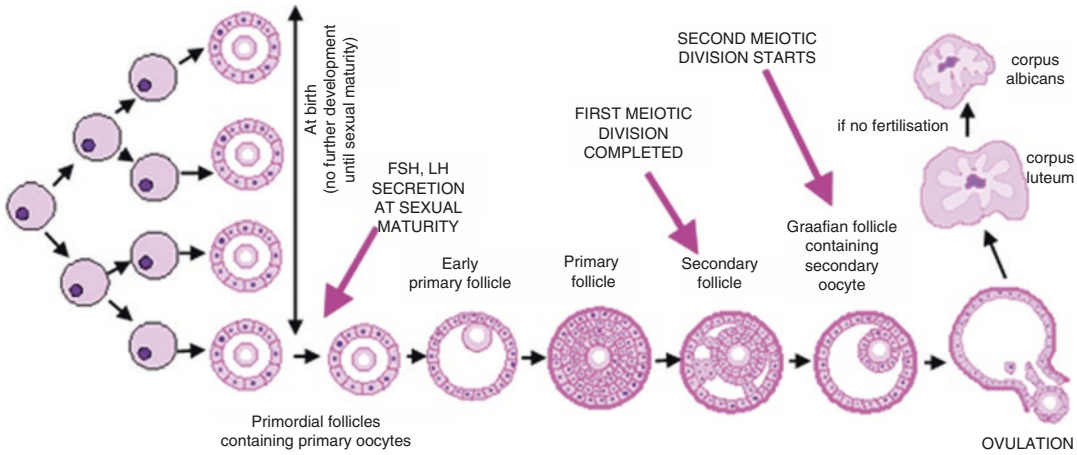


Fig. 38.2 Ovarian follicular development. Used with permission from Professor Michelle Peckham, Professor of Cell Biology, University of Leeds, School of Molecular and Cellular Biology, accessed via http://www.histology.leeds.ac.uk/female/FRS_ova.php

At birth, the ovary contains approximately 400,000 primordial follicles, with each one containing a primary oocyte. Primary oocytes do not undergo any further mitotic divisions and remain arrested in the **prophase** stage of **meiotic division I**, until after sexual maturity has been reached.

Following sexual maturity (completion of puberty), FSH and LH cause these primordial follicles to develop. In each ovarian cycle, FSH induces follicular growth in the ovaries and about 20 primordial follicles are activated to begin maturation and recruited for accelerated growth. Usually in each cycle, only one follicle fully matures and achieves ovulation (Fig. 38.2). This dominant follicle releases its oocyte at ovulation and promotes atresia of the other previously recruited follicles (please refer to ovulatory and luteal phases below for more details).

Over a woman's reproductive life, only ~300–400 eggs will be released, through ovulation.

38.3 Puberty

Puberty is the sequence of events that occur in order for a child to eventually sexually mature into an adolescent and eventually become an adult, acquiring adult physical characteristics and the capacity to reproduce. It is associated both with the development of secondary sexual characteristics, as well as rapid growth in height and weight.

Circulating LH and FSH levels are elevated at birth but fall to low levels within the first few months of life and remain low until puberty (see Fig. 38.7). The reproductive target organs undergo very few qualitative changes before the onset of puberty. While puberty primarily involves a series of physical transformations, the process can also have an effect on the psychosocial, behavioural and emotional development of the adolescent.

The mechanisms that initiate puberty are still not entirely clear. Central influences that regulate release of GnRH include neurotransmitters and peptides (e.g. gamma-aminobutyric acid [GABA] and kisspeptin [KISS1]). These and other factors may inhibit release of GnRH during childhood, but then initiate its release, to induce puberty in early adolescence (Watanabe et al. 2014; Zeydabadi Nejad et al. 2017).

Kisspeptin (KISS1), is a neuropeptide that acts upstream of GnRH-neurons and appears to be critical for maturation and function of the reproductive axis (Watanabe et al. 2014). Kisspeptins bind to and activate the G protein-coupled receptor, GPR54, located on the GnRH-neurons of the hypothalamus (Zeydabadi Nejad et al. 2017). Kisspeptin appears to be one of the

major activators of the GnRH-neurons and a prerequisite for the onset of puberty and maintenance of normal reproductive function. Abnormal KISS1/GPR54 system has been reported in both animal models and patients with certain forms of infertility, e.g. idiopathic hypogonadotropic hypogonadism (IHH) and polycystic ovarian syndrome (PCOS) (Zeydabadi Nejad et al. 2017; Seminara et al. 2003).

38.3.1 Age of Onset of Puberty

The timing of the onset of puberty is not completely understood and is most likely determined by a number of different factors. The age of onset of puberty varies amongst individuals and the rate of development through different stages is influenced by different factors. Over the last 150 years, the age at which puberty starts has been decreasing, primarily because of improved health and nutrition (Knudston and McLaughlin 2018; MedicineNET 2018). This trend has plateaued over the last few decades and occurs on average between the ages of 10 and 14 in girls (MedicineNET 2018).

Both environmental and genetic factors are involved in the onset of puberty. One theory is that reaching a critical weight or body-fat composition may be crucial, in the onset of puberty. It may be, that the overall earlier onset of puberty in the general population in recent years is related to the increase in childhood obesity (MedicineNET 2018).

Puberty appears to occur later than average in severely underweight and undernourished girls (Rosenfield et al. 2009). These observations suggest that there is a critical body weight or amount of fat necessary for the onset of puberty (Knudston and McLaughlin 2018; MedicineNET 2018; Soliman et al. 2014; Rosenfield et al. 2009), which may in turn vary between individuals or populations (Herman-Giddens et al. 1997).

Leptin, a hormone produced by the adipocytes, has been suggested as one possible mediator of the timing of puberty (MedicineNET 2018; Gueorguiev et al. 2001). In research studies, animals deficient in leptin, did not undergo puberty and administration of replacement leptin, resulted in restoration of puberty (Gueorguiev et al. 2001). Furthermore, girls with higher concentrations of leptin are known to have an increased percentage of body fat and an earlier onset of puberty than girls with lower levels of leptin. The concentration of leptin in the blood is known to increase just before puberty in both boys and girls.

Many other factors can influence the onset and progression of puberty. Genetic factors are also involved, as puberty occurs earlier in girls whose mothers underwent sexual maturity earlier. It has also been found that the onset of puberty also occurs earlier in girls who live in urban areas (Ameade and Garti 2016; Choudhary et al. 2016) and in blind girls (Flynn-Evans et al. 2009), but the underlying mechanisms for these observations are still unclear. The age of onset of puberty also varies amongst ethnic groups (Herman-Giddens et al. 1997) and it has been suggested that perhaps this is secondary to the mechanisms discussed above, i.e. genetic factors and body-fat composition.

38.3.1.1 Precocious Puberty

Precocious puberty is when a child enters puberty too early, often defined as before the age of 8 in girls and before the age of 9 in boys. It leads to the development of the secondary sexual characteristics because of increased sex steroid production, either because of aberrant gonadotropin stimulation or because of intrinsic disease of the ovaries or adrenals. The classic definition of sexual precocity is the appearance of secondary sexual characteristics before the age of 8 years in girls, but this cut-off may vary in ethnic minorities. The overall incidence of sexual precocity in America is estimated around 1:5000 to 1:10,000 with a female preponderance of around 10:1 (http://www.endotext.org). For more details, refer to the Chap. 4 in the Paediatric Part I of the textbook. Early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion is the most common mechanism and it is usually idiopathic but it can rarely be due to serious conditions such as hypothalamic tumours.

38.3.1.2 Pubertal Delay

The guidelines for initiating an evaluation of girls with pubertal delay are as follows (http://www.endotext.org):

- If there is no breast development by the age of 13 years
- If there is absence of menarche by the age of 14 years in the presence of hirsutism or if there is a history suggestive of an eating disorder or excessive exercise or an outflow abnormality
- If there is absence of menarche by the age of 15 years

These guidelines should be used in context of the patient circumstances and presentation.

In more than 90% of cases, delayed puberty is due to constitutional delay in growth and puberty. It, therefore, occurs in children who are otherwise healthy but have slower physical development than average. Typically, these children will be shorter than other children of the same age, they are often thin and there's a family history of delayed puberty. Sometimes delayed puberty and growth can be secondary to a chronic illness (e.g. Crohn's disease or cystic fibrosis), malnutrition (e.g. malabsorption), excessive exercise (e.g. competition athletes), or physical and psychological stress.

38.3.2 The Physical Changes of Puberty

Early in puberty, the hypothalamus becomes less sensitive to the inhibitory actions of oestrogen and progesterone on GnRH-release. This results in an increase in the release of GnRH, which in turn stimulates gonadotropin (LH and FSH) secretion. Gonadotropin secretion then stimulates production of the sex hormones, primarily oestrogen, which drives the development of secondary sexual characteristics.

Adrenarche occurs when a child's adrenal cortex starts to secrete adrenal androgen precursors and ultimately an increase in the production of the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS). Adrenarche occurs several years before the onset of puberty and is thought to stimulate pubic and axillary hair growth (Novello and Speiser 2018). DHEA, a weak androgen agonist, is the most abundant product of the adrenal cortex and is thought to be responsible for the clinical signs of pubarche (first appearance of pubic hair) by conversion to more potent androgens, testosterone, and dihydrotestosterone. DHEA becomes sulphated outside the adrenals to DHEAS, which is a stable marker for adrenal androgenic activity. Pubarche is the physical manifestation of androgenic hormone production and includes the development of pubic and axillary hair, adult body odour, and acne.

In general, there is a typical pattern in the physical changes that an individual undergoes during puberty, and the sequence of events tends to be fairly predictable (please refer to Chap. 4 in Paediatric Part I in the textbook). In most girls, the first sign of puberty is thelarche (breast budding) which is the beginning of breast development, and occurs at an average age of approximately 11 years. Pubic hair growth typically begins next, followed by the growth of axillary hair. However, in a minority of girls, pubic hair growth begins before breast development. The growth spurt tends to peak after the appearance of pubic and axillary hair.

Menarche (the onset of menstruation) usually happens after all the other physical changes and occurs approximately 2.5–3 years after the first signs of the onset of puberty. An underlying growth spurt also occurs in parallel to puberty, which peaks immediately before or around the time of the menarche. Body habitus changes, body fat increases and the pelvis and hips widen, partly due to accumulation of fat in the hips and thighs (Fig. 38.3). The growth spurt is limited after menarche, as the epiphyses fuse. Menstrual cycles are usually irregular at menarche and can take up to 5 years (average 2–3 years) to become regular.

The sequence of changes in puberty is referred to as the sexual maturity rating or Tanner stages, named after Tanner, a physician who in 1969 published a description of the sequence of physical changes that occur during

puberty (Figs. 38.3 and 38.4). The Tanner stages are determined by the development of secondary sex characteristics and encompass changes in the size and appearance of the external genitalia, the development of pubic hair, and breast development in girls from thelarche (breast budding) to adult female breast development. Tanner stages allow doctors to classify the extent of development of sex characteristics into five distinct steps ranging from stage 1 (pre-pubertal) to stage 5 (mature adult type) (Marshall and Tanner 1969; Novello and Speiser 2018).

Immediately after the start of menarche, there is a temporary period with anovulatory cycles. Several studies have shown this period of anovulatory cycles tends to be longer as the age at menarche increases (Hosokawa et al. 2012; Lee et al. 2013; Apter 1996). Therefore, girls who experience menarche before the age of 12 have a more rapid onset of ovulatory menstrual cycles than girls whose menarche started later (Apter 1996). Furthermore, studies have shown that 50% of adolescent girls whose first menstruation was after the age of 13 will not ovulate regularly over the next 4.5 years (MedicineNET 2018).

38.4 The Menstrual Cycle

Menstruation is the periodic discharge of blood and disintegrated endometrium, from the uterus through the cervix and vagina. It is caused by the rapid drop in progesterone and oestrogen levels secondary to reduced production from the ovaries, which takes place during each cycle if egg fertilisation, implantation, and pregnancy don't occur.

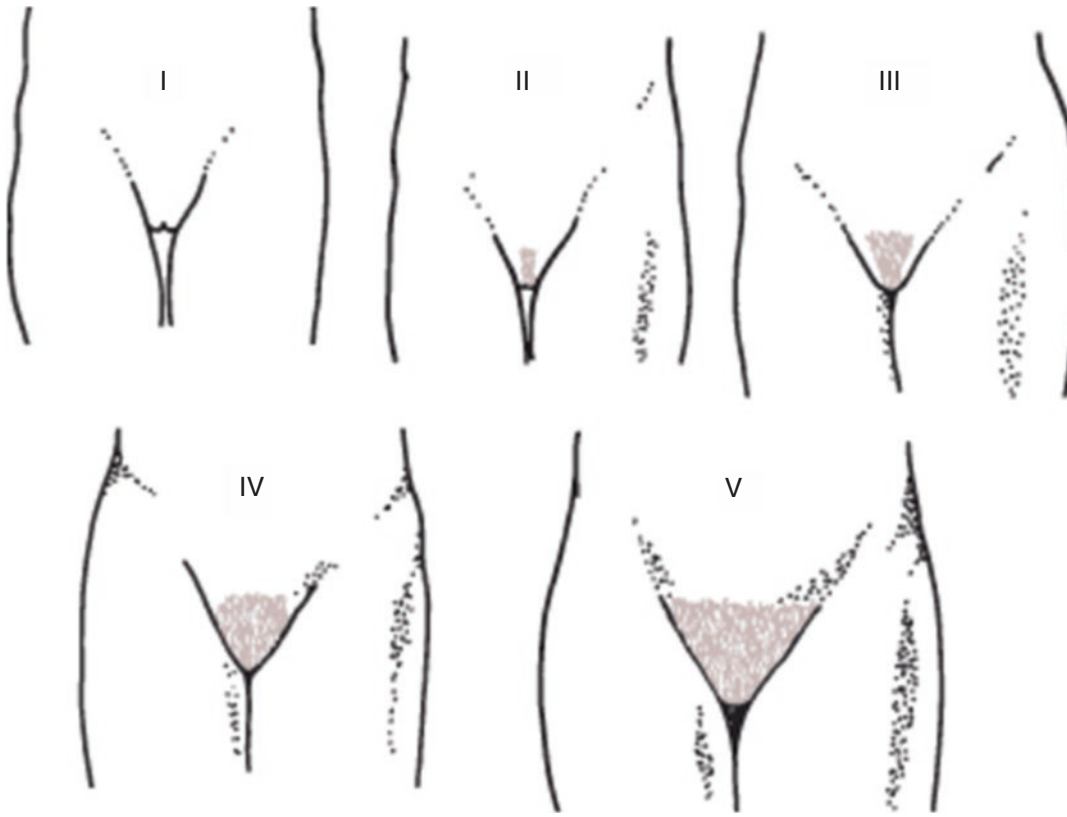


Fig. 38.3 The Tanner Stages I–V for pubic hair development in girls (Marshall and Tanner 1969)

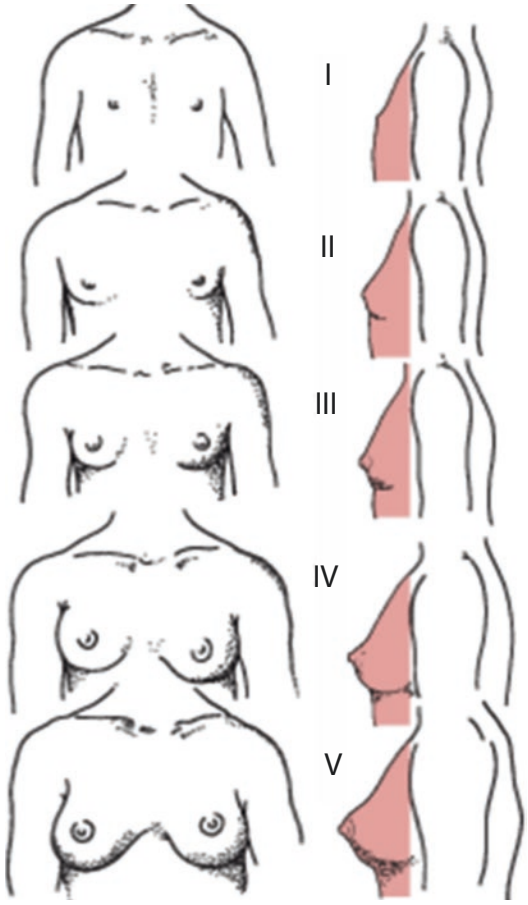


Fig. 38.4 The Tanner Stages I–V for breast development in girls. Used with permission from Marshall WA, Tanner JM: Variations in patterns of pubertal changes in girls. Arch Dis Child 1969;44:291–303

Menstruation occurs throughout a woman's reproductive life in the absence of pregnancy. Menopause is the permanent cessation of menstruation.

The average duration of bleeding is around 5 (normal range 3–7) days. The average blood loss per cycle is around 30 mL (normal range 15–80 mL) and is usually maximal on the second day. Menstrual blood does not usually clot (unless bleeding is very heavy), probably because of fibrinolysin and other factors that inhibit clotting (Dockeray et al. 1987). Menorrhagia is the term used to describe heavy blood loss which can be because of a number of different reasons, e.g. uterine fibroids, clotting disorders.

The median menstrual cycle length is 28 days (usual range 21–35 days in adult women; 21–45 in adolescents). In general, menstrual cycles are longer and most variable in the years immediately after menarche and immediately before menopause, when ovulation is less regular. Irregular periods are more likely to be anovulatory. Based on consensus the menstrual cycle begins and ends with the first day of menstruation (day 1).

As depicted in Fig. 38.5, oestrogen levels are low in childhood and start rising during prepuberty, reaching a critical level at puberty when the development of secondary sexual characteristics begins. The peak level induces the onset of menarche and remains at a similar level with

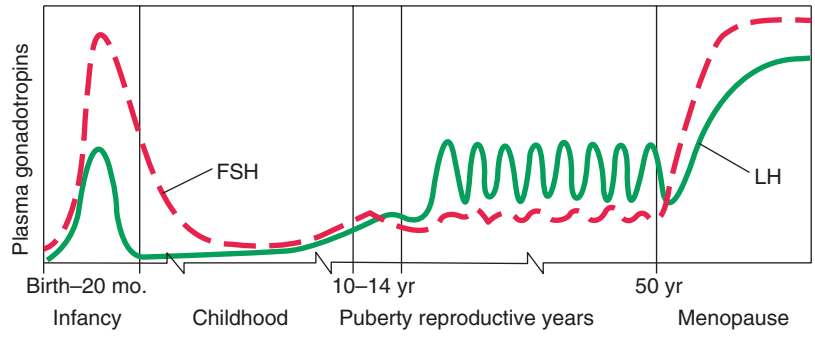


Fig. 38.5 LH and FSH levels throughout a female's life [Hall JE (2017) Disorders of the female reproductive system, chapter 13. In: Jameson JL (Eds) Harrison's Endocrinology, 4th Edition, McGraw Hill Education, New York, pages 192–201]

cyclical fluctuations during the woman's reproductive years, in synch with ovulation. Ovulation is irregular in the first few years following menarche and the few years prior to menopause (climacteric). After the menopause, the levels decline rapidly due to ovarian failure and lack of further production. The hormonal changes of the menstrual cycle cause ovulation and induce changes in the endometrium that prepare it for implantation.

38.4.1 Menstruation

The menstrual cycle is generally 28 days and includes the following phases: menstruation, proliferative phase, follicular phase and luteal phase.

Days 1–4 of the cycle is menstruation:

At the start of the menstrual cycle, the endometrium is lost and its hormonal support is withdrawn. Myometrial contraction, which can be painful, is accompanied by vasoconstriction to reduce blood loss.

38.4.2 The Proliferative Phase

Days 5–13 of the cycle are the proliferative phase:

The proliferative phase of the menstrual cycle can be sub-divided into two ovarian stages: follicular (pre-ovulatory) and luteal (post-ovulatory) phases.

The dominant follicle develops through a three-stage process: (1) Recruitment, (2) Selection, and (3) Dominance. Recruitment takes place during days 1–4 of the menstrual cycle, when FSH leads to recruitment of several follicles from the available cohort of non-proliferating follicles. Between days 5–7 of the cycle, a single follicle is selected amongst the recruited follicles, for ovulation and the remaining follicles undergo atresia. By the 8th day of the cycle, one follicle becomes dominant and promotes its own growth, suppressing the maturation of the other ovarian follicles thus becoming the dominant matured follicle, which subsequently releases its ovum in the process of ovulation (Fig. 38.6).

38.4.2.1 The Follicular Phase

This phase is the most variable in terms of length. During the early follicular phase (the first half), the recruited follicles become larger.

The gonadotrope cells in the anterior pituitary contain little LH and FSH at this stage. Oestrogen and progesterone levels are also low. However, pulses of GnRH from the hypothalamus stimulate LH and FSH release by the anterior pituitary. Overall, FSH secretion increases slightly, stimulating growth of the recruited follicles, with slower subsequent rise in circulating LH levels (1–2 days after the peak in FSH). The recruited ovarian follicles are eventually able to produce oestradiol which in turn stimulates the synthesis of LH and FSH but also inhibits their secretion, via a negative feedback mechanism. This usually results in only one follicle maturing and one ovum being released into the fallopian tube.

During the late follicular phase (second half), the follicle selected for ovulation matures and accumulates granulosa cells, which secrete hormones.

The antrum of the follicle enlarges with follicular fluid, reaching a size of approximately 18–20 mm immediately before ovulation. The levels of the gonadotropins decrease, with FSH being markedly more affected than LH. From this point on, the levels of FSH and LH begin to diverge because oestradiol inhibits FSH secretion more than LH secretion, but also because the developing follicles produce inhibin, a hormone which inhibits FSH secretion (Fig. 38.1), but not LH secretion (Berga and Naftolin 2012). Furthermore, the half-life of LH is around 20–30 min, whereas that of FSH is much longer at 2–3 h. Levels of oestrogen, particularly oestradiol, rise exponentially.

As the oestradiol levels continue to rise and reach their maximum, a positive feedback effect on the hypothalamus and pituitary, causes LH levels to rise sharply and ovulation follows.

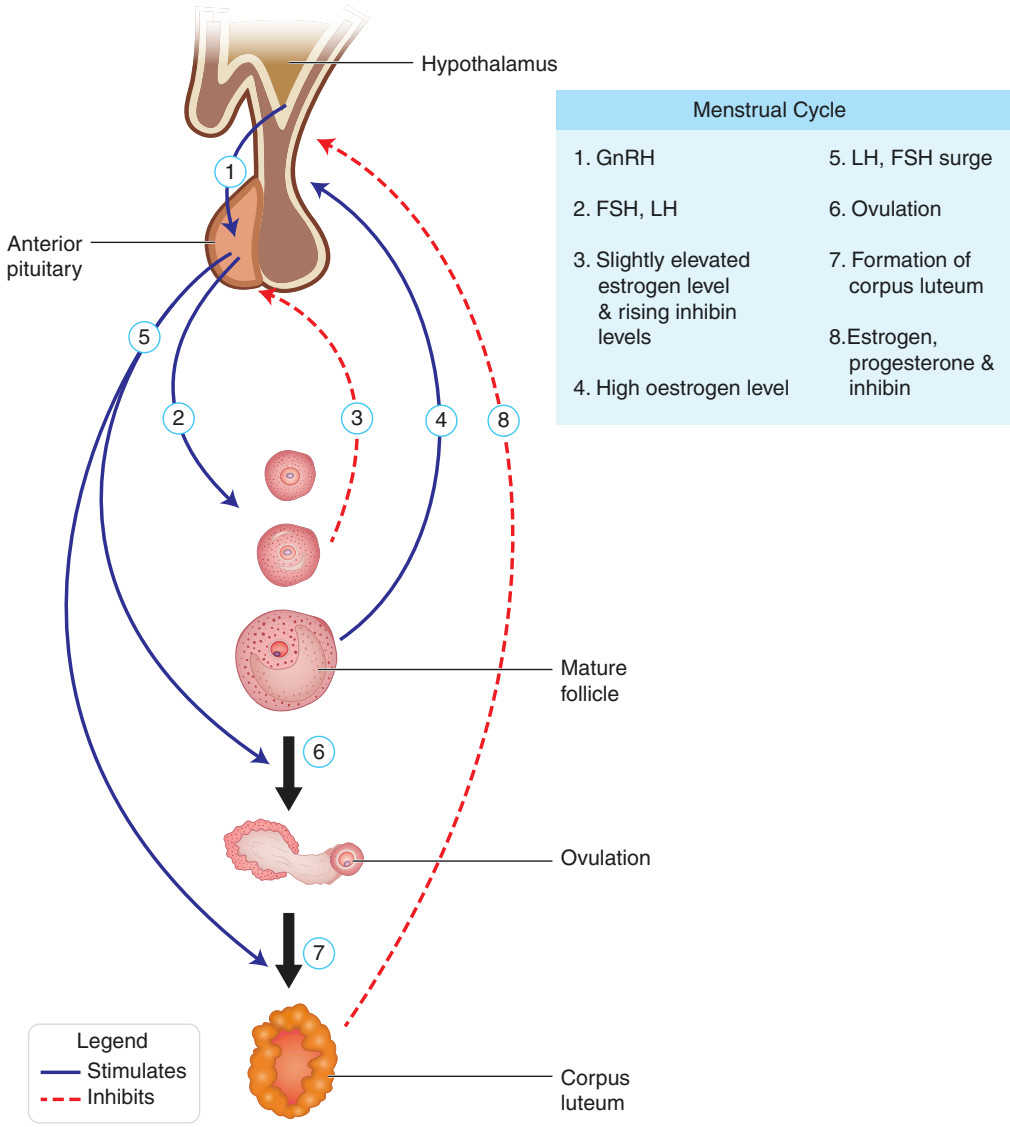


Fig. 38.6 Regulation of menstrual cycle and ovulation in the hypothalamic-pituitary-ovarian axis

Oestradiol levels usually peak as the ovulation begins. Progesterone levels also begin to increase. The LH stored in the pituitary is released in massive amounts in a process called the "LH surge", which occurs over 36–48 h. There is a smaller increase in FSH.

The LH surge occurs primarily because the high levels of oestradiol trigger LH secretion by the gonadotrope cells of the pituitary, via a positive feedback mechanism. The LH surge is also stimulated by GnRH and progesterone. The LH surge stimulates the release and activation of enzymes that initiate breakdown of the wall of the follicle and release of the now mature ovum within about 16–32 h. The LH surge also triggers completion of the first meiotic division of the oocyte within about 36 h. During the LH surge, the oestradiol levels decrease, but progesterone levels continue to rise (Fig. 38.6).

38.4.2.2 Luteal Phase

After releasing its ovum, the dominant follicle transforms into the corpus luteum. The length of this phase is the most consistent, averaging 14 days (range: 11–17 days). If pregnancy doesn't occur within these 14 days, the corpus luteum degenerates. A shortened luteal phase may indicate luteal phase deficiency (LPD) and a proposed diagnostic criterion for LPD is a shortened luteal phase of <9 days. However, a short luteal phase can occur in up to 5% of healthy fertile women which is often comparable to the luteal phase seen in the infertile population (Mesen and Young 2015).

The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg/day 6–8 days after ovulation. Progesterone stimulates development of the endometrium (the lining of the uterus), which is necessary for implantation of the zygote, should fertilisation occur and establishment of pregnancy. Progesterone is thermogenic, leading to an increase in the basal body temperature of about 0.5 °C.

During most of the luteal phase, the levels of circulating oestradiol, progesterone, and inhibin are high and negative feedback on the pituitary causes a reduction on the LH and FSH levels. Eggs can survive about 12–24 h after release (and sperm can live for 3–5 days). If pregnancy does not occur, the egg disintegrates and progesterone levels fall. About 12–16 days later, tissues from the lining of the uterus are expelled as menstrual bleeding and the cycle starts again. If pregnancy doesn't take place, oestradiol and progesterone levels fall late in the luteal phase and the corpus luteum degenerates, into the corpus albicans. If implantation does occur, the corpus luteum does not degenerate and remains functional in early pregnancy, with the support of human chorionic gonadotropin (hCG) that is produced by the developing embryo.

38.5 Pregnancy

During the luteal phase, progesterone stimulates the endometrium to change from proliferative to secretory form, which is very vascular and composed of spiral arteries. The glandular secretory endometrium secretes chemokines, growth factors, and cell adhesion molecules, all of which establish and maintain a favourable environment for implantation.

After ovulation and fertilization, the zygote (fertilised egg) remains in the ampulla of the fallopian tube for up to 3 days and undergoes a sequence of cell divisions, differentiation and eventually forms the morula (the group of cells from the dividing zygote). This process is independent of the hormones in the fallopian tube and uterus and can be performed in vitro during in vitro fertilisation (IVF). The morula then travels along the isthmus to the uterus, in a process that takes around 10 h and enters the uterus as an embryo. It continues to develop and 3–6 days after fertilisation, it becomes a blastocyst and floats in the endometrial cavity.

The blastocyst secretes several substances that improve the chances of implantation via enhanced maturation of the endometrium. These also render the endometrium more receptive to an imminent implantation. The success of implantation relies on the precise synchronisation between the developing blastocyst and the maturing endometrium. The blastocyst then becomes implanted into the thickened endometrium and implantation is complete (Fig. 38.7).

After implantation is initiated, the embryo actively secretes human chorionic gonadotropin (hCG), which stops the corpus luteum from disintegrating into the corpus albicans. This allows the corpus luteum to continue producing progesterone and therefore maintains the thickened endometrium for continued gestation. The main hormones produced by the corpus luteum are progesterone, 17 β-progesterone, oestradiol, and androstenedione. Low-density lipoprotein (LDL) cholesterol is the main precursor of these steroid hormones. The function of the corpus luteum naturally begins to decline between sixth and seventh week of gestation. The production of progesterone gradually shifts from the corpus luteum to the developing placenta, over a few days in a process called the "luteal-placental transition period", which occurs at approximately the seventh to ninth weeks of gestation.

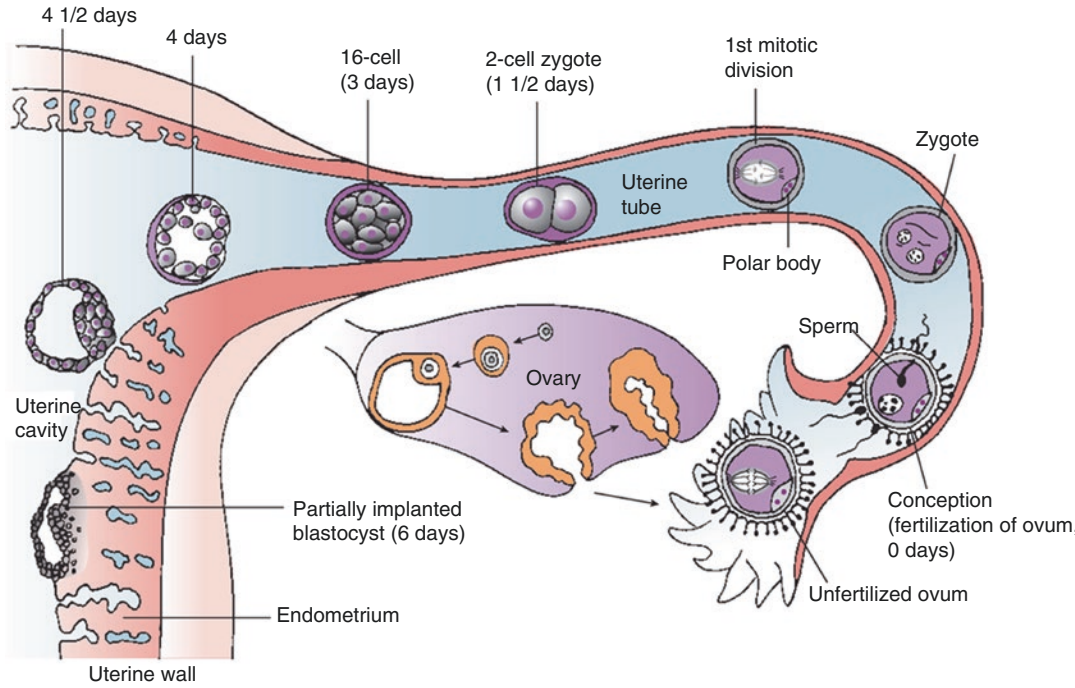


Fig. 38.7 The fertilisation and implantation stages

This process is vital for maintaining a viable pregnancy, as progesterone is the most important hormone as it can single-handedly maintain an early pregnancy that would be aborted if the corpus luteum was to be lost prematurely. Progesterone can be given as an injection to women pregnant through IVF from an egg donor to maintain the pregnancy, in the absence of a corpus luteum, during the first trimester until the secretion of progesterone is established by the placenta (Sauer et al. 1990). Similarly, in patients with corpus luteum dysfunction, exogenous progesterone is frequently administered until around the tenth week of gestation (Mesen and Young 2015; Sauer et al. 1990).

The outer blastomere cell layer of the blastocyst is known as the trophectoderm, and they can be identified at as little as 5 days following fertilisation. These cells eventually form the placenta. The main structural and functional units of the placenta are the chorionic villi, which increase in number during the first trimester of pregnancy. The villi provide a large surface area for absorption and nutrient and gaseous exchange between the mother and foetus. The maternal blood is delivered via the spiral arteries, circulates through the intervillous space, whilst the foetal blood moves in the core of the chorionic villi of the villous vessels. The foetal and maternal blood therefore never mix.

The trophoblasts are key cells within the chorionic villi, and they have the ability to multiply, invade, migrate, and differentiate through aggregation and fusion. By 10 days after fertilisation, the invading trophoblasts form two separate layers. The inner layer is called the cytotrophoblasts which are individual and rapidly dividing cells. The outer, thicker layer is known as the syncytiotrophoblasts which is a syncytial layer of multinucleate cells that line the placental villi of the foetal side of the intervillous space.

The syncytiotrophoblasts appear to be present in two distinct forms, each of which appears to produce either hypothalamic-like hormones: GnRH, CRH, and TRH or pituitary-like hormones: hCG, ACTH, and human chorionic thyrotropin (hCT). The Syncytiotrophoblasts are therefore the main site of hormone production in the placenta.

Due to their large surface area and the fact that they line the intervillous space, the hormones are directly released into the maternal blood stream, almost exclusively and at much higher concentrations compared to the foetal circulation.

The decidua (the endometrium during pregnancy) is a site of maternal hormone production, which maintains and protects the pregnancy from the mother's immune system. Cortisol secreted by the decidual endometrium in synergy with the foetal progesterone and hCG suppresses potential immunological rejection. The decidua also produces decidual prolactin which is a peptide hormone with identical chemical and biological properties to the pituitary prolactin and its production is induced by progesterone. It is released into the amniotic fluid and is not affected by administration of dopamine agonists (e.g. Bromocriptine and Dopamine) as its control is not dopamine dependent. It reduces the permeability of the amnion in the foetal to maternal direction and therefore regulates fluid and electrolyte movement through the foetal membranes. Pituitary prolactin is also secreted in the foetal circulation (by the foetal pituitary) and the maternal circulation (by the maternal pituitary) and these are both suppressed by maternal ingestion of Dopamine agonists.

Relaxin is a peptide hormone produced by the corpus luteum (in pregnant women only), the placenta, decidua, and chorion. Its main function in the mother appears to be with ripening (softening) the cervix, inhibiting uterine contractions and relaxing the pubic symphysis in preparation for labour. In the foetus, it binds to the foetal membranes, increases cytokine levels which in turn activate matrix metalloproteinases, and ultimately leads to a cascade of events that result in the rupture of membranes.

38.6 Menopause

This is a natural event that marks the end of spontaneous ovulation in a woman's life and therefore the ability to reproduce. The average age in the western world is 51 years (http://www.endotext.org). The classical symptoms of hot flashes, vaginal irritation, sleep disturbance, fatigue, and weight gain are most likely due to oestrogen deficiency. The symptoms are unique to each individual and vary markedly, with some women experiencing few or no symptoms and other women being majorly affected.

Menopausal transition (climacteric) usually starts in the late 40s and lasts around 5–7 years, with gradually reduced ovarian function. It is characterised by erratic ovarian oestradiol production and irregular length of menstrual cycle. FSH levels increase due to reduced inhibin produced by the granulosa cells. An FSH > 10 mIU/mL measured between 2–5 days of the cycle indicates ovarian aging (http://www.endotext.org). Oestradiol levels gradually become lower and lower and eventually secretion stops. The post-menopausal ovary no longer produces oestradiol but continues to produce androstenedione and testosterone at pre-menopausal levels. Oestrone produced via peripheral aromatisation of androstenedione is then the main circulating oestrogen.

While age at menopause ranges from 49–52 years, cigarette smokers can undergo menopause 1–2 years earlier compared to non-smokers (Gold et al. 2001).

Menopausal symptoms can be alleviated by the temporary replacement of oestrogen either orally or using patches. However, unopposed oestrogen action can lead to endometrial hypertrophy and ultimately increases the risk of endometrial cancer and therefore unless a woman has undergone a hysterectomy, she should be treated with combined oestrogen and progesterone preparations or have topical progesterone administration in the form of an intrauterine device, as well as the oestrogen replacement (please refer Chap. 41 in Part VI). The typical blood results of a post-menopausal woman is low oestrogen due to primary ovarian failure and high gonadotropins (LH and FSH), as the negative feedback of oestrogen has been removed. Initially, FSH and LH are high in the neonatal period, but by the age of 2, they drop, until a gradual increase during puberty. There is cyclical release during the fertile years and increase substantially in the post-menopausal period (Fig. 38.5), due to ovarian failure which results in low levels of oestrogen and therefore loss of negative feedback.

38.7 Conclusions

This chapter presented a summary of the anatomy and physiology of the female reproduction. It describes hormonal changes and how this influences the development of sexual characteristics and ovulation in a female throughout their lifetime.

References

Ameade EP, Garti HA. Age at menarche and factors that influence it: a study among Female University Students in Tamale, Northern Ghana. PLoS One. 2016;11(5):e0155310.

Apter D. Hormonal events during female puberty in relation to breast cancer risk. Eur J Cancer Prev. 1996;5:476–82.

Berga S, Naftolin F. Neuroendocrine control of ovulation. Gynecol Endocrinol. 2012;28(Suppl 1):9–13.

Choudhary S, Khichar S, Dabi D, Parakh M, Dara PK, Parakh P, Vyas S, Deopa B. Urban rural comparison of Anthropometry and Menarcheal Status of Adolescent School going girls of Jodhpur, Rajasthan, India. J Clin Diagn Res. 2016;10(10):SC08–12. Epub 2016 Oct 1.

Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. Eur J Obstet Gynecol Reprod Biol. 1987;24(4):309–18.

Flynn-Evans EE, Stevens RG, Tabandeh H, Schernhammer ES, Lockley SW. Effect of light perception on Menarche in Blind Women. Ophthalmic Epidemiol. 2009;16(4):243–8.

Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001;153(9):865–74.

Gueorguiev M, et al. Leptin and Puberty: a review. Pituitary. 2001;4(1–2):79–86.

Herman-Giddens ME, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997;99:505–12.

Hosokawa M, Imazeki S, Mizunuma H, Kubota T, Hayashi K. Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985. BMC Womens Health. 2012;12:19.

Knudston J, McLaughlin JE. Female reproductive endocrinology. 2018. https://www.msdmanuals.com/professional/gynecology-and-obstetrics/female-reproductive-endocrinology/female-reproductive-endocrinology. Accessed 16 June 2018.

Lee SE, Yang JY, Lee JH, Kim HW, Kim HS, Lee HJ, Oh JY, Sung YA. Relationship of age of menarche on anthropometric index and menstrual irregularity in late adolescent girls in Seoul. Ann Pediatr Endocrinol Metab. 2013;18(3):116–21.

Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child. 1969;44:291–303.

MedicineNET. Reproductive Health. 2018. https://www.medicinenet.com/reproductive_health/article.htm#menstruation_and_menopause. Accessed 16 June 2018.

Mesen TB, Young SL. Progesterone and the luteal phase. A requisite to reproduction. Obstet Gynecol Clin N Am. 2015;42(1):135–51.

Novello L, Speiser PW. Premature adrenarche. Pediatr Ann. 2018;47(1):e7–e11.

Rosenfield RL, et al. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.

Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. N Engl J Med. 1990;323:1157–60.

Seminara SB, et al. The GPR54 gene as regulator of puberty. N Engl J Med. 2003;349(17):1614–27.

Soliman A, De Sanctis V, Elalaily R. Nutrition and pubertal development. Indian J Endocrinol Metab. 2014;18(Suppl 1):S39–47.

Watanabe M, Fukuda A, Nabekura J. The role of GABA in the regulation of GnRH Neurons. Front Neurosci. 2014;8:387.

Zeydabadi Nejad S, Ramezani Tehrani F, Zadeh-Vakili A. The role of Kisspeptin in female reproduction. Int J Endocrinol Metab. 2017;15(3):e44337.

39 Assessment and Management of Women with Polycystic Ovary Syndrome (PCOS)

Rhonda Garad, Soulmaz Shorakae, and Helena Teede

Contents

39.1 **Introduction** 756

39.2 **Epidemiology** 756

39.3 **Pathophysiology** 756

39.4 **Diagnostic Criteria (Rotterdam Criteria)** 756
39.4.1 PCOS and Obesity 757
39.4.2 Clinical Features 759
39.4.3 Reproductive Features 759
39.4.4 Metabolic Features 759
39.4.5 Psychological Features 759

39.5 **Diagnosis and Investigations** 760

39.6 **Presentation of PCOS at Different Life Stages** 760
39.6.1 Young Women (<20 Years) 760
39.6.2 Adult Women (Reproductive Years) 760
39.6.3 Peri/menopausal Women 760

39.7 **Patient-Centred Care Model** 760
39.7.1 Key Patient Messages Once Diagnosis Established 761

39.8 **Management of Hyperandrogenism** 761

R. Garad (✉)
Knowledge Translation in Polycystic Ovary Syndrome (PCOS), Monash Centre for Health Research and Implementation (MCHRI), School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, Australia
e-mail: rhonda.garad@monash.edu

S. Shorakae
Monash Centre for Health Research and Implementation (MCHRI), School of Public Health and Preventative Medicine, Monash University, Clayton, VIC, Australia
e-mail: soulmaz.shorakae@monash.edu

H. Teede
Monash Centre for Health Research and Implementation (MCHRI), Monash Partners, Clayton, VIC, Australia
e-mail: helena.teede@monash.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_39

39.9 **Management of Reproductive Features** 761
39.9.1 Therapeutic Benefits of Metformin in PCOS 762
39.9.2 Preconception and Early Pregnancy Care 762
39.10 **Early Screening and Management of Metabolic Complications** 762
39.10.1 Metabolic Risk Management in PCOS (Next Section Will Be Put in Table Format) 763
39.11 **Conclusions** 768
39.12 **Online Resources** 768
References 768

Abstract

Polycystic ovary syndrome (PCOS) is a complex, common endocrine condition affecting reproductive aged women with a reported prevalence of between 8 and 13%, depending on the diagnostic criteria and the population studied. Diagnosis, based on Rotterdam criteria, commonly requires two of the three following features: oligo/amenorrhoea, polycystic ovaries on ultrasound, biochemical/or clinical hyperandrogenism, with exclusion of other aetiologies. Nurses are ideally situated to provide evidence-based care and education within an interdisciplinary model to optimise the health outcomes of women with PCOS.

PCOS affects health and well-being over the lifespan. The presentation of PCOS can be heterogeneous with reproductive (hyperandrogenism, anovulation, and subfertility), metabolic (dyslipidaemia, type 2 diabetes, and CVD risk factors), and psychological features (depression, anxiety, and poor self-esteem). Women with PCOS are also predisposed to weight gain, which in turn increases PCOS prevalence and exacerbates its severity. PCOS is underpinned by intrinsic insulin resistance. Obesity exacerbates insulin resistance, and lifestyle modification alleviates this feature.

Despite the high prevalence of PCOS many women with PCOS remain undiagnosed, clinical practice is inconsistent, psychological issues are neglected, and there is little focus on lifestyle modification and chronic disease prevention with most services targeting fertility and offering costly assisted reproductive technology. In addition, women report dissatisfaction with diagnosis experiences, poor quality information, and inadequate support.

Given the multi-system dimensions of PCOS and duration of impact over the lifespan, PCOS places a large financial burden on health systems with affected women also suffering the social costs of stigmatisation and isolation, largely due to non-conformity with societal expectations relating to femininity and fecundity. In addition, due to the diversity of PCOS health impacts, affected women may be marginalised within the health system and often fall between the gaps in a specialty-focused health care system, with knowledge gaps among practitioners and, inconsistency in care delivered. In the primary care sector, health practitioners report feeling confused and ill equipped to manage PCOS, listing PCOS as the highest priority for education in women's health. With women feeling isolated, disempowered, and underserviced, PCOS places a personal burden on affected women and their significant others, and highlights the lack of systemic, evidence-based responsiveness to their needs. This chapter provides an overview of PCOS for endocrine nurses who can play a critical role in providing evidence-based, person-centred care, within an interdisciplinary, biopsychosocial model of care.

Keywords

Polycystic ovary syndrome · Metabolic syndrome · Subfertility · Hyperandrogenism Menstrual irregularity · Emotional well-being Lifestyle management

Abbreviations

AMH	Anti-Müllerian hormone
BMI	Body mass index
FAI	Free androgen index
FSH	Follicle stimulating hormone
GnRH	Gonadotropin-releasing hormone
LH	Luteinising hormone
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone binding globulin
T	Testosterone

Key Terms

- **Body image:** is the way a person may feel, think, and view their body including their appearance.
- **Disordered eating:** refers to eating and weight-related symptoms and can include behavioural, cognitive, and emotional factors.
- **Emotional well-being:** a broad subjective concept encompassing; feelings, behaviour, relationships, goals, and personal strengths. Well-being may manifest differently due to sociocultural and individual factors.
- **Hirsutism:** excessive hair growth (face, stomach).
- **HRQoL:** Health-Related Quality of Life is a multidimensional (physical, psychological, social) and subjective concept related to a variety of patient outcomes.
- **Hyperandrogenism:** is characterised by excessive production and/or secretion of androgens.
- **Metabolic syndrome:** is a clustering of risk factors such as excess abdominal weight, lipid abnormalities, hypertension, and elevated glucose levels that are underpinned by the pathophysiological causes of insulin resistance associated with central adiposity.
- **Psychosexual dysfunction:** encompasses sexual problems or difficulties that have a psychological basis.

Key Points

- PCOS is a highly prevalent, complex, heterogeneous condition with reproductive, metabolic, and psychological features.
- It is under-recognised with up to 70% of affected women undiagnosed. This lack of recognition leads to significant delays in diagnosis and inconsistent management practices with affected women reporting unsatisfactory diagnosis experiences and inadequate support and information provision.
- Emotional well-being and increased metabolic risks are often under-recognised in PCOS and ethnic differences are often poorly appreciated.
- Subfertility is a prevalent feature of PCOS with approximately 75% of PCOS-related subfertility due to anovulation, yet with simple medical assistance the majority of women with PCOS can attain desired family size.
- Insulin resistance is a cardinal feature in PCOS, affecting 75% of lean women and 95% of obese women, contributing to an increased risk of impaired glucose metabolism and chronic diseases such as diabetes, obesity, and CVD risk factors.
- There is a bi-directional relationship between PCOS and obesity. Weight loss is a highly effective way to reduce the severity of PCOS symptoms and reduce long-term health risks. Healthy lifestyle (diet, exercise, and reduction of harmful behaviours such as smoking) is the first-line treatment for symptom management and prevention of chronic diseases.
- A holistic, person-centred approach within a biopsychosocial model of care is recommended, with a primary focus on a healthy lifestyle, emotional well-being, and prevention of chronic diseases.

39.1 Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting reproductive aged women (Yilmaz et al. 2018). It is a prevalent, complex condition with a heterogeneous range of reproductive, metabolic, and psychological symptoms. The condition is undiagnosed in up to 70% of affected women and key features such as a psychological burden and metabolic risks are under-recognised. Women with PCOS report dissatisfaction with diagnosis experiences, poor quality information, and inconsistent management practices. To achieve optimal health outcomes for women with PCOS a holistic, person-centred approach implemented within a biopsychosocial model of care is recommended.

39.2 Epidemiology

PCOS is increasingly recognised as a condition affecting women across the lifespan with hyperandrogenic symptoms (acne, hirsutism) most evident in adolescents and increased metabolic risks (diabetes, central obesity, and CVD risk factors) more prominent later in life. The prevalence of PCOS ranges from 8 to 13% depending on the criteria used to diagnose the condition (March et al. 2010; Boyle et al. 2012; Yildiz et al. 2012). Women at higher risk of developing PCOS include those who are overweight, and those with a family history of PCOS or type 2 diabetes (T2DM).

39.3 Pathophysiology

The pathophysiology of PCOS is not fully understood despite the identification of a genetic predisposition (Fig. 39.1). Studies have shown women with a positive family history for PCOS are at increased risk of developing the condition, with up to 80% heritability (Kahsar-Miller and Azziz 1998). Hyperandrogenism and insulin resistance, caused by both genetic and environmental factors, are the key hormonal features underpinning the pathophysiology of PCOS (Teede et al. 2011). Insulin resistance is present in up to 85% of women with PCOS, including lean and obese women (Stepto et al. 2013) and hyperandrogenism is present in 60–80% (Teede et al. 2011). In addition, alterations in hormonal signalling is evident with increased gonadotropin releasing hormone (GnRH) and luteinising hormone (LH) pulse frequency and increased LH to follicular stimulating hormone (FSH) ratio, resulting in impaired follicular development and increased ovarian androgen production. Also, hyperinsulinaemia, through the gonadotropic action of insulin on follicular cells, further exacerbates these hormonal derangements (Azziz et al. 2016).

Note: The current name—polycystic ovary syndrome—is increasingly recognised as redundant with moves afoot to rename the condition to more accurately reflect the underpinning pathophysiology.

39.4 Diagnostic Criteria (Rotterdam Criteria)

PCOS is diagnosed based on excess androgens (clinical or biochemical hyperandrogenism), menstrual irregularity (secondary to ovulatory dysfunction), and polycystic ovarian morphology (PCOM) on ultrasound.

The Rotterdam diagnostic criteria (Fig. 39.2) highlights the refined diagnostic criteria in adolescents, which require both hyperandrogenism and irregular cycles, with ultrasound now not recommended for diagnosis within 8 years of menarche, owing to overlap with normal reproductive physiology.

Patient Quote 1

"When I found out that what was happening to me had a name and was fairly common I was greatly relieved. Up to that point, I thought I was I going crazy. When I asked my doctor she just it was nothing to worry about and just stop eating so much. I felt very isolated".

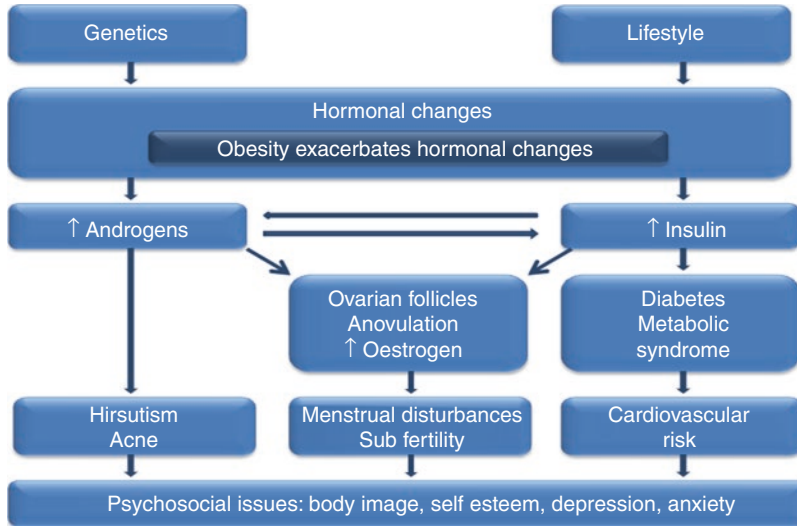


Fig. 39.1 The aetiological, hormonal, and clinical features of polycystic ovary syndrome (Teede et al. 2011)

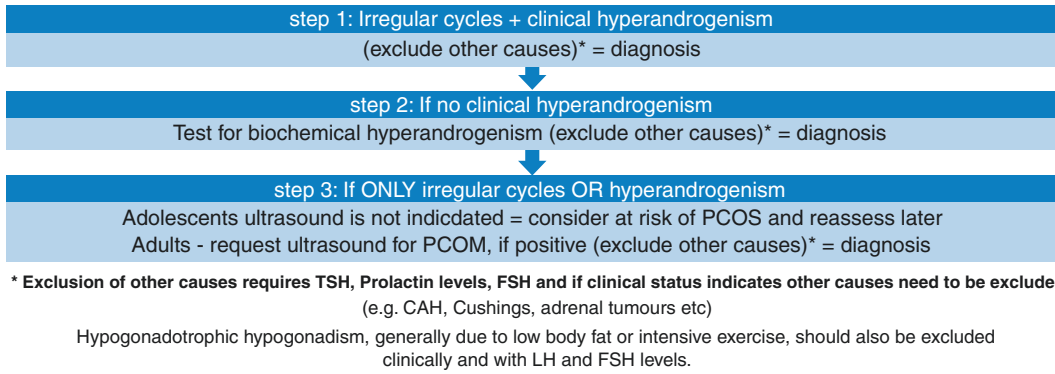


Fig. 39.2 The refined Rotterdam diagnostic criteria

39.4.1 PCOS and Obesity

There is a strong bi-directional relationship between PCOS and obesity. Whilst PCOS occurs independently of obesity, there is an increased prevalence of obesity in women with PCOS. In turn, there is an increased prevalence of PCOS as BMI increases, with obesity exacerbating metabolic, reproductive, and psychological features of PCOS (Teede et al. 2013; Lim et al. 2013). Studies have shown that women with PCOS have a higher calorie intake and a more sedentary lifestyle than women without PCOS (Moran et al. 2013). Further research is required into the biopsychosocial drivers of obesity such as increased hunger signalling and/or the impact of emotional well-being on lifestyle habits. Mechanistically, insulin resistance and hyperandrogenism are both exacerbated by obesity with adipose tissue producing pro-inflammatory signals mediating insulin resistance and hyperandrogenism. Moreover, decreased production of sex hormone binding globulin (SHBG) associated with obesity and insulin resistance results in increased levels of free circulating androgens and hyperandrogenism. Whilst a higher body mass index (BMI) is a common feature in women with PCOS, there is a need for vigilance in order not to miss the diagnosis of PCOS in lean women.

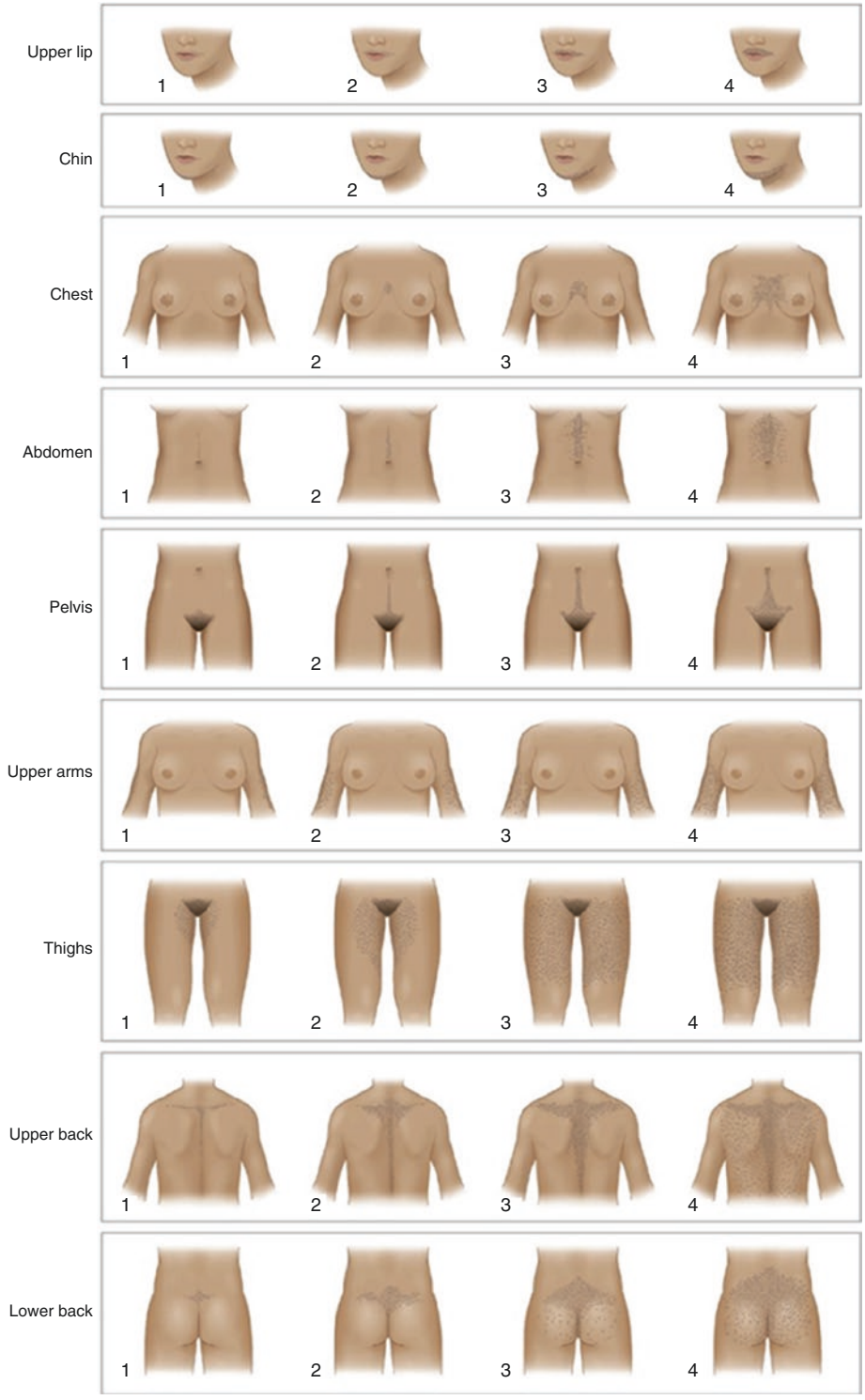


Fig. 39.3 Hirsutism scoring scale of Ferriman and Gallwey. Figure used with permission from Ehrmann DA (2017) Hirsutism, Chapter 17. In: Jameson JL (Eds) Harrison's Endocrinology, 4th Edition, McGraw Hill Education, New York, pages 226–231 (Figure 17-1). Permission also obtained from original source: Hatch, R., Rosenfield, R. L., Kim, M. H. & Tredway, D. 1981. Hirsutism: implications, aetiology, and management. *Am J Obstet Gynecol,* 140, 815–30

39.4.2 Clinical Features

Women with PCOS may present with a constellation of symptoms that can vary according to the age at presentation. Reproductive symptoms may dominate in younger women whilst metabolic features become of great concern later in life. Clinical features can be categorised under the three domains: reproductive, metabolic, and psychological.

39.4.3 Reproductive Features

These include hyperandrogenism and oligomenorrhoea, subfertility, and pregnancy complications. Biochemical (identified by increased free androgen levels) or clinical hyperandrogenism (identified by hirsutism using the Ferriman-Gallwey (mFG) scoring tool (Fig. 39.3) [Hirsutism assessment tool - Ferriman-Gallwey (mFG)] scoring tool http://www.hirsutism.com/hirsutism-biology/ferriman-gallwey-score.shtml), and to a lesser extent acne and scalp alopecia is one of the key diagnostic and clinical features of PCOS. Menstrual irregularity (cycle length greater than 35 days or less than 21 days or fewer than eight cycles per year) and fertility issues are common reproductive manifestations of PCOS.

PCOS is the most common cause of oligo/anovulation and subfertility secondary to dysregulated reproductive hormones and follicular development (Homburg 2004). Moreover, women with PCOS were more likely to receive hormonal treatment for fertility assistance than women without PCOS (Joham et al. 2015). Importantly, family size can reach desired goals, where ovulation induction is available.

Women with PCOS are also at increased risk of pregnancy complications including pre-eclampsia, preterm delivery, and gestational diabetes (GDM). These risks are mediated by multiple factors (including genetic and environmental factors, the metabolic and reproductive characteristics of PCOS), as well as higher rates of subfertility and use of assisted fertility treatments. The aforementioned may act independently or in concert (Palomba et al. 2015). Obesity further exacerbates these risks. Therefore, women with PCOS should be recognised as having a high-risk pregnancy and have more frequent assessment of weight gain, blood pressure, and glucose tolerance during pregnancy.

There is also an association between PCOS and endometrial cancer as these women share many of the risk factors including obesity, hyperinsulinaemia, T2DM, and anovulation with unopposed uterine oestrogen exposure. However, routine ultrasound screening for endometrial thickness is not recommended unless risk factors (prolonged amenorrhoea or oligomenorrhoea) or symptoms are present.

39.4.4 Metabolic Features

Insulin resistance is a cardinal feature in PCOS, affecting 75% of lean women and 95% of obese women (Stepto et al. 2013). PCOS is associated with an increased risk of developing impaired glucose tolerance, pre-diabetes, GDM, and T2DM. It is noteworthy that these metabolic abnormalities occur at a younger age and are increased independent of body weight, but are further exacerbated by increased BMI.

Women with PCOS also have increased risk factors for cardiovascular disease including dyslipidaemia and obstructive sleep apnoea (OSA). BMI is a key driver of dyslipidaemia, which is characterised by higher triglycerides and lower high-density lipoprotein (LDL) cholesterol levels.

39.4.5 Psychological Features

PCOS is associated with higher rates of depression, anxiety, disordered eating, psychosexual dysfunction, and low self-esteem (Teede et al. 2011). Symptoms challenging feminine identity, including obesity, acne, excess hair growth, and subfertility, are associated with a higher risk for anxiety and depression. However, studies have shown this increased prevalence of psychological symptoms in PCOS also exists independent of obesity and reproductive abnormalities. Overall, quality of life is significantly reduced in women with PCOS (Barnard et al. 2007).

39.5 Diagnosis and Investigations

Nurses should have a high level of suspicion of PCOS in women who present with menstrual irregularity (2 years or more after menarche), overweight or obesity, fertility issues, acne or hirsutism, pre-diabetes, gestational diabetes, or early-onset T2DM. The Rotterdam criteria is the most universally accepted diagnostic criteria (Fig. 39.2).

In young women (<20 years) only 1 and 2 are required due to the high prevalence of polycystic ovarian morphology (PCOM) in this group.

39.6 Presentation of PCOS at Different Life Stages

39.6.1 Young Women (<20 Years)

Two years after the onset of menarche, if young women report irregular menstrual cycles (>35 or <21 days) a diagnosis of PCOS should be considered. The value and optimal timing of assessment and diagnosis of PCOS should be discussed, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors. When commencing hormonal contraception in adolescents, who have presented with 12 months of irregular menstrual cycles (>35 or <21 days) following onset of menarche, take a baseline assessment of clinical and biochemical hyperandrogenism and cycle patterns before commencement of hormonal contraception. If baseline assessment is abnormal, potential increased risk of PCOS could be discussed with the patient and future reassessment planned (Need to cease oral contraception for a period of 3 months to attain an accurate assessment). Ultrasound is not recommended in this age group and not required if hyperandrogenism (clinical or biochemical) and irregular periods are present.

39.6.2 Adult Women (Reproductive Years)

Irregular menstrual cycles (>35 days of <21 days) in adult women clinically reflect ovulatory dysfunction. However, ovulatory dysfunction can still occur with regular cycles and luteal phase progesterone levels can be measured to assess ovulation when PCOS is clinically suspected and cycles are regular.

39.6.3 Peri/menopausal Women

Diagnosis at this life stage may be based on a history of oligomenorrhoea and hyperandrogenism during the reproductive years. In addition, whilst some aspects of PCOS improve at this life stage, the risk of metabolic abnormalities may persist.

39.7 Patient-Centred Care Model

Women with PCOS report delayed diagnosis and dissatisfaction with the care and information provided by health professionals. A patient focused, multidisciplinary approach targeting both short- and long-term reproductive, metabolic and psychological features is required given the complexity and chronicity of PCOS. A thorough clinical evaluation is necessary to explore all associated features and to enable the tailoring of treatment for each individual. Nurses need to actively engage women in a partnership approach to their own care. Ongoing management in primary care is the mainstay of management. However, interdisciplinary care is often required and referral to an obstetrician/gynaecologist, endocrinologist, psychologist, or a dermatologist maybe needed for targeted medical therapy of reproductive, metabolic, and psychological complications. In addition, the provision of high quality PCOS-specific education and resources are vital to optimise patient empowerment and self-management.

Patient Quote 2

"Once I received a proper diagnosis and realised that this condition was well understood and that there was a lot of help for me, I feel to much better. It was the not knowing why I had these symptoms and what I could do that was so difficult. I know now that there is a lot I can do to help myself".

39.7.1 Key Patient Messages Once Diagnosis Established

- PCOS is common.
- PCOS is a long-term condition.
- PCOS affects individuals differently and therefore treatment needs to be individualised.
- There are some long-term health risks.
- Lifestyle management improves all aspects of PCOS.
- Treatment can reduce symptoms and risk of complications.
- A great deal of support is available and education is important.
- Continue the effort to reduce the risk of health complications.

39.8 Management of Hyperandrogenism

Hyperandrogenism is mainly manifested by excessive hair growth and to some extent acne and androgen-related alopecia. Whilst various options are available for management of hirsutism, the choice of therapy depends on the severity of the condition and its impact on individual well-being, patient preference, access and affordability of the treatment, and potential side effects. Cosmetic therapy, including laser therapy and electrolysis, are considered first line in management of hirsutism.

Combined oral contraceptive pills (COCPs) are first-line management and are generally effective but need 6–12 months to work. COCPs or alternative forms of contraception can be used with antiandrogens although the evidence for these agents in limited.

Patient Quote 3

"For me the symptoms I struggle with the most are my facial hair and my weight. Also, I used to also have very severe acne which was really tough but this was cleared up by medication".

39.9 Management of Reproductive Features

Oligo/anovulation and menstrual irregularity is best managed by combined oral contraceptive pills in women who do not seek fertility. COCPs are effective in reducing ovarian androgen production by supressing GnRH. Androgen production is also inhibited by the progestins in these pills, which impairs androgen receptor binding. The oestrogen in COCPs increases production of SHBG which in turn reduces availability of free androgens. Combined oral contraceptive pills also provide progestins which protect the endometrium.

Age, BMI, metabolic and thromboembolism risk factors as well as history of smoking need to be considered when prescribing COCPs. Whilst COCPs are effective in resuming cycle regularity, providing contraception and controlling hirsutism, they may have a negative influence on venous, thromboembolic and metabolic risk factors including dyslipidaemia and insulin resistance. Therefore, a low dose COCP is preferred and evidence does not support one preparation over another.

Intermittent progestin every 3 months can be considered as an alternative to induce a withdrawal bleed and protect the endometrium from hyperplasia in women with oligo/amenorrhoea who do not wish to take the COCP, or if there is a contraindication to their use. In women with oligomenorrhoea, routine ultrasound screening for endometrial thickness is not recommended unless risk factors are present; these may include obesity, older age, and amenorrhoea.

Fertility declines as women get older and with obesity. Therefore, early family planning, when possible, and weight management should be initiated to preserve and optimise fertility. Lifestyle intervention is first-line treatment and increases spontaneous pregnancy. Early intervention is required to prevent weight gain and to engage women in intensive lifestyle programmes with regular exercise and caloric restriction to achieve a BMI of less than 30 kg/m^2. Achieving optimal body weight is beneficial for regulation of menstrual cycles, ovulation, and spontaneous pregnancy and for

prevention of potential pregnancy complications and should be initiated at the primary care level (Clark et al. 1998). First-line therapies include pharmacological ovulation induction with aromatase inhibitors, clomiphene citrate, metformin, gonadotropins, and surgical options such as laparoscopic ovarian drilling could be considered second line when appropriate. Third-line IVF is not often required in isolated PCOS. Early specialist referral for consideration of assisted reproductive techniques is warranted once infertility is established (12 months of failure to conceive). Referral should be initiated earlier in older women if infertility is suspected (6 months of failure to conceive).

39.9.1 Therapeutic Benefits of Metformin in PCOS

The role of metformin is now clearer. Metformin is not first-line treatment. In the general population with impaired glucose tolerance, metformin prevents diabetes and is known to be effective in the prevention of weight gain and restoration of menstrual cyclicity and ovulation in women with PCOS. The addition of metformin to structured lifestyle programmes may improve BMI, yet it is not recommended as a substitute for diet and exercise (Teede et al. 2011; Legro et al. 2013). In PCOS, it reduces BMI (a high priority endpoint for women) and has positive effects on ovulation and metabolic features.

Metformin does not have the same adverse metabolic or homeostatic effects of COCPs; however it does not provide contraception. It also causes mild, self-limiting gastrointestinal side effects. Metformin is not as effective as COCPs in managing symptoms of clinical hyperandrogenism. In women resistant to clomiphene, the addition of metformin to clomiphene citrate increases live birth rates when compared with clomiphene alone or laparoscopic ovarian drilling. Metformin was also effective in preventing ovarian hyperstimulation syndrome in women with PCOS undergoing IVF treatment.

Metformin is a low cost and readily available medication, its use to prevent weight gain, impaired glucose tolerance and T2DM in PCOS is primarily in those whose lifestyle programmes alone are ineffective. It also could be considered to alleviate menstrual irregularity in women who do not desire contraception or have contraindications to the use of COCPs and to assist reproduction in women who are resistant to ovulation induction with clomiphene.

39.9.2 Preconception and Early Pregnancy Care

There is an increased risk of pregnancy complications in women with PCOS. Preconception and early antenatal lifestyle intervention, assessment of BMI, blood pressure, and OGTT are recommended in all women with PCOS to reduce the risk of developing GDM, pregnancy-induced hypertension, and pre-eclampsia (Legro et al. 2013; Boomsma et al. 2006).

39.10 Early Screening and Management of Metabolic Complications

According to both national and international guidelines, all women with PCOS should undergo regular screening for early detection of metabolic complications including IGT, T2DM, and other cardiovascular risk factors including dyslipidaemia and hypertension (Teede et al. 2011).

Current guidelines recommend screening all women with PCOS for glucose intolerance using a 2-h oral glucose tolerance test (OGTT).

Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of gestational diabetes, impaired glucose tolerance, and type 2 diabetes (fivefold in Asia, fourfold in the Americas, and threefold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by obesity. Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every 1–3 years, influ-

enced by the presence of other diabetes risk factors. An oral glucose tolerance test (OGTT) should be performed at baseline in high risk women with PCOS (including a BMI >25 or in Asian >23 kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes, hypertension or high risk ethnicity). Fasting plasma glucose or HbA1c may be substituted in women with PCOS with no other diabetes risk factors; however, these may be less ideal for detecting impaired glucose tolerance, as a key predictor for diabetes. An OGTT should be offered in all women with PCOS who are planning pregnancy or seeking fertility treatment preconception, and if negative at <20 weeks gestation and at 28 weeks gestation, given their high risk of hyperglycaemia and the associated comorbidities in pregnancy.

Measurement of fasting insulin levels is not appropriate clinically as the commercially available assays are not adequately sensitive and accurate; therefore, results are potentially misleading and hard to interpret. Measurement of fasting glucose alone is also not recommended as this is not adequately sensitive for detection of impaired glucose tolerance and diabetes in PCOS. The mechanism underpinning insulin resistance in PCOS mainly affects the skeletal muscle and adipose tissue rather than the liver. Therefore, women with PCOS are more likely to demonstrate postprandial dys/hyperglycaemia rather than abnormal fasting glucose levels. Frequency of screening for glucose intolerance varies according to each individual's risk profile. These risk factors include age, ethnicity, parental history of diabetes, history of high glucose levels, smoking, use of COCPS or antihypertensive medications, physical inactivity, and waist circumference greater than 80 cm.

Screen and assess all women with PCOS for risk factors for cardiovascular disease at diagnosis. This includes screening for overweight and obesity, dyslipidaemia, hypertension, and taking a history for smoking. Frequency of re-screening is still under discussion; however, current guidelines recommend subsequent assessments based on each individual's overall risk profile, age, and family history of cardiovascular disease (Teede et al. 2011; Legro et al. 2013).

39.10.1 Metabolic Risk Management in PCOS (Next Section Will Be Put in Table Format)

- Encourage smoking cessation.
- Check BP once a year if BMI is less than 25 kg/m^2 and at every visit if BMI is equal to or greater than 25 kg/m^2.
- Measure fasting lipids at diagnosis and monitor based on additional obesity and cardiovascular risk factors.
- OGTT at baseline in all women with PCOS, then assess every 1–3 years, influenced by the presence of other diabetes risk factors. OGTT should be performed at baseline in high risk women with PCOS (including a BMI >25 or in Asian >23 kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes, hypertension or high risk ethnicity).
- Screen all women for impaired glucose tolerance or diabetes preconception and early in pregnancy and all women at 24–28 weeks.

39.10.1.1 Weight Management

- Offer regular monitoring for weight changes and excess weight, in consultation with and where acceptable to the individual woman. Monitoring could be at each visit or at a minimum 6–12 monthly, with frequency planned and agreed between the health professional and the individual.
- Target prevention of weight gain for all and achieving at least 5–10% weight loss if overweight. Note: education alone and unachievable goals are generally unsuccessful.
- Key message: 5–10% weight loss will greatly assist in symptom control.
- Encourage simple behaviour change—prioritisation of healthy lifestyle, family support, lifestyle and exercise planning, setting of small achievable goals.
- Consider referral if appropriate to: dietitian (tailored dietary advice, education, behav-

ioural change support), exercise physiologist (exercise motivation, education), psychologist (motivational interviewing, behaviour management techniques, emotional health, and motivation), and/or group support (diet and exercise programme).

39.10.1.2 Management of Psychological Features

Given the psychological burden associated with PCOS, the assessment and monitoring of psychological well-being is essential for making lifestyle changes, to promote ongoing engagement with management strategies and to improve quality of life. PCOS guidelines recommend emotional health screening using evidence-based screening tools.

It is important to note that treatment of factors such as hirsutism and excess body weight, which can negatively affect quality of life, can be as important as conventional treatments (cognitive behavioural therapy, psychotherapy, and pharmacotherapy) available for management of mood disorders (Teede et al. 2011). It is equally critical to empathise the role lifestyle can play is improving emotional well-being (Thomson et al. 2010).

39.10.1.3 Emotional Health Simple Screening Tools

If the answers to any of the questions in any of the domains are positive, further exploration of that domain should be considered. Moreover, proper management of the problem including consideration of a mental health care plan and referral to a mental health professional is required.

In addition to the above questions, health professionals should capture and consider women's perceptions of their symptoms, impact on their quality of life, and personal priorities for care to improve patient outcomes.

Additional recommended tools:

- Modified Polycystic Ovary Syndrome Questionnaire (MPCOSQ)
- The female sexual function index Female Sexual Function Index (FSFI)
- The Arizona sexual experience scale Arizona Sexual Experience Scale (ASEX Summary of treatment strategies in PCOS

39.10.1.4 Oligo/amenorrhoea

- Lifestyle changes (5–10% weight loss through structured exercise and calorie restriction).
- COCPs (low oestrogen doses, i.e. 20 micrograms may have less impact side effects and second-generation progestins are associated with lower risk of thromboembolism).
- Cyclic progestins to induce withdrawal bleed if COCPs not desired or contraindicated (i.e. 10 mg medroxyprogesterone acetate 10–14 days every 2–3 months if no cycle in interim).
- Metformin improves menstrual cyclicity and ovulation.

39.10.1.5 Hirsutism

- Cosmetic therapy (laser or electrolysis) is considered first line.
- Consider pharmacotherapy if cosmetic therapy is ineffective, inaccessible, or unaffordable. Each medication should be tried for at least 6 months before making changes in dose or introducing a new medication.
- COCPs are first line. If ineffective after 6–9 months, an antiandrogen can be added (i.e. spironolactone or cyproterone acetate).
- Monotherapy with antiandrogens should not be considered in premenopausal women as they increase irregular vaginal bleeding and have adverse foetal outcomes should pregnancy occur.
- Ensure adequate contraception when prescribing antiandrogens.

39.10.1.6 Infertility

- Advise early family planning and initiation where possible.
- Emphasise prevention of weight gain prior to conception.
- Encourage weight loss if overweight. Lifestyle changes (5–10% weight loss through structured exercise and calorie restriction). If a significant weight loss occurs, consider a period of 3–6 months of weight stability prior to conception.
- Smoking cessation.
- Folate supplementation.
- Specialist referral for consideration of assisted reproductive techniques is essential in women who fail to conceive after 12 months and earlier in women over 35 years.

- Ovulation induction techniques include pharmacotherapy with letrozole, clomiphene citrate ± metformin, gonadotropins, or laparoscopic ovarian drilling. IVF is uncommonly needed in isolated PCOS.

39.10.1.7 Weight Management and Cardiometabolic Risk Reduction

- Encourage cessation of smoking.
- Prevention of weight gain through ongoing attention to lifestyle and weight monitoring.
- Note: no specific diet is recommended as ideal in PCPS and generally healthy principles apply.
- Encourage reduction of sedentary behaviour and increase in physical activity.
- If overweight or obese, encourage 5–10% weight loss through structured exercise and calorie restriction.
- Metformin aids prevention of weight gain, assists lifestyle induced weight loss, and prevents diabetes onset.

39.10.1.8 Psychological Symptoms

- Screen women using the emotional health simple screening tool (Box 39.1)
- Address factors which can negatively affect quality of life
- Consider a mental health care plan and referral to psychologist/psychiatrist when needed

Box 39.1 Emotional Health Simple Screening Tool

Depression and/or anxiety

1. During the last month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?
3. During the last month, have you been bothered by feeling excessively worried or concerned?

Negative body image

1. Do you worry a lot about the way you look and wish you could think about it less?
2. On a typical day, do you spend more than 1 h per day worrying about your appearance? (More than 1 h a day is considered excessive). If positive what are your specific concerns and how does it affect your life?
3. Does it make it hard to do your work or be with your friends and family?

Disordered eating and eating disorders

1. Do you worry you have lost control over your eating?
2. Do you ever feel disgusted, depressed, or guilty about eating?
3. Have you tried fasting or skipping meals in an attempt to lose weight?
4. Have you tried vomiting, laxatives, or diuretics in an attempt to lose weight?
5. Have you had significant (i.e. >5–7%), recurrent fluctuation in body weight?

Psychosexual dysfunction

1. During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, diminished desire, pain, or any other problems?
2. Do you feel that polycystic ovary syndrome affects your sex life?
3. (If relevant) Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?

Considering the high prevalence of depression and anxiety in PCOS appropriate screening and a timely referral to psychologist/psychiatrist is important.

39.10.1.9 Use of Metformin

When indicated, metformin can be started at a low dose (500 mg daily) to enhance GI tolerance with dosage titrated (by 500 mg every 2–4 weeks as tolerated) to a maximum dose of 1500–2000 mg daily.

Metformin may also be used

- To prevent weight gain, IGT, and T2DM in PCOS where lifestyle programmes fail
- To improve menstrual irregularity in women who do not desire or have contraindications to the use of COCPs
- To assist reproduction in women who are resistant to ovulation induction with clomiphene alone

Case Studies

Scenario 1: Fei

26 year old, Chinese woman

History

– menarche at age 14 with irregular cycles (45–60 days).
– strong family history of T2DM and CVD on father's side

Presenting Symptoms

– amenorrhoea (last 4 months)—Fei concerned about this
– weight gain (7 kg over the past 2 years)—struggling to lose

Lifestyle

– currently sexually active (uses condoms)
– sedentary lifestyle, little time for exercise

Examination

– Not cushingoid
– normotensive
– BMI 28
– central adiposity, waist circumference 89 cm

On Further Questioning

– excessive facial hair growth, requires regular waxing
– self-rating of 11 on the modified Ferriman-Gallwey scoring system

Investigations

– testosterone 2.0 (0.1–1.7), SHBG 15 (18–136), FAI 13% (0.7–10.9)
– TSH, prolactin, FSH, LH, hCG—normal
– transvaginal ultrasound: multiple follicles consistent with PCOM
– OGTT normal, mild dyslipidaemia—normal total cholesterol and LDL-C, low HDL-C

Diagnosis and Treatment

– Fei chooses to start a COCP for regulation of her periods, considers laser therapy for hirsutism
– sees a dietician, attends regular aerobic exercise sessions at the local gym to achieve weight loss

Sequela

Four years later—presents to emergency department with vaginal bleeding and abdominal pain
  – pregnant and referred for an ultrasound, a live pregnancy at 8 weeks
  – bleeding stopped, Fei reassured pregnancy still viable

On Examination

– weight is 73 kg, BMI 26, normotensive
– stopped taking COCP about 6 months ago to get pregnant
– referred for early OGTT to screen for gestational diabetes—fasting glucose 5.1, 2 hourly glucose 9

Critical Thinking Questions: Scenario 1

1. How could the nursing process be used to prioritise Fei's care?
2. What would your key lifestyle messages to Fei be?
3. What other health professionals may form part of Fei's care team?

Scenario 2: Katie

29 year old, caucasian woman

History

– menarche at age 13, irregular menstruation until she started taking a COCP at age 15
– no regular medication
– works fulltime
– does not smoke, drinks alcohol occasionally

Presenting Symptoms

- presents to GP with 12 months irregular menstruation
- cycle lengths 50–70 days
- stopped COCP last year—planning to conceive
- no success after 6/12

On Further Questioning

- disappointed with weight gain of 8 kg over 9 year
- believes weight gain is disproportionate as very active

Examination

- normotensive
- BMI 29
- central adiposity, waist circumference 89 cm
- no physical features suggestive of secondary causes of weight gain
- modified Ferriman-Gallwey scores 5, reports waxing face frequently
- normal testosterone, low SHBG, elevated FAI
- thyroid function, 17-OH progesterone, and prolactin levels—normal

On Further Screening

- mildly elevated LDL, low HDL
- OGTT normal, no signs or symptoms suggestive of OSA

Emotional well-being—using simple screening tool Katie found to be concerned about weight gain but not distressed about body image.

- mood, energy levels, and social relationships—good

Diagnosis and Treatment

- diagnosed with PCOS (Rotterdam)
- advised to commence lifestyle changes, aim weight loss of 5–10% of body weight
- referred to a dietitian, calorie-restricted diet, and exercise programme (dramatic weight loss to be avoided)
- Medroxyprogesterone acetate prescribed to induce a withdrawal bleed as Katie does not want to commence COCPs
- will continue waxing (can't afford laser therapy)

Sequela

returns to GP after 3/12—lost 4 kg
cycles shorter and lipid profile normalised
advised to continue active lifestyle for 6/12
if not conceived, further examination, ovulation induction considered
will refer to reproductive/infertility specialist after 12 months of trying to conceive
after a further 2 kg weight loss—Katie conceives, although she develops gestational diabetes.

Critical Thinking Questions: Scenario 2

1. What would your key lifestyle messages to Katie be to optimise her fertility?
2. What percentage of body weight reduction has been shown to improve PCOS symptoms?
3. How does excess weight impact the symptoms of PCOS?

Scenario 3: Anju

33 year old, South-east Asian woman

Presenting Symptoms

- presents to GP with irregular menstruation <4 cycles per year
- menarche at age 14, COCP until 30
- not planning to conceive—uses condoms

Examination

- Normotensive, BMI 29, central adiposity
- waist circumference 86 cm, no features of secondary causes of obesity
- modified Ferriman-Gallwey score 4, however reports laser therapy
- normal testosterone, low SHBG, and elevated FAI
- transvaginal ultrasound—unilateral PCOM
- elevated LDL, low HDL
- OGTT–IGT
- no signs and symptoms of OSA
- thyroid function, 17-O progesterone, prolactin levels—normal

Diagnosis and Treatment

- diagnosis of PCOS (three Rotterdam criteria)
- lifestyle programmes with personal trainer 6/12
- lost 2 kg (reports being stressed about not losing weight due to effects on fertility)
- failed to lose weight on diet and exercise alone

Started metformin 500 mg daily—dose gradually titrated to 2000 mg (for IGT and weight gain prevention)

– referred to psychologist—anxiety

Sequela

– visits GP after 3/12, lost 3 kg
– cycles returned
– reports psychologist helpful—learnt behavioural techniques to overcome anxiety
– advised to plan family (risk of age-related infertility)
– starts folate, conceives naturally after 3/12
– advised to cease metformin
– referred for early screening for gestational diabetes
– advised to aim for optimal gestational weight gain to reduce risk of complications in pregnancy

Critical Thinking Questions: Scenario 3

1. Which of Anju's presenting symptoms may lead you to suspect a diagnosis of PCOS?
2. What are the pathological processes that lead to irregular menstrual cycles in PCOS?
3. How can lifestyle changes improve the regularity of menstrual cycles?

39.11 Conclusions

PCOS is a complex, prevalent, life-long endocrine condition with long-term metabolic, reproductive, and psychological features. It is independent of, yet exacerbated by, obesity. Many women remain undiagnosed because of the heterogeneity of clinical presentation. Affected women report diagnostic delays (>2 years) (Gibson-Helm et al. 2017), inconsistent practices and inadequate health practitioner knowledge (Dokras et al. 2017), poor diagnostic experiences (Gibson-Helm et al. 2017), and inadequate health system responsiveness leading to additional costs (Jason 2011; Azziz et al. 2005).

Therefore, awareness of this condition and its features is important for nurses who positively contribute to early and accurate diagnosis, raising PCOS-related health literacy and being a critical member of an interdisciplinary care team. This will avoid missing the diagnosis and assist with appropriate screening of all women with PCOS for the presence of potential metabolic, psychological, and reproductive manifestations. Nurses can play a critical role in delivering evidence-based, holistic care through the provision of targeted education, and preventative and therapeutic strategies within a biopsychosocial model of care.

39.12 Online Resources

- **Web resources for the eBook**—This chapter is based on; *The international evidenced-based guideline for the assessment and management of polycystic ovary syndrome* (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline)

References

Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metabol. 2005;90(8):4650–8.

Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, et al. Polycystic ovary syndrome. Nature reviews Disease primers. 2016;2:16057.

Barnard L, Ferriday D, Guenther N, Strauss B, Balen A, Dye L. Quality of life and psychological well being in polycystic ovary syndrome. Hum Reprod. 2007;22(8):2279–86.

Boomsma CM, Eijkemans MJC, Hughes EG, Visser GHA, Fauser BCJM, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12(6):673–83.

Boyle JACJ, O'Dea K, Dunbar T, Norman RJ. Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin. Australia. Med J Aust. 2012;196(1):62–6.

Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod. 1998;13(6):1502–5.

Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. Fertil Steril. 2017;107(6):1380–6.e1.

Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metabol. 2017;102(2):604–12.

Homburg R. Management of infertility and prevention of ovarian hyperstimulation in women with polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2004;18(5):773–88.

Jason J. Polycystic ovary syndrome in the United States: clinical visit rates, characteristics, and associated health care costs. Arch Intern Med. 2011;171(13):1209–11.

Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. J Womens Health (Larchmt). 2015;24(4):299.

Kahsar-Miller M, Azziz R. The development of the polycystic ovary syndrome: family history as a risk factor. Trends in Endocrinology & Metabolism. 1998;9(2):55–8.

Legro SR, Arslanian AS, Ehrmann AD, Hoeger MK, Murad HM, Pasquali KR, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2013;98(12):4565–92.

Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. 2013. p. 95–109.

March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25(2):544–51.

Moran LJ, Ranasinha S, Zoungas S, McNaughton SA, Brown WJ, Teede HJ. The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome. Hum Reprod. 2013;28(8):2276–83.

Palomba S, de Wilde MA, Falbo A, Koster MPH, La Sala GB, Fauser BCJM. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21(5):575.

Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. Hum Reprod. 2013;28(3):777–84.

Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BGA, Wong JLA, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust. 2011;195(6):S65.

Teede HJ, Joham AE, Paul E, Moran LJ, Loxton D, Jolley D, Lombard C. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. Obesity. 2013;21(8):1526–32.

Thomson RL, Buckley JD, Lim SS, Noakes M, Clifton PM, Norman RJ, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. Fertil Steril. 2010;94(5):1812–6.

Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;27(10):3067–73.

Yilmaz B, Vellanki P, Ata B, Yildiz BO. Metabolic syndrome, hypertension, and hyperlipidemia in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis. Fertil Steril. 2018;109(2):356.

Key Reading

1. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Copyright Monash University; 2018. (Link to be provided); https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline.
2. Shorakae S, Boyle J, Teede H. Polycystic ovary syndrome: a common hormonal condition with major metabolic sequelae that physicians should know about. Intern Med J. 2014;44(8):720–6.
3. Legro SR, Arslanian AS, Ehrmann AD, Hoeger MK, Murad HM, Pasquali KR, et al. diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565–92.
4. Fauser BCJM, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28–38.e25.
5. Dokras A. Improving care for women with polycystic ovary syndrome. Fertil Steril. 2018;110(1):50–1.

40 Diagnosis and Management of Turner Syndrome in Children and Adults

Helen E. Turner and Irena R. Hozjan

Contents

40.1 **Introduction** ... 773

40.2 **Epidemiology** ... 773

40.3 **Diagnosis and Genetics** ... 774
40.3.1 Prenatal Diagnosis ... 775
40.3.2 Postnatal Diagnosis ... 775

40.4 **Low Level Mosaicism in Adult Women** ... 776

40.5 **Disclosure** ... 776

40.6 **Cardiovascular Disease and Risks** ... 776
40.6.1 Acquired Cardiac Disease in Turner Syndrome ... 778
40.6.2 Hypertension ... 778
40.6.3 Aortic Dissection ... 778
40.6.4 Conduction Anomalies ... 779

40.7 **Short Stature, Growth Failure, and Growth-Promoting Therapies** ... 780
40.7.1 Growth Hormone Therapy in Turner Syndrome ... 781

40.8 **Pubertal Development, Ovarian Failure, and Ovarian Hormone Replacement Therapies (HRT)** ... 783
40.8.1 Hormone Replacement Therapies and Cardiac, Thrombosis, Cancer Risk ... 784

40.9 **Breast Development in Turner Syndrome** ... 785

40.10 **Fertility and Reproductive Assistive Technologies and Pregnancy** ... 785

40.11 **Lifelong Screening and Management in Women with Turner Syndrome** ... 786

H. E. Turner (✉)
The Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford, UK
e-mail: Helen.Turner@ouh.nhs.uk

I. R. Hozjan
Endocrine Program, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada
e-mail: irena.hozjan@sickkids.ca

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_40

40.11.1 Autoimmune System and Autoimmune Disorders 786
40.11.2 Metabolic Issues; Diabetes, Insulin Resistance, and Glucose Intolerance 787
40.11.3 Vascular Malformations of Gastrointestinal System 788
40.11.4 Liver Function Abnormalities and Lipid Disorders 788
40.11.5 Ear Health 789
40.11.6 Skeletal Manifestations in Turner Syndrome 789
40.11.7 Renal/Urinary Findings in Turner Syndrome 790
40.11.8 Ocular Abnormalities 791
40.11.9 Lymphedema and Dermatological Related Issues 791
40.11.10 Orthodontic and Dental Manifestations in Turner Syndrome 792
40.11.11 Intelligence, Psychological, Neurocognitive, and Social Issues 792
40.12 **Transition to Adulthood** 794
40.13 **Nursing and Team Considerations** 795
40.14 **Working with Patient Advocacy Groups** 795
40.15 **Conclusion** 796
References 797

Abstract

Turner syndrome affects approximately 1 in 2500 live female births and is characterised by an abnormal or missing X chromosome. It is associated with increased morbidity and mortality due to the associated phenotypic abnormalities. The commonest presentation is aged 10–16 with short stature and primary amenorrhoea, however the considerable phenotypic variation some of which is associated with a particular/mosaic karyotype may lead to delay/missed diagnosis. Girls and women with TS should be followed up for life with screening for complications, and management of short stature, primary (and more rarely secondary) ovarian failure, cardiovascular complications, and increased autoimmune and metabolic risk. Recent guidelines provide useful guidance for the successful lifelong management of girls and women. A multidisciplinary approach addressing (Fig. 40.6) all aspects of their care including expert cardiological monitoring and intervention when required, access to fertility and obstetric expertise when appropriate, expert genetic counselling if indicated, and discussion of psychosocial, education, employment issues is key to the successful outcome for all women with Turner syndrome.

Keywords

Turner syndrome · Karyotype · Fertility · Aortic dissection · Oestrogen · Autoimmunity

Abbreviations

AMH	Anti-Mullerian Hormone
APS	Autoimmune polyglandular syndrome
ASI	Aortic size index
BAV	Bicuspid aortic valve
CMR	Cardiac MRI
CoA	Coarctation of aorta
ECG	Electrocardiogram
GH	Growth hormone
HRT	Hormone replacement therapy
HTN	Hypertension
IVF	In vitro fertilisation
OR	Odds ratio
R	Recommendation of International Guidelines
SMR	Standardised mortality ratio
TS	Turner Syndrome
TTE	Transthoracic echo

Key Terms

- **Short stature:** a child or an adult is more than two standard deviations below the mean for age and gender or less than the 3rd percentile.

- **Primary amenorrhoea:** the failure of menses to occur by age 16 years, in the presence of normal growth and secondary sexual characteristics.
- **Karyotype:** the number and visual appearance of the chromosomes in the cell nuclei of an organism or species.
- **Genotype:** is the set of genes in our DNA which is responsible for a particular trait.
- **Phenotype:** is the physical expression, or characteristics, of a trait.
- **Mosaic karyotype:** one kind of karyotype in some cells, and a different karyotype in other cells.

Key Points

- Turner syndrome is the commonest sex chromosome abnormality in women characterised by an abnormal or missing X chromosome.
- Turner syndrome is associated with increased mortality due to cardiovascular disease, aortic dissection, and adverse metabolic risk profile.
- Characteristic clinical features are short stature and ovarian failure.
- The phenotype is highly variable and includes autoimmune, metabolic, hepatic, bony, cutaneous, renal, and neurocognitive abnormalities.
- Lifelong management and multidisciplinary care is key to successful outcome for girls and women with Turner syndrome.

40.1 Introduction

Turner Syndrome (TS) is the most common sex chromosome aneuploidy affecting females and is caused by the loss of part or all of an X chromosome. It is a major cause of primary hypogonadism and short stature in young girls. Girls and women with a diagnosis of TS require comprehensive multi-system assessment, active management of growth-promoting therapies, pubertal induction and maintenance, management of developing comorbidities, and ongoing health surveillance of increased lifetime risks of a number of conditions.

The clinical triad of impaired sexual development, webbed neck, and cubitus valgus was first described in the English language literature by Turner in 1938 (Turner 1938) with ovarian failure and streak gonads noted in 1944 (Wilkins and Fleischmann 1944). Much earlier in Europe, Ullrich and Bonnevie described similar case findings in a young girl and mouse in 1930 and 1934, respectively (Ullrich 1930; Bonnevie 1934).

40.2 Epidemiology

TS occurs in approximately 1 in 2000 to 1 in 2500 live births and a 45,X Karyotype is implicated in 3 of 100 female conceptuses. The prenatal prevalence is higher, with increased mortality during the first trimester leading to a high rate (7–10%) of spontaneous abortion (Stochholm et al. 2006). The diagnosis of TS still occurs across the female lifespan. The true prevalence of TS is difficult to determine as those with mild phenotypes may remain undiagnosed until late adulthood. It is important to recognise clinical and phenotypic findings and risks with specific chromosome anomalies for affected females.

Population studies show both significant delay (Fig. 40.1) and under-diagnosis of TS (Stochholm et al. 2006). A population study in Denmark of 746 girls and women with TS showed the median age of diagnosis to be 15 years, with a peak at birth and subsequent second peak age 15 secondary to evaluation for short stature and primary amenorrhea. However, it is important to be aware and recognise the potential for diagnosis throughout the entire adult life as demonstrated by cases diagnosed up to the age of 86 (Stochholm et al. 2006). The diagnosis is confirmed by karyotype analysis.

Morbidity and mortality is increased in TS. In a UK study, overall mortality was raised (SMR 3.0) (Schoemaker et al. 2008) and a Danish population study demonstrated a similar SMR of 2.86 (Stochholm et al. 2006). The increased mortality is multifactorial but is predominantly due to cardiovascular disease (41% excess mortality in UK study), aortic dissection, and metabolic disease. Some of the increased morbidity and risk for

increased death rate are amenable to treatment and emphasise the importance of both making the diagnosis and early appropriate management of associated conditions.

40.3 Diagnosis and Genetics

Diagnosis of Turner Syndrome (TS) requires complete or partial absence of the second sex chromosome with or without cell line mosaicism and the presence of characteristic features. A 30 cell karyotype identifies at minimum 10% mosaicism with 95% confidence and is recommended by the American College of Medical Genetics (Hook and Warburton 2014) (Table 40.1).

Although a specific karyotype does not necessarily predict the phenotype of an affected individual, recognised associations between clinical phenotype and underlying karyotype do exist as shown in Table 40.2 and described below.

45, X 45, X (monosomy X) is found in approximately 45% of the live births with TS.

45, X mosaicism—More than half of all patients with TS have a mosaic karyotype for example 45X/46, XX or 45,X/47, XXX, or 45,X mosaics with additional X chromosome abnormalities of isochromosome Xq (46,X,i(X)q), ring chromosome X (rX), or Xp or Xq deletion.

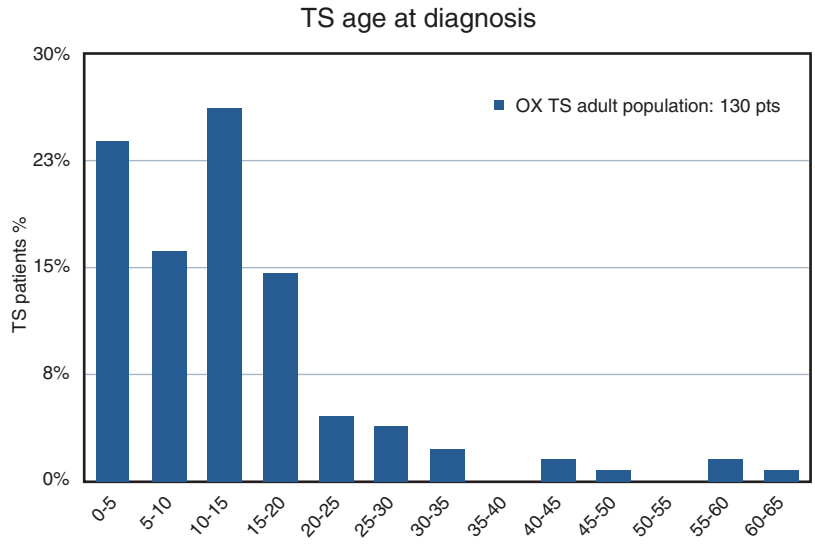


Fig. 40.1 Time of diagnosis in Turner syndrome diagnosis from birth (unpublished author's data from Oxford TS cohort 2018)

Table 40.1 Incidence of different karyotype in 410 adult women with Turner syndrome (adapted from Birkebaek et al. (2002))

45,X	49%
45,X/46,XX mosaicism	19%
45,X mosaicism with structural anomaly of second X	23%
45,X/46,Xi(Xq)	
45,X/46,Xr(X)	
45,X/47,XXX	
46,XX and structural anomaly of second X	9%
46,Xdel(Xp)	
46,Xi(Xq)	
46,Xr(X)	
45,X/46,XY mosaicism (the Y can be normal or structurally abnormal—**NB only called TS if phenotypically female**)	

Table 40.2 Common genotype/phenotype associations in women with TS (Gravholt et al. 2017)

- 45,X—classic genotype
  - Highest incidence of renal and cardiovascular anomalies
- 45,X, 46,XX cell line mosaicism
  - Lowest risk of short stature
  - Greatest incidence of spontaneous menarche
- Isochromosome X
  - Increased incidence of autoimmune disorders and deafness
  - Reduced risk of internal malformation
- Ring chromosome r(X)
  - Spontaneous menses in 33%
  - Increased incidence of cognitive difficulties
- Y material 5–10%—FISH, gonadoblastoma risk

Isochromosome Xq—represents a structurally abnormal X chromosome that consists of two copies of the long arm of the X chromosome that are connected head to head. Those with isochromosome Xq are monosomic for the short arm of the X chromosome and are believed to be at higher risks for autoimmune disorders particularly thyroiditis.

Ring chromosome X—those with a ring chromosome X (rX) are at risk for significant developmental delay and cognitive difficulties may have early severe growth failure, atypical facial dysmorphic features, and/or increased risk for irritable bowel disease syndrome.

Xp or Xq deletion—signifies a deletion of a portion of the short arm of the X chromosome [del(X)p] or long arm of the X chromosome [del(X)q] with or without cell line mosaicism. Xq deletions are associated with ovarian failure but rarely other features of TS (Maraschio et al. 1996).

45,X/46,XY affects up to 10% of TS patients with a cell line containing Y chromosome material (Jacobs et al. 1997). If sex chromosome material of uncertain origin (marker chromosome elements) is detected on karyotype, further assessment is warranted because of increased risks for gonadoblastoma. It is important to note that 45,X/46,XY karyotypes have been associated with a variety of phenotypes that range from TS to ovotesticular disorder of sex development to a normal phenotypic male with infertility. Thus, the diagnosis of TS should only be applied to individuals who have a documented abnormality of the X chromosome and phenotypic features. TS should be distinguished from Noonan syndrome, mixed and complete or pure gonadal dysgenesis (dos Santos et al. 2013).

A karyotype analysis identifying Y-chromosomal material may be present in approximately 5% of those with TS, and additionally up to 3% may have marker chromosomes, an X or Y chromosome fragment (Alvarez-Nava et al. 2013; Rivkees et al. 2011). The risk of developing gonadoblastoma, a neoplasm that occurs in dysgenetic gonads, with Y material identified ranges up to 30%. As a result, early gonadectomy is recommended when Y material has been identified. These patients may be at future risk for other malignancies.

Future directions for screening of TS may capitalise on recent advances of high throughput pyrosequencing of buccal swabs for TS (Rivkees et al. 2011; Rivkees 2012). This testing has the potential to provide a very useful non-invasive screening tool that can detect loss of an entire X chromosome or mosaicism with up to 97% sensitivity. The potential for clinical use and future mass screening or new-born screening is appealing.

40.3.1 Prenatal Diagnosis

Ultrasound findings (increased nuchal translucency, coarctation of the aorta and/or left-sided cardiac defects, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation) and/or an abnormal triple or quadruple maternal serum (alpha fetoprotein, human chorionic gonadotropin, inhibin A, and unconjugated estriol) screening may suggest TS (Gravholt et al. 2017) however are not diagnostic and require karyotype confirmation. Postnatally, all infants require re-evaluation of karyotype to confirm, as the degree of mosaicism detected prenatally is not generally predictive of the severity of the TS phenotype (Gunther et al. 2004; Bondy 2007). Prenatal diagnosis of TS should include counselling regarding the wide variability of phenotype and the high probability of short stature and ovarian failure due to ovarian dysgenesis. It is very challenging to predict phenotype of infants with TS and particularly those with 45, X/46, XX mosaicism who tend to have a milder phenotype.

40.3.2 Postnatal Diagnosis

Lymphedema and/or coarctation in the new-born period are perhaps the more common reasons to screen for TS in infancy, and short stature generally leads to further evaluation and identification of the majority of cases of TS during childhood and adolescence (Pinsker 2012). The phenotype of a girl with TS after the new born period that represents the classic gestalt of TS findings is

very variable but includes short stature and delayed puberty related to ovarian failure often associated with phenotypic features such as epicanthal folds, low lying palpebral fissures, low-set and/or posteriorly placed ears, low anterior and/or posterior hair lines, webbed or shortened neck, high-arched palate, malocclusion, overcrowded dentition, pigmented nevi, shield-like or broad chest with wide spaced nipples, cubitus valgus, shortened fourth metacarpals and/or metatarsals, nail dysplasia, scooped or hyperconvex nails, puffy and broad hands and feet, Madelung deformity of the hands and wrists. Table 40.3 lists the common abnormalities adapted from Gravholt et al. (2017).

40.4 Low Level Mosaicism in Adult Women

Mosaicism may develop in adult women over the age of 50 years as part of the ageing process and those with less than 5% 45, X cells should not be diagnosed with TS. For women less than 50 years of age, there has not been a defined specific lower limit for 45, X that would confer a diagnosis of TS (Gravholt et al. 2017), however many have used 5%.

40.5 Disclosure

When a child is diagnosed with a sex chromosome aneuploidy before birth, during childhood or adolescence, parent's and clinicians face the decision of when and how to disclose the diagnosis to the child. Many with TS have reported that their diagnosis or other important information was inappropriately withheld from them. In one study conducted in the United States, up to one-third of patients with TS reported that their families and/or health providers withheld all or part of the Turner syndrome diagnosis from them (Sutton et al. 2006). Additionally, many young women with TS were not informed of the infertility associated with their diagnosis. A timely, caring and age-appropriate disclosure of diagnosis and what this means for the individual child is recommended. While every aspect or risk of TS does not have to be elucidated on first discussion, open and truthful communication is key and serves as a foundation for future interactions, discussions, and revelations. Early factual knowledge gives children time to adapt gradually in steps appropriate to their age and emotional maturity. Very young children can be told of the diagnosis in general terms with further disclosures timed or provided based on the child's own understanding and inquisitive questions, age or health needs. While some parents may strongly prefer to withhold information for a "right-time", this becomes increasingly more difficult to do particularly when signs and symptoms may progress or evolve or when comprehensive health surveillance screening or active treatment is being instituted and family and health care practitioners have to explain why they withheld timely disclosure. With the internet children can easily do their own research on symptoms they experience (Sutton et al. 2006). An atmosphere of secrecy discourages children from asking questions, knowing themselves and participating in their own health care, and it may cause child to be distrustful of parents and health care providers once disclosure has been made.

40.6 Cardiovascular Disease and Risks

The pathogenesis of cardiovascular developmental defects in TS is not well understood (Bondy et al. 2013). Structural cardiovascular anomalies affect more than 50% of individuals diagnosed with TS (Bondy and Turner Syndrome Study Group 2007) and cardiovascular disease is a major cause of morbidity and mortality in this syndrome. The presence of webbed neck, which is indicative of foetal lymphedema, is significantly associated with coarctation of the aorta (COA) and bicuspid aortic valve (BAV) (Pinsker 2012). Additionally, the presence of neck webbing and increased thoracic anterior-to-posterior diameters are predictors for cardiovascular abnormalities. The prevalence of cardiovascular malformations varies across studies and case

Table 40.3 Clinical features in Turner syndrome and reported frequency (adapted from Gravholt et al. (2017))

Clinical appearance/abnormality		Reported frequency (% affected)
Growth failure and short stature	Prenatal poor growth Childhood failure to thrive Adult height 20 cm (average) below general female population	95
Skeletal abnormalities	Decreased bone mineral content Short fourth metacarpal Cubitus valgus Genu valgum Scoliosis Congenital hip subluxation Madelung deformity	50–80 35 50 35 10 20 5
Ovarian failure with hypergonadotropic hypogonadism	Delayed/arrested/absent pubertal development Primary amenorrhoea	75 (delay; commoner in mosaic) 95
Cardiovascular abnormalities	Bicuspid aortic valve Coarctation of the aorta Pulmonary venous drainage abnormalities Increased risk of dilatation of aorta and increased risk of dissection	15–30 7–17 3–42 100-fold increased risk Mean age 35
Metabolic abnormalities	Glucose intolerance	15–50
	Type 2 diabetes mellitus	10
	Type 1 diabetes mellitus	
	Hypertension	50
	Central obesity	
	Dyslipidaemia	50
Renal abnormalities	Horseshoe kidney Abnormalities of renal pelvis, ureters, or vessels	10 15
Autoimmune disorders	Hashimoto's thyroiditis Coeliac disease	15–30; annual incidence 3% 6
Hepatic and gastrointestinal disorders	Elevated liver enzymes	50–80
	Non-alcoholic fatty liver disease	
	Cirrhosis	
	Inflammatory bowel disease	3
Phenotypic characteristics	Lymphedema hands and feet	25
	Broad neck/webbed neck	40
	Low posterior hairline	40
	Broad/shield chest	30
	Micrognathia (small lower jaw)	60
	Multiple pigmented nevi	25
Eyes	Epicanthus Strabismus	20 15
Ears	Otitis media Hearing defects	60 30
Psychological/neurocognitive	Emotional immaturity Learning disorder Visual-spatial organisation difficulties Social interaction problems and social isolation Increased anxiety Low self-esteem	40

reports based on whether echocardiography or cardiac magnetic resonance imaging (CMR) were used. There is a complex and extensive cardiovascular phenotype seen in TS and CMR has identified that many women with TS have abnormal cardiovascular anatomy (Matura et al. 2007). Following diagnosis of TS, evaluation for both *congenital* cardiac structural anomalies, (commonly left-sided heart defects including hypoplastic left heart, COA, BAV, and anomalous pulmonary veins/venous return) and *acquired* (aortic dilation) should take place (Table 40.4).

40.6.1 Acquired Cardiac Disease in Turner Syndrome

The increased morbidity and mortality in adult women with TS is most commonly due to the increased risk of acquired cardiac abnormalities as shown in Table 40.5.

40.6.2 Hypertension

Hypertension is common in TS with a prevalence of up to 30% in children and 60% in adults often beginning in mid-childhood and increasing with age. As a result, regularly monitored blood pressure and aggressive early treatment and management of hypertension is indicated. Careful assessment or reassessment for cardiac and/or renal causes should be undertaken though hypertension may be idiopathic.

Table 40.4 Estimated prevalence of congenital cardiac abnormalities with increased incidence in women with TS (Mortensen et al. 2012)

Congenital cardiac abnormalities in TS	Prevalence (%)
Bicuspid aortic valve	15–30
Coarctation of aorta	17
Atrial septal defect	1–2
Ventricular septal defect	1–4
Partial anomalous pulmonary venous drainage	13–15

Table 40.5 Acquired cardiac abnormalities in women with Turner syndrome

Acquired cardiac abnormalities in TS	
Aortic dissection	1–2%
Ischaemic heart disease	
Hypertension	50%
Prolongation of QT interval on ECG	20%

40.6.3 Aortic Dissection

The increased risks for cardiovascular malformations compounded by renal abnormalities and hypertension leads to the increased risk for aortic dilatation and dissection in TS. The risk for aortic dissection is approximately 100-fold higher than that seen in women of similar age without TS. The aetiology is ill understood. The risk of aortic dissection or rupture is felt to be related to a high rate of generalised dilatation of major vessels (aorta, brachial, and carotid artery in TS) (Granger et al. 2016). The risk factors include bicuspid aortic valve, hypertension, coarctation of the aorta, and pre-existing aortic dilation. BAV is present in approximately 30% of patients with TS (Sachdev et al. 2008) and in one TS registry in 95% of patients who experience dissection (Turtle et al. 2015). This is a risk across the lifespan as there have been reports of aortic dissection both in children and adults with TS with and without risk factors. The consequences of late recognition can be devastating. The added vascular strain in pregnancy in women with TS significantly increases this risk further (Bondy 2014).

To minimise the risk for aortic dissection all patients should have regular and continuous cardiovascular monitoring (Granger et al. 2016) and especially closer follow-up for those with dilated ascending aorta, bicuspid aortic valves, history of coarctation, and/or hypertension. Dissection is not always preceded by progressive dilatation. Aortic parameters are corrected for body surface area (BSA) as this is a major determinant of aortic size and allows standardisation of recommendations and sequential monitoring. The ascending aorta is the most affected and informative site and dissection risk is highest for those with an aortic size index (ASI) of >/=2.5 cm/m^2. Those with an ASI of >2.0 cm/m^2 require close cardiovascular

surveillance. An ASI of >2.0 cm/m^2 (>99th percentile) is considered a dilated ascending aorta (Carlson et al. 2012). Surgical intervention is recommended for coarctation of the aorta, and/or if significant aortic dilatation develops.

Women with aortic dilation need more frequent echocardiographic/CMR monitoring of change in size, aggressive management of blood pressure, advice regarding exercise, careful assessment if pregnancy is planned, and education regarding the symptoms of aortic dissection and appropriate action to take. Classic signs and symptoms of aortic dissection include sudden onset of chest or back pain and may include shortness of breath, nausea, diaphoresis, and syncope. Wearable medical alert documentation should be worn for those identified with increased risk for dissection or rupture.

40.6.4 Conduction Anomalies

Conduction abnormalities such as prolonged QT intervals have been reported in TS including in young children (Bondy et al. 2006a). Prolonged QT intervals may occur at any heart rate and is associated with reduced heart rate variability, resting tachycardia and absence of the normal nocturnal dip in blood pressure, indicating autonomic dysregulation. In those with a prolonged corrected for heart rate (QTc) on ECG, care should be taken when prescribing medication which may further prolong repolarisation. Figure 40.2 presents the protocol for monitoring women aged over 16 years old based on the international guidelines (Gravholt et al. 2017).

Thus, cardiovascular screening is essential from the time of diagnosis and continued with regularity throughout childhood and adult life. Evaluation by a cardiologist should include regular echocardiography from childhood. In addition, CMR is recommended in older girls and women as this provides a more accurate assessment and serial measurements, in addition to reducing the error due to the common chest abnormalities in women with TS (Fig. 40.3). Repeat imaging should be performed every 3–5 years and more often if aortic dilatation or other pathology is detected and/or pregnancy or fertility treatment is considered. Blood pressure should be monitored annually and hypertension treated early and vigorously, particularly in the

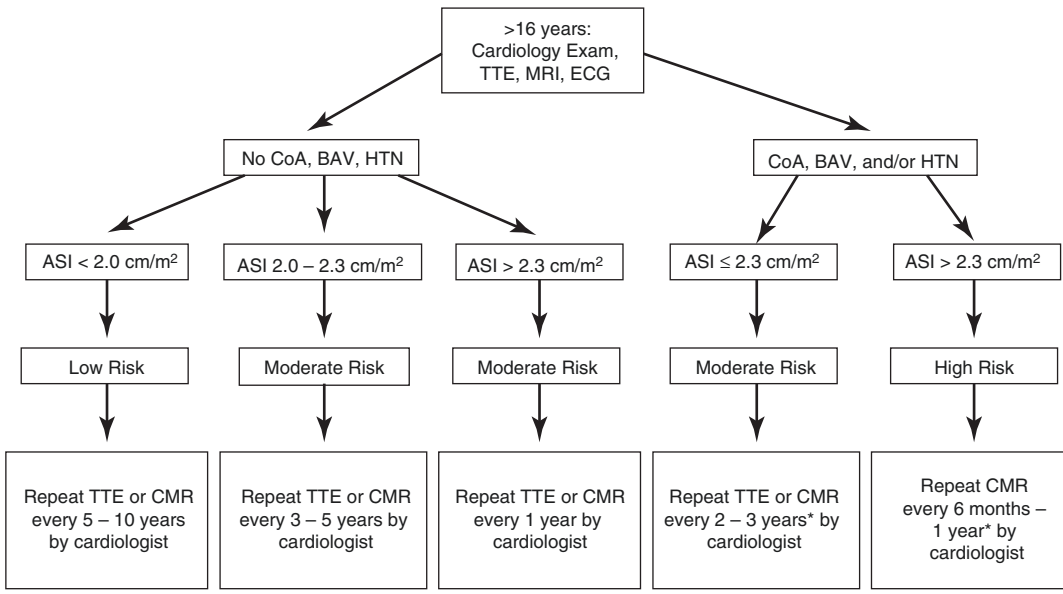


Fig. 40.2 Suggested monitoring protocol for women aged over 16. Used with permission from International guidelines 2017 (Gravholt et al. 2017). Key: *TTE* transthoracic echo, *CMR* cardiac MRI, *ECG* electrocardiogram, *HTN* hypertension, *CoA* coarctation of aorta, *BAV* bicuspid aortic valve, *ASI* aortic size index

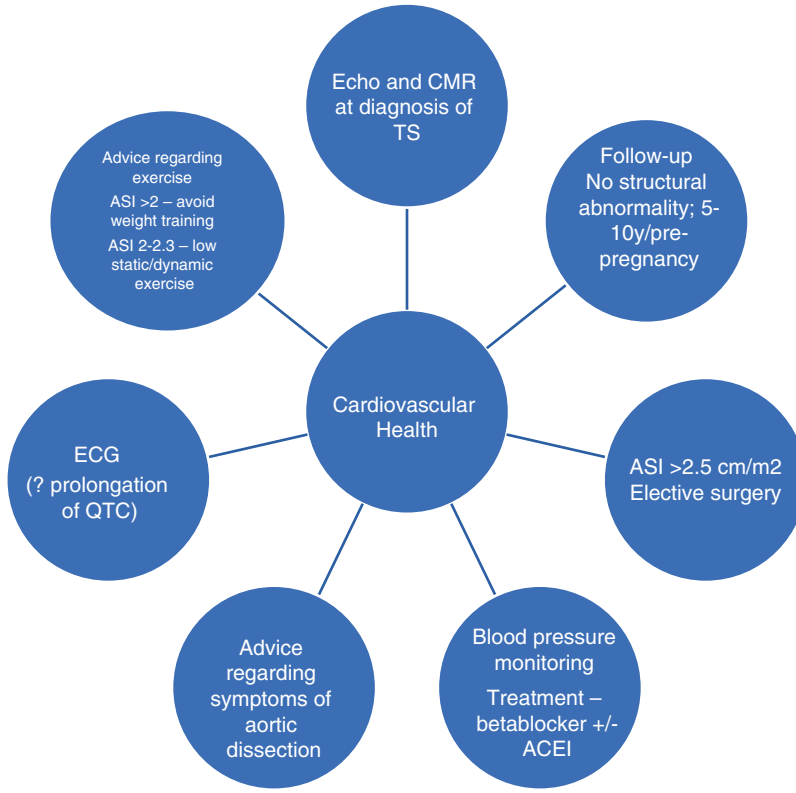


Fig. 40.3 Suggested investigations and management of cardiovascular parameters in Turner syndrome

presence of other cardiac abnormalities. According to the 2007 American Heart Association (AHA) guidelines, antimicrobial prophylaxis to prevent bacterial endocarditis is not required for valvular heart disease including those with BAV (Wilson et al. 2007).

40.7 Short Stature, Growth Failure, and Growth-Promoting Therapies

Short stature is a major clinical finding associated with 45,X karyotype and is the main phenotypic abnormality present in nearly all patients with TS. It is thought to be primarily due to haploinsufficiency (deficient expression) of the short stature homeobox (SHOX) gene expression in chondrocyte. This region does not undergo X-inactivation and it appears that two active copies of this gene are required for full expression of the protein and normal linear growth. Specific skeletal anomalies such as cubitus valgus, Madelung deformity, and shortened fourth metacarpals may also be manifestations of SHOX deficiency. Growth hormone insensitivity may also play a role in the development of short stature.

Growth failure generally begins prenatally, with eventual poor growth that may be evident within the first 3–5 years of life (Davenport et al. 1999). Final adult height is generally 20 cm below expected average female population norms. This translates to an average height of 143 cm (4′8″). It is important to note that girls and women with TS are generally not growth hormone deficient (GHD) as they have increased insulin binding protein-3 (IGFBP-3) proteolytic activity and normal to lower insulin growth factor-1 (IGF-1).

For monitoring growth, height should be tracked using a TS-specific growth curve. Lyon,

Preece, and Grant combined the growth data from four European studies representing a total of 366 patients to create the TS-specific growth chart (Lyon et al. 1985) that documents the expected growth trajectory of girls with TS on a given centile. The standard TS chart may be used from 2 years of age onward. All girls with TS should be tracked on a TS-specific growth chart which allows for the simultaneous opportunity of tracking the patterns of growth of an individual child relative to both the general female population and to other girls with TS. Of note the 50th centile of growth on the TS curve is below the fifth centile of the standard growth charts for North American females. By 5 years of age, 90% of girls with a 45,X karyotype will be below the fifth centile on non-TS female growth charts. During childhood girls with TS gain, on average, less than 5 cm of linear height each year, and this eventually translates to growth below the fifth centile, though it is not uncommon for those with mosaic and/or isochromosome karyotypes to have normal growth velocity during early childhood. For girls whose growth shows crossing of growth centiles in a downward direction on the TS growth curve consideration may be given to further assessing for growth hormone deficiency (GHD).

40.7.1 Growth Hormone Therapy in Turner Syndrome

Use of growth hormone (GH) is an approved indication of GH therapy in Europe, and North America. The optimal age of initiating GH therapy has not been firmly established and generally, treatment with GH is justified as soon as growth failure becomes evident (Davenport et al. 1999). A controlled, randomised study to final adult height of patients with TS showed a gain of 7.2 cm over a mean of 5.6 years of using higher doses of GH as compared to the usual doses used in the United States and Europe (Stephure and Canadian Growth Hormone Advisory Committee 2005). This translates into an expected approximate 1 cm of additional growth for every year on GH therapy. GH is required for a minimum of 3–4 years or more to see a meaningful impact on adult height.

Even with GH treatment, adult height remains at least 10 cm below the average height of healthy females thereby correcting up to 50% of the adult height deficit. Final adult height in TS is highest for those with a mosaic karyotype, taller stature at initiation of GH therapy, taller parents, and those that received higher dosing and longer duration of GH therapy (Hughes et al. 2011; Ranke et al. 2007; Ross et al. 2011a). Cochrane Reviews published in 2003 and 2007 reviewed four randomised control trials (RCT) using recombinant GH and noted that GH increased short-term growth in girls with TS by approximately 3 cm in the first year of treatment and 2 cm in the second year of treatment and noted the final adult height (FAH) was still more than 2 SDS below the normal population mean (Cave et al. 2003; Baxter et al. 2007).

Many jurisdictions, health systems, and/or insurance companies require evidence and documentation of growth failure or growth fall off prior to providing financial coverage, and/or initiating financially supported expensive GH therapy in TS. Subsequently, funding sources may require proof of continued enhanced growth benefit, documented in centimetres or inches over and above the pre-GH therapy growth rate.

40.7.1.1 Additional Benefits of Growth Hormone Treatment

The literature suggests that GH treatment may also confer a number of additional benefits such as improving body proportions; contributing to cardiac health by lowering diastolic blood pressure even after GH treatment has been discontinued (Bannink et al. 2009a); as well as lowering of total cholesterol and low-density lipoproteins, elevating high-density lipoproteins (Bannink et al. 2009b), and improving insulin resistance as abdominal adiposity is reduced during treatment.

40.7.1.2 Safety of Growth Hormone Treatment

The general safety of GH Treatment in the literature has been reassuring; however, observational

data indicate that when compared with children with idiopathic GHD or idiopathic short statue on GH, girls with TS appear to be at increased risk of intracranial hypertension, slipped capital femoral epiphysis, development and/or progression of scoliosis, and development of pancreatitis during treatment (Allen 1996). Data from large GH registries provide no evidence of an increase in risk of neoplasia in GH-treated patients with TS (Bell et al. 2010; Bolar et al. 2008; Tuffli et al. 1995).

The Food and Drug Administration has approved 0.375 mg/kg/week (generally given as 6 or 7 divided doses per week) for the GH treatment of TS. Higher doses of GH do not correlate with much increased height gain but do correlate with elevated insulin growth factor 1 (IGF-1) levels (van Pareren et al. 2003). As girls with TS are not GHD and may in fact be somewhat GH resistant, therapy for this population requires greater doses of GH than those used for children with GHD to impact growth. There is significant and substantial variation in GH treatment response among girls with TS, and there is no way to predict how well an individual child with TS will respond to therapy. Most will likely not achieve their genetic potential based upon mid-parental heights. In childhood, girls with TS tend to grow 2.5–4 cm or a year without GH, thus clinicians need to be mindful of this in their ongoing therapeutic assessments and not to ascribe all future growth to GH therapy if and when it has been instituted. Risks of GH therapy in TS include slipped capital femoral epiphysis and idiopathic intracranial hypertension (with persistent visual defects) that are higher than in those treated with GH for GHD and idiopathic short stature (Noto et al. 2011) and worsening scoliosis (Bell et al. 2010). Growth should be monitored every 4–6 months while on GH therapy (Gravholt et al. 2017). GH treatment is given by subcutaneous injection generally 6 or 7 days each week. This therapy requires considerable commitment by both children and families. Many families also choose not to pursue GH treatment and this is also appropriate.

The previous clinical practice of delaying pubertal development until 15 years of age with the goal of preventing earlier epiphyseal closure, to allow more time for growth to improve final adult height, is no longer acceptable as it generally failed to recognise the importance of age-appropriate pubertal development and maturation for overall general and psychosocial health.

40.7.1.3 Very Early Growth Hormone Treatment

Somewhat recent studies have reviewed the safety and efficacy of beginning GH treatment in very young girls with TS prior to the expected and eventual fall off in growth velocity. The Toddler Turner Study showed that GH rapidly normalised height standard deviation score (SDS) after 2 years of treatment for those that initiated treatment between 9 months and 4 years of age (Davenport et al. 2007). In the French Collaborative Young Turner Study Group, 80% of girls with TS who started GH at a mean age of 2.6 years of age achieved height within the normal range within 4 years (Linglart et al. 2011); however, 75% of this treatment group had elevated IGF-1 levels. The clinical implications and significance of long-term elevated IGF-1 levels in the childhood years in TS is unknown.

40.7.1.4 Early Oestrogen and Growth Hormone Treatment

Early low dose oestrogen has been studied as a way to supplement GH treatment. Some studies have trialled low dose oestrogen (oral ethinyl oestradiol) as early as 5 years of age and showed a synergistic effect of increasing adult height of 2.1 cm beyond the 5 cm of height gain expected when GH treatment was used alone (Ross et al. 2011b). However, this treatment also reported frequent findings of inappropriate early pubertal development or feminisation of young girls. The long-term consequences of early and prolonged oestrogen exposure and relation to future risk of breast cancer are unknown. At this time, use of early low dose oestrogen as a growth-promoting therapy is not supported by the literature and is not recommended (Gravholt et al. 2017).

40.7.1.5 Oxandrolone Adjuvant Therapy

The use of the synthetic anabolic steroid and derivative of testosterone, Oxandrolone, is con-

sidered to be an adjuvant therapy. Oxandralone has been shown to improve growth by acting directly at the growth plate, and by increasing IGF-I concentrations, and blocking the bone maturation effects of oestrogen which may provide up to 4 cm of growth with the use of GH therapy in TS (Rosenfeld et al. 1998). Oxandrolone is FDA-approved for treating osteoporosis, aiding weight gain, and counteracting the catabolic effect of long-term corticosteroid treatment; use of it in TS is considered off-label. Caution is required as the use of Oxandrolone may be associated with virilisation (enlargement of clitoris, deepening voice), hypertension, delay or deceleration of breast development, and liver dysfunction (Matura et al. 2007). If girls are experiencing these side effects, the doses of Oxandrolone would require reduction thereby reducing the effectiveness of the treatment. It is unclear if the taller height associated with this adjuvant treatment is due to more time for growth, more time on Oxandrolone, or more time on GH (Sheanon and Backeljauw 2015). Doses range between 0.03 and 0.05 mg/kg/day. Oxandrolone therapy would be discontinued prior to initiating hormone replacement therapy. The long-term beneficial effect of Oxandrolone on adult height in TS women has been debated due to the small sample size of studies, varied results in adult height outcomes, and the concern of virilisation due to this treatment. As it has not demonstrated a real benefit for adult height, it is not considered standard of care.

40.7.1.6 Diminished Pubertal Growth in Turner Syndrome

It is important to note that the absence of, or the generalised diminished pubertal growth spurt, with or without HRT will ultimately reduce FAH, and height predictions in TS. Ultimately, GH increases linear growth and height in the childhood years with generally rapid plateauing of height in the pubertal years. It is not uncommon to later question how much GH therapy ultimately added to FAH when tracking where a girl started (using height standard deviation scores SDS) on the TS curve, and where she ultimately ended up.

40.7.1.7 Discontinuing Growth Hormone Therapy

Discontinuing of GH therapy in TS is an individualised clinical decision. Though the literature supports the discontinuation of treatment when little growth potential remains (bone age of >/=14 years or growth velocity is less than 2–3 cm/year). Other considerations could and should sway earlier discontinuation decision-making. These include increasing body disproportion, particularly enlarged hands and feet; coarsening of facial features (rare); very elevated IGF-1; poor adherence; a voiced desire to end therapy; and contentment with current height. It should be noted that those who discontinue therapy between 14 and 15 years of age will still grow an additional 1–2 or more centimetres over the following years.

40.8 Pubertal Development, Ovarian Failure, and Ovarian Hormone Replacement Therapies (HRT)

Up to one-third of girls, especially those with mosaic karyotypes, may have normal spontaneous pubertal development (Pasquino et al. 1997). Ovarian function is generally related to underlying karyotype; those that achieve menarche or very rarely pregnancy are predominately individuals with a mosaic karyotype. Spontaneous thelarche occurs in approximately one-third of girls with TS. Normal puberty may occur and there have been some numerous reports of precocious puberty in TS underscoring the phenotypic variability that occurs whereby girls with TS may have normal functioning ovarian tissue. If gonadotropins are within the normal range for age, continued observation for the development of spontaneous puberty is appropriate.

The majority of girls with TS will have primary hypogonadism and/or primary or secondary amenorrhea related to gonadal dysgenesis. Streak gonads are seen in at least two-thirds of patients. Girls with TS have viable oocytes in foetal life however undergo accelerated oocyte degeneration that may begin as early as 18 weeks

gestation, when fibrous degeneration/erosion of ovarian follicles begins. Follicular loss continues following birth and will affect pubertal development and spontaneous menarche in a majority of individuals with TS. Elevated and/or rising gonadotropins (luteinising hormone (LH) and follicle stimulating hormone (FSH)) are associated with progressive ovarian failure. Spontaneous pregnancies are reported to be rare, in the 3–5% range. Most will require exogenous oestrogen therapy for pubertal initiation, sexual maturation and/or maintenance of secondary sexual characteristics, optimising uterine growth, attaining peak bone mass, supporting brain, and cardiovascular health.

Current recommendations encourage initiation oestrogen therapy between 11 and 12 years of age (Gravholt et al. 2017). This allows for age-appropriate secondary for those that require it here sexual characteristic development and menarche in line with peers without compromising adult height. It also supports normalised uterine and bone mineral development, improved cognitive and hepatic function and quality of life (Bannink et al. 2009b; Kanaka-Gantenbein 2006). Prolonged oestrogen deficiency in TS is linked to low BMD (Bondy 2007).

Transdermal preparations are preferred as this is more physiological and avoids excessive hepatic exposure to oestrogen (Gravholt et al. 2017). However, generally staged 17B ethinyl oestradiol use is started with 0.25 oral. 0.5 mg increased to 1.0 mg, increased to 1.5 mg, increased to 2.0 mg every 6 months then medroxyprogesterone 10 mg for 10–12 days each month once breakthrough bleeding occurs or after 2 years of oestrogen treatment (Gravholt et al. 2017). Unopposed oestrogen therapy causes uterine hyperplasia and increases risks for spontaneous and unexpected spotting and increases uterine cancer risk. Eventual transition is to monophasic oral contraceptive pill packs taken as directed or that may be used in the extended or continuous regime (using 3 or more 21 day packages sequentially before a withdrawal bleed is instituted with a no-pill or sugar-pill week). Newer continuous HRT products may be considered whereby menses occurs every 3 months or more.

Once adult replacement is reached, treatment should generally persist until menopause, around 51 years of age, unless the risk of continuation outweighs the benefits. The use of transdermal oestradiol (TDE) facilitates a more physiologic mode of delivery without hepatic first-pass metabolism effects. TDE has been reported to result in: faster bone accrual in the spine; improved uterine growth; possible increased FAH; and reduced thrombotic risk, when used. Though touted to be amenable to dose modification by cutting of the patches, to customise dosing and dose adjustment, this is not recommended by the manufactures. Transdermal gels are often well tolerated and avoid the difficulty with patches. There will be increased use of TDE in pubertal induction and adult replacement in TS in the coming years once optimal dosing has been further elucidated.

40.8.1 Hormone Replacement Therapies and Cardiac, Thrombosis, Cancer Risk

Recent studies have suggested that thrombosis may be more common than previously believed in TS raising concerns for increased thrombosis risk with HRT (Calcaterra et al. 2011). The use of transdermal oestradiol (TDE) may lower the risk of thrombosis when compared with oral oestrogens (Vrablik et al. 2008; Canonico et al. 2007). It is not uncommon for many young women with TS to have poor adherence to treatment and/or have declining use of HRT in general (Bondy et al. 2006b).

HRT treatment in TS has not been shown to increase risk for myocardial infarction or cancer risk in women with TS (Bosze et al. 2006).

A national cohort study in the UK noted that in addition to having an increased risk of gonadoblastoma, women with Turner syndrome seem to be at increased risk for meningioma and childhood brain tumours, and possibly bladder cancer, melanoma, and corpus uteri cancer. However, they were at a decreased risk for breast cancer. Reasons for these risks might relate to genetic and hormonal factors or to the effects of

hormonal treatments given to women with Turner syndrome (Schoemaker et al. 2008).

40.9 Breast Development in Turner Syndrome

Poor breast development is not uncommon in TS. This is related to the broad shield-like chest with wide spaced nipples that is remnant of foetal lymphedema whereby a tight fibrous mesenchymal layer resists growth in any or all of the breast quadrants, except at the areola which is an area of low resistance resulting in tubular breast development with large areolas for some. A paucity of medial and inferior breast tissue/skin leads to inner quadrant tightness and a tendency for areolas to face medially and inferiorly. Poor breast development may make pubertal breast staging difficult or inaccurate with or without the use of HRT. Poor breast development may have psychosocial implications for adolescents and adult women with TS affecting self-esteem and establishing intimacy. Plastic surgery consultation for breast enhancement should be considered for older teens and women who have experienced this. In many jurisdictions, surgical breast augmentation may be covered by national health systems or insurance by being categorised as a congenital anomaly or defect.

40.10 Fertility and Reproductive Assistive Technologies and Pregnancy

As a result of ovarian failure, most women with TS are infertile. The literature has noted this to be a major issue affecting quality of life (QOL). Spontaneous pregnancies occur in 4.8–7.6% of women with TS. Unfortunately, the frequency of foetal loss from miscarriage after spontaneous pregnancy is quite high and reported to be 30.8–45.1% (Gravholt et al. 2017). Also, pregnancies in TS are complicated by higher rates of foetal malformation (TS and Down syndrome). Women with TS also have higher rates of pregnancy complications including hypertension, pre-eclampsia, and aortic dissection. Delivery is frequently via caesarean section due to body habitus and complications, which increases morbidity and mortality for both the mother and foetus. In the past, TS has been categorised as a relative contraindication for pregnancy and absolute contraindication for those with documented cardiac anomaly (surgically repaired cardiovascular defect BAV, evidence of aortic dilatation, systemic hypertension) by the American Heart Association (Hiratzka et al. 2010). More recently, a risk stratification approach is accepted which involves careful assessment by a multidisciplinary team and careful cardiac imaging pre-conception (Gravholt et al. 2017).

Most women with TS are infertile due to primary ovarian failure but approximately 5% may achieve spontaneous pregnancy particularly if they have a mosaic karyotype 45X/46XX. Integrity of the long arm of the X chromosome is required for maintaining fertility (Quilter et al. 2010). Most women will therefore require assisted reproduction with in vitro fertilisation (IVF) using donor oocytes to attempt pregnancy. It is important to assess and counsel women who have not yet developed ovarian failure in order to plan pregnancy because of the risk of premature ovarian failure. Anti-Mullerian Hormone (AMH) is the best endocrine marker of the size of the population of the reserve pool of small antral follicles within the ovaries (Broer et al. 2014). In the near future, consideration of oocyte, ovarian, or embryo cryopreservation will be important in this group (Oktay et al. 2016).

Pregnancy and fertility in a woman with TS requires discussion, assessment, and education *a*. pre-conceptually, *b*. during any pregnancy, and *c*. when planning delivery of the offspring. A multidisciplinary approach with input from cardiology (including echocardiography and CMR before any pregnancy consideration), genetics, fertility, and obstetrics is essential to discuss and optimise the likelihood for safe attempts or successful outcome. Multiple embryo transfer is contraindicated. Particular risks of pregnancy for a woman with TS include progression of aortopathy with 1–3.3% risk of dissection particularly associated with assisted reproduction; due to pregnancy-associated

increased haemodynamic strain and also hormonal factors (Bondy 2014; Hadnott et al. 2011). Complications of the pregnancy itself include higher rates of spontaneous abortion, foetal anomaly, premature birth, low birth weight offspring, and cephalopelvic disproportion. Less than 40% may have an entirely normal pregnancy. While vaginal delivery may be possible delivery needs to be carefully planned with elective or emergency caesarean section anticipated for most (Hewitt et al. 2013).

40.11 Lifelong Screening and Management in Women with Turner Syndrome

Girls and women with TS need to be followed for life with regular screening not only for the management of age-appropriate issues, e.g. growth and puberty, fertility and pregnancy, but also for the development of complications, e.g. cardiovascular and autoimmune disorders (Conway et al. 2010; Culen et al. 2017) (Figs. 40.4 and 40.6).

Women with TS should be seen at an annual visit for physical examination, e.g. blood pressure, body mass index, and for biochemical investigations to assess for glucose intolerance, dyslipidaemia, liver abnormalities, and thyroid function. Education is an essential component to lifelong care with advice regarding weight management, hypertension, diabetes, hepatic steatosis, and osteoporosis.

40.11.1 Autoimmune System and Autoimmune Disorders

Many autoimmune conditions are commoner in girls and women (Table 40.6) (Bondy 2007) and their incidence increases with age. It is unclear what the underlying mechanism of the TS-associated increased risks of autoimmunity are. One theory is the higher rate of autoimmunity is related to the haploinsufficiency of immunoregulatory genes on the X chromosome, like FOXP3, which encodes a transcription factor that is critical for natural regulatory T cell control

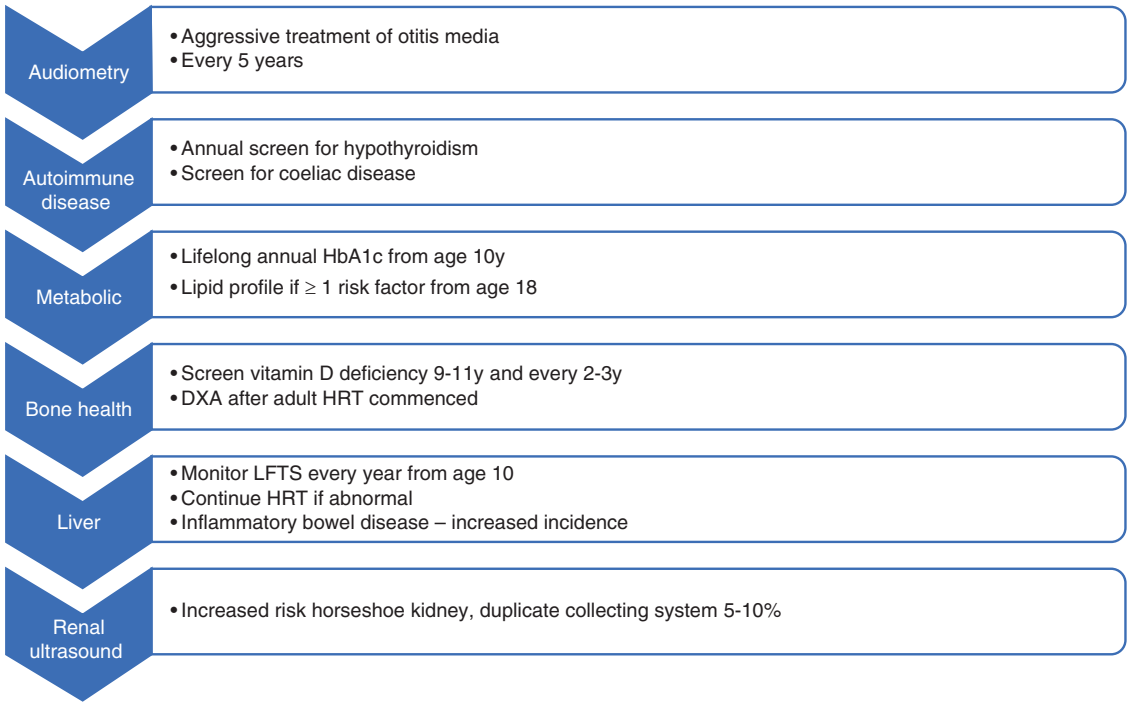


Fig. 40.4 Screening and lifelong monitoring in Turner syndrome

Table 40.6 Autoimmune conditions associated with Turner syndrome showing those which are commoner than the background female population

Increased	No increase
• Primary hypothyroidism? 3.2%	• Addison's disease
• Graves'	• Autoimmune polyglandular syndrome 1 and 2
• Coeliac disease	
• T1 DM	
• Alopecia areata • Rheumatoid arthritis	
• Uveitis	
• Inflammatory bowel disease	

(Invernizzi et al. 2005; Pessach and Notarangelo 2009) and thus may play a role in autoimmune conditions (Bakalov et al. 2012). FOXP3 deletions cause immunodysregulation, polyendocrinopathy, and enteropathy (Bakalov et al. 2012). Currently, there are at least ten genes located on the X chromosome which have been identified with possible immune regulatory functions (Pessach and Notarangelo 2009).

40.11.1.1 Autoimmune Thyroiditis

Autoimmune thyroiditis is the most common autoimmune diagnosis in TS and occurs in 10–37% with prevalence increasing with advancing age. It rarely develops in those less than 4 years of age. Hypothyroidism develops in approximately 15% of those under 18 and up to 30% in adulthood and up to 50% of adults will have positive thyroid antibodies (Elsheikh et al. 2001a). Women with the isochromosome X are at particular risk of developing autoimmune thyroid dysfunction (Elsheikh et al. 2002). Screening at diagnosis, and regular annual thyroid function screening beginning at 4 years of age, along with thyroid antibodies every 3–5 years to identify those at risk for future thyroid disease is recommended (Bondy 2007).

40.11.1.2 Coeliac Disease

Intestinal autoimmunity, such as coeliac disease (CD), is an autoimmune disease prevalent in 1–2% of Western populations. Individuals with TS are at a threefold increased risk of CD and the recommendation of active case finding for CD in TS continues to be supported by the literature (Marild et al. 2016). Regular, every 2–5 years, screening of tissue transglutaminase immunoglobulin A antibodies (tTG-IgA, usually combined with total IgA) should begin in childhood (Bondy 2007). Testing should take place regularly throughout the lifespan as classic overt symptoms of coeliac disease may not be present in TS, though tTG-IgA testing, endoscopy, and intestinal biopsy may confirm active disease.

40.11.1.3 Inflammatory Bowel Disease

The prevalence of inflammatory bowel disease (IBD) in TS approximately 3–4% whereby the rate in the general population is less than 0.5%. Onset of inflammatory bowel disease tends to be earlier with more severe symptoms in TS. Crohn's disease is more frequently diagnosed than ulcerative colitis and isoXq karyotype makes up more than half of those with IBD (Gravholt et al. 2017; Elsheikh et al. 2002).

40.11.1.4 Juvenile Rheumatoid Arthritis

An association with juvenile rheumatoid arthritis and psoriatic arthritis has been noted in TS, and it is important to have an underlying suspicion of inflammatory arthritis when there is radiologic evidence and/or clinical joint symptoms (Wihlborg et al. 1999).

40.11.2 Metabolic Issues; Diabetes, Insulin Resistance, and Glucose Intolerance

Metabolic issues, diabetes, insulin resistance, and glucose intolerance occur more frequently in TS than in the general population. Epidemiological studies have demonstrated the risk of diabetes mellitus, both type 1 and type 2, is about tenfold and fourfold higher in girls in women with TS. Annual lifelong monitoring for diabetes is essential in TS, as the risk of both type 1 and type 2 diabetes is significantly increased and occurs at a younger age, when compared to the general population (Gravholt et al. 2017). Impaired

glucose tolerance, insulin resistance, and other abnormalities of glucose metabolism are more common and found in up to one-third of women with TS. Recently presented data suggest that diabetes in TS may be different to that in the general population as TS-associated diabetes has features of both type 1 and type 2 diabetes. The association with autoimmune hypothyroidism suggests an autoimmune pathway may be more prominent than previously thought and that being overweight could compound the autoimmune risk (Cameron-Pimblett et al. 2017) (Fig. 40.5).

Overweight, obesity, and growth hormone treatment exacerbate insulin resistance. Monitoring of fasting blood glucose concentrations should be regularly completed on any who are significantly overweight, have a strong family history of type 2 diabetes mellitus, are a member of a higher risk ethnic group have signs of insulin resistance such as acanthosis nigricans and/or are on GH therapy. Annual measurement of HbA1c with or without fasting serum glucose starting at age 10 years or sooner if significant risk factors present is recommended.

40.11.2.1 Obesity

While the TS literature frequently mentions obesity associated with this syndrome, there is a paucity of literature. The prevalence of obesity in TS reflects population means in most studies. TS is a high-risk condition for complications related to the development of early cardiovascular disease and hypertension independent of obesity. Supportive active medical management is required to reduce and avoid risk factors that additionally predispose to this increased risk. Obesity increases the risk for insulin resistance in the general population and girls and women with TS should be counselled and encouraged to maintain their weight within an appropriate range for height. Girls and women with TS tend to have increased cholesterol and LDL. GH treatment and obesity exacerbate insulin resistance. Thus, counselling and guidance regarding weight control and healthy lifestyle behaviours including decreasing intake of problematic foods and fluids and maintaining increased rates of physical activity especially weight bearing exercises (Frias et al. 2003), with referral to weight management programmes if needed, should be strongly encouraged.

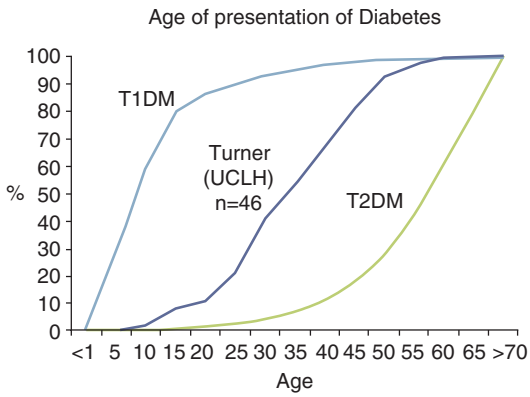


Fig. 40.5 Graph showing age of presentation of diabetes in women with TS compared with non-TS individuals (used with permission from Cameron-Pimblett et al. (2017))

40.11.3 Vascular Malformations of Gastrointestinal System

Gastrointestinal vascular malformations that may cause bleeding such as haemangiomas, telangiectasias, and venous ectasias may involve the small bowel, large bowel, or mesentery have been described in up to 7% of individuals with TS. As discussed earlier, while gastrointestinal bleeding should initially prompt an evaluation for IBD gastrointestinal vascular malformations may also need to be actively considered and evaluated.

40.11.4 Liver Function Abnormalities and Lipid Disorders

Liver function abnormalities are a common finding with increasing prevalence with age. Liver enzyme elevations (ALT, AST, GGT) tend to persist and remain stable or increase over time. The risk of cirrhosis is fivefold that of the general population (Bannink et al. 2009a). Persistent elevated liver enzyme tests warrant further investigation and referral as fibronodular disease, portal hypertension, fibrosis, or steatosis may be present. Several studies have documented improve-

ment or resolution of elevated liver enzymes with HRT regardless of the route of administration (Elsheikh et al. 2001b; Gravholt et al. 2007).

40.11.4.1 Liver Disease

Asymptomatic biochemical changes in liver function are common in TS (Fig. 40.4), and while usually benign, may in some progress to structural changes including fibrosis and cirrhosis. While obesity and insulin resistance undoubtedly lead to increased incidence of non-alcoholic fatty liver disease, more rarely vascular abnormalities and autoimmune conditions such as primary biliary cirrhosis and sclerosing cholangitis may develop (Roulot 2013). Liver biochemistry should be monitored throughout life from age 10 years with further investigation and referral to liver specialist if found to be abnormal.

40.11.4.2 Lipids

An atherogenic lipid profile is very common in TS. Hypercholesterolaemia may affect up to 50% of women with TS with higher total cholesterol, LDL cholesterol, and triglycerides than the general population. There is evidence that oestrogen modifies lipid concentrations (Taboada et al. 2011; Torres-Santiago et al. 2013).

While some studies show an elevation in cholesterol in up to 50% women with TS, others have shown no increased prevalence compared to the karyotypically normal population. The relationship with increased BMI and obesity make it difficult to establish whether TS is an independent risk for developing hyperlipidaemia. However as part of an assessment and optimisation of the potentially atherogenic metabolic profile in TS it is recommended that a lipid profile should be checked from age 18 years or earlier if there are other metabolic risk factors (Gravholt et al. 2017).

40.11.5 Ear Health

Recurrent otitis media is common in the early years in TS and is due to anatomical placement of the eustachian tubes that lie more horizontally and impede drainage. Conductive hearing loss is common due to recurrent otitis media and middle ear effusions (Davenport et al. 2010) in childhood and progressive mid-frequency sensorineural hearing loss development, in the 1500–2000-Hz range often begins in childhood and will affect up to 50% of adult women with TS. An audiological assessment should take place at diagnosis and regularly thereafter.

There is a high prevalence of the development of a cholesteatoma in Turner syndrome particularly with 45X and isochromosome Xq karyotypes (Lim et al. 2014). Early recognition, otolaryngology referral, and surgical treatment of this destructive erosive and expanding growth that consists of keratinising squamous epithelium in the middle ear and/or mastoid process is required for this persistent disease. A cholesteatoma may result in destruction of middle ear ossicles causing hearing loss and may grow through the base of the skull. These may become infected and result in chronically draining ears and conductive hearing loss, classic signs of this condition.

40.11.6 Skeletal Manifestations in Turner Syndrome

Congenital developmental dysplasia of the hip occurs more frequently in TS than in the general population (Saenger et al. 2001) and predisposes individuals to arthritis of the hips. Scoliosis and kyphosis is being increasingly recognised as affecting a larger percentage of children with TS than previously thought. Scoliosis develops in up to 40% and kyphosis in up to 50%. The use of GH in girls with TS and scoliosis may exacerbate single or double curves. While the presence of scoliosis in childhood does not preclude the use of growth-promoting therapies it does warrant close monitoring during therapy (Bondy 2007) and referral to orthopaedic specialists if or when curvature progresses. Other abnormalities of the skeleton include short neck (hypoplasia of the neck vertebrae), Madelung deformity (bayonet deformity), cubitus valgus (increased carrying angles in greater than 50%), and genu valgum (knock-knee) causing an in-toeing gait or genu

varum (bow leggedness), short fourth metacarpal or metatarsal bones.

40.11.6.1 Osteoporosis

Although there may be an element of delayed bone maturation, bone density is lower in TS than the normal population when corrected for height and skeletal maturation (Lanes et al. 1999). Women with TS have reduced bone mass associated with increased risk of fracture, and assessment of bone density and treatment of osteopenia/osteoporosis is therefore essential. Clearly, GH and oestrogen replacement during childhood and adolescence are crucial for achieving peak bone mass. Adolescents, who undergo puberty spontaneously and continue with normal pubertal development have been noted to have normal BMD into early adulthood (Carrascosa et al. 2000). Optimisation of oestrogen replacement through adulthood is essential and is associated with higher bone mineral density (BMD). Regular screening for vitamin D deficiency commencing at age 9–11 and continuing throughout the lifespan with replacement as required is a key recommendation in the recent International guidelines (R 6.14) (Gravholt et al. 2017; Granger et al. 2016). Bone densitometry assessment after transition to the adult clinic allows risk assessment, monitoring, and treatment where appropriate.

40.11.7 Renal/Urinary Findings in Turner Syndrome

Congenital malformations of the renal/urinary system are 10 times more likely to be present in TS (25–40% of patients) (Flynn et al. 1996) compared with 3–4% in the general population. Renal function tends to be normal despite the high incidence of renal tract abnormalities in TS (Nathwani et al. 2000). The common abnormalities include collecting system malformations (20%), horseshoe kidneys (10%), mal-rotated kidneys, and other positional abnormalities (5%). Anomalies associated with the obstruction of the ureteropelvic junction can produce clinically significant hydronephrosis and increased risk for pyelonephritis.

Three primary types of defects are recognised according to the stage of gestational development in which the defect occurs. Defects of the collecting system occur in the first 5 weeks of gestation and these include partial or complete duplications. Generally, renal duplications are of no clinical importance. The second type of defect occurs during the period from 5 to 9 weeks of gestation and relates to the position of the kidneys and includes horseshoe kidney, ectopic, or mal-rotated kidneys. Finally, the third type of defect develops during the end of the first trimester and involves abnormalities of the renal vascular supply.

With the renal fusion of a horseshoe kidney, the kidneys lie vertically instead of obliquely and are joined at their lower poles by midline parenchymal tissue (the isthmus). The horseshoe kidney lies lower in the abdomen (at L3 to L4 vertebral level). With a horseshoe kidney the normal rotation of the kidney is also prevented and the renal pelvis lies anteriorly with the ureters also passing anteriorly over the kidneys and isthmus however enter the bladder normally. Patients with horseshoe kidney can be reassured that these kidneys generally function normally however, symptoms such as abdominal or back pain should raise the question of urinary tract obstruction. Also, these patients require information and about the risks of trauma as there is increased risk of renal injury associated with abdominal trauma as the kidney is not protected by the ribcage.

For horseshoe kidney, the collecting system of each half is usually normally developed and the renal system is also generally normal. However, because the ureters tend to run anterior to the fused portion of the kidney, urine flow may be impeded and ureteric obstruction or secondary urinary tract infection may develop. If severe or inadequately treated, hydronephrosis or pyelonephritis may result. Patients with structural renal abnormalities are at increased risk for urinary tract infections and vesicoureteric reflux. Renal ultrasonography for examination of renal abnormalities at the time of diagnosis is indicated with referral to a Nephrologist Specialist if needed for consultation and/or management of renal disease.

40.11.8 Ocular Abnormalities

Ocular abnormalities are common in TS and the detection and surveillance of eye abnormalities is necessary in all patients diagnosed with TS. The prevalence of visual disturbances in TS is significant as near-sightedness affects 40%, farsightedness 13%, strabismus 15–30%, amblyopia >15%, epicanthal folds up to 45%, ptosis up to 30% hypertelorism 10%, and red-green colour blindness 8–10% (Chrousos et al. 1984; Wikiera et al. 2015). There is no known association between the presence of eye defects and karyotype. Case reports have also noted keratoconus, glaucoma, cataracts, and retinal detachments in TS. Regular ongoing evaluation by an eye specialist optometrist, ophthalmologist will provide surveillance, prevent irreversible deterioration of eye function and permanent poor vision and is recommended from age 12 to 18 months, at the time of diagnosis, and regularly during paediatric years annually and as indicated in adult years.

40.11.9 Lymphedema and Dermatological Related Issues

40.11.9.1 Lymphedema

Abnormal lymphatic development in utero is responsible for many of the traits and physical manifestations in TS. Lymphedema is more common in girls with 45,X karyotype, in the newborn period and tends to regress over time particularly in the first 2 years. Jugular lymphatic obstruction during embryogenesis and early gestation results in nuchal cystic hygroma (Lowenstein et al. 2004). When collateral lymphatic drainage develops, the cystic hygroma resolves leaving a webbed neck (pterygium coli) and the cystic hygroma is no longer present at birth. Referral to Plastic Surgery may be considered for surgical options for improving neck aesthetics and function if limited range of motion, due to moderate to severe webbed neck is present.

Congenital lymphedema of the hands, and feet is present in over 60% of females with TS. Lymphedema may recur or occur at any time especially during puberty or with hormonal treatment such as growth hormone or ovarian stimulation therapy (Bondy 2007) and is caused by a failure of the lymph-conducting system that may be due to failure of lymph reabsorption by the initial lymphatic capillaries (Atton et al. 2015). Lymphedema may be controlled in most cases by support stockings, lymphatic drainage massage therapy, and/or physical therapy. Aggressive therapy should be considered when prolonged swelling leads to pain, skin changes, poor circulation, and/or infections. A four-step intervention with attention to skin and nail care, compressive massage, compression bandaging, and remedial exercise programming may be required (Bondy 2007) to reduce oedema, improve circulation, and reduce risk of infection. Vascular surgery should be avoided when possible.

A low posterior hairline or hair that extends onto the back of the neck, occurs in 40% of girls in TS. Bushy eyebrows and low-set ears are also associated with congenital lymphedema. This develops secondarily to lymphedema and cell migration abnormalities and is thought to be affected by stretching of the skin by the underlying cystic hygroma at around 10–12 weeks gestation with hair follicles growing downward into the underlying tissues. The bushy eyebrows and low-set ears have been attributed to the altered tension on the skin during this same period of development.

40.11.9.2 Nail Dysplasia

Abnormal nail formation or nail dysplasia is found in approximately 70% of those with TS. Peripheral lymphedema is also implicated in the developmental abnormalities of the nails which may be small, narrow, thin, curved, and deeply inserted (Kaplowitz et al. 1993). Nail dysplasia may be particularly marked in the feet with some individuals having very small or complete absence of toenails. Good foot care and well-fitting shoes are important. Individuals with short broad feet may have difficulty purchasing properly fit shoes leading to increased susceptibility to ingrown toenails and other toe, foot, nail, skin problems, and infections. This may lead to

increased risk of infection and cellulitis especially when coupled with lymphedema.

40.11.9.3 Moles and Nevi

There is an increased number of pigmented nevi seen in TS of which the cause is unknown. These nevi have generally been reported as benign melanocytic nevi in 25–70% of individuals with TS (Becker et al. 1994). As with the general population, nevi often increase in number and size throughout childhood and particularly during puberty and adolescence. While there is increased prevalence of nevi in TS there is not an increase in melanoma, and this has led to theories about a tumour suppressive factor operating in TS (Gibbs et al. 2001). Overall, an increased number of nevi is the strongest established risk factor for melanoma (Lowenstein et al. 2004) and as such individuals with a large number of nevi should learn the ABCDEs of mole assessment and have regular assessment of their nevi by their health care provider (HCP) and/or dermatologist. Studies of GH and OHR have failed to confirm any pathologic or harmful impact of these therapies on the number and density of melanocytic nevi (Zvulunov et al. 1998; Wyatt 1999).

40.11.10 Orthodontic and Dental Manifestations in Turner Syndrome

The orthodontic manifestations of TS are well documented and require ongoing evaluation and active management. The mandible in many is positioned posteriorly and is hypoplastic compared with the rest of the face. As a result of this underdevelopment and posterior positioning of the mandible, retrognathia and micrognathia are common. Micrognathia has been reported in more than 50% of TS patients. The palate in TS has been described as high-arched, with either an inverted U-shape or narrow vault. Malocclusion with increased incidence of anterior open bite and lateral cross bite (maxillary teeth are positioned inside the mandibular teeth) when the mouth is closed may be seen. It is not uncommon for girls with TS to have advanced dental age which contrasts with the other conditions of delayed skeletal maturation. Early palatal expansion corrects lateral cross bite. Shortness of dental roots and increased risk for root resorption in TS is problematic for orthodontic movements.

Early paediatric specialty dental and orthodontic referral is indicated in TS with regular follow-up and communication regarding any active growth therapies being utilised (GH or anabolic steroid) as these therapies affect craniofacial growth. As growth hormone improves mandibular growth, it may help to improve and/or normalise retrognathia. Active orthodontic therapy is usually delayed until completion of growth-promoting therapies to avoid the need for re-treatment. As a result of the known craniofacial abnormalities in TS, these patients often benefit from meeting the inclusion criteria for evaluation, surveillance, and active treatment for dental and orthodontic services from various health systems (national, provincial, state) cleft lip and palate programmes funding. Access to these programmes may provide significant financial support for dental and/or orthodontic treatment.

40.11.11 Intelligence, Psychological, Neurocognitive, and Social Issues

Intelligence is within the normal population range; however, many with TS are at higher risk for neurocognitive, behavioural and social domain impairments (Frias et al. 2003), and educational deficits. Non-verbal IQ may be lower than verbal IQ. The learning disability profile associated with TS is unique and may require special accommodations and/or modifications in education in many cases. Verbal abilities or skills are usually quite strong. Many are described as avid early readers and perform well with spelling. There is a high degree of individual variability in the somatic, cognitive, and psychosocial phenotypes (Gravholt et al. 2017). Many are very successful with post-secondary education at colleges or universities.

Selective impairments include non-verbal or specific neurocognitive deficits or challenges particularly with visuospatial, executive function, and/or a non-verbal learning disorder. Those with a ring chromosome ring X chromosomes may have severe mental retardation because ring chromosomes fail to undergo X-inactivation.

Visuospatial deficits tend to be in spatial memory and orientation. Many will also have issues with directional sense, knowing their right and left orientation, extra-personal space perception along with spatial reasoning and visual sequencing (Hart et al. 2006). Visuospatial processing impairments are intensified when tasks require increased working memory. Tasks that involve aspects of driving, finding one's way around new or familiar places, judging distances or geometric mathematics may pose problems.

Executive functioning deficits may include difficulty on tasks of planning, fluency of communication, poor working memory and focusing, which is needed to solve complex problems in a step-by-step fashion.

Non-verbal disabilities include issues with being able to understand incoming visual and spatial information such as being able to recognise what and where an object is, and visualising objects changing position. Some may have difficulties with global processing and "seeing the whole picture".

Genomic imprinting may be relevant, as those who have maternally derived X chromosome have been shown in some studies to have deficits or impairments in social competence and in social adjustment and verbal function compared to those with a paternally derived X chromosome (Skuse et al. 1997). This implies that social functioning may be influenced by an imprinted gene on the X chromosome that is switched off when this gene is inherited from the mother.

Behavioural issues differ by age, younger girls may be very hyperactive, immature, and not particularly cognisant of social cues, and therefore socially vulnerable. In contrast older girls may exhibit continued immaturity, or be inhibited and shy, and experience anxiety, depression, and difficult or unsatisfactory peer relationships and be more socially withdrawn than their peers. There is no evidence of significant psychiatric disorder in TS.

Clinicians working with individuals with TS should be attuned to the neuropsychological phenotype in TS which may significantly impact their patients' ability to successfully navigate social, home, school, personal, and work environments (Hong and Reiss 2012). Any child who is not achieving appropriate developmental or educational milestones deserves assessment, intervention, and regular follow-up from developmental and/or educational specialist services. Neuropsychological and/or educational testing is recommended before enrolment in school or when educational issues become apparent. Re-evaluation will be needed at identified intervals throughout their education. Strengths will be recognised and identified issues and areas for development should be addressed by specific implementation of educational strategies both in the school and home setting.

Psychosocial assessment and support addressing home environment, friends and relationships, and employment should be considered at each visit. Discussions regarding ongoing health surveillance and the importance of lifelong follow-up is essential. Population studies show a broad variation in socioeconomic profile, with a reduced prevalence of TS women in relationships with a partner (Stochholm et al. 2006). While educational attainment does not vary from the background population, employment, and income tend to be lower. A recent 6-year follow-up of women with Turner syndrome showed that women with TS were more likely to live alone and have fewer sexual partners and less sexual confidence compared with controls (Fjermestad et al. 2016). In addition, they had lower self-esteem and life satisfaction. Gender dysphoria is uncommon.

Targeted clinic psychology support is beneficial and optimal for the wide-ranging problems that may exist. Support groups can be invaluable in providing peer group support, information, and practical management advice (Fig. 40.6).

Fig. 40.6 Spectrum of the many aspects of lifelong management in women with Turner syndrome

40.12 Transition to Adulthood

Adolescence and the transfer of a young woman with TS from the paediatric service to adult clinics is a critical time when many young women may be lost to the recommended targeted lifelong management and health surveillance. There is a risk of increased morbidity and mortality associated with lack of follow-up in TS. The emphasis to engage adolescents early on and develop their abilities and knowledge to actively plan and participate in their own care is needed. There are many differences between paediatric and adult health care systems. The paediatric clinic is involved in GH administration, introduction of oestrogen and induction of puberty, initiation of screening for cardiovascular health and autoimmune conditions, and management of musculoskeletal challenges all with their supportive and responsible parent(s) by their side. In contrast, the adult clinic focuses interactions and discussion with the patient themselves rather than the parent and the patient is expected to be a participating partner in her health care, arrive prepared with specific questions for her team and make decisions about treatment by herself. This may be problematic for some young women who still may require parental involvement, due to the intellectual and related functional capabilities and the complexity of number of health issues that may be affecting them. Continued discussion and education surrounding genetic, fertility, and lifestyle issues is essential, along with recognition of potential psychosocial challenges (Culen et al. 2017). It is crucial that care-givers recognise the importance of creating an open dialogue and willingness to address sensitive issues such as sexual health, risk-taking behaviours, sexuality, romantic relationships, and self-esteem in addition to the specific TS health issues and health surveillance recommendations for each individual patient.

40.13 Nursing and Team Considerations

The endocrine nurse plays a crucial role in all phases of the health care journey for the girls and women with TS, their families, and the health care team by providing the appropriate and recommended education and support across the lifespan. An individualised family-centred, multidisciplinary team approach is required to provide medically complex care and long-term surveillance. The endocrine nurse will be able to provide general, TS specific, and detailed health condition information, anticipatory guidance, education and emotional support, and mobilise psychosocial support. The endocrine nurse will participate in and facilitate the coordination and management of multidisciplinary team-related care and ongoing health surveillance and identify when additional evaluations and early interventions may be appropriate for each individual patient. The nurse will recommend and support appropriate strategies for optimal therapy adherence and reinforce the importance of wearable medical alert documentation when needed. The nurse will connect individuals and families to external information and support networks including the Turner Syndrome Support Society (TSSS). Education, information, and provision of useful resources when appropriate throughout the lifetime of a woman with TS is invaluable. The key to successful management of a woman with TS is the relationship which continues throughout their life. Continuity of follow-up, adjustment of direction of care according to the particular stage in their life, and the ability to detect and address sensitive issues is essential.

40.14 Working with Patient Advocacy Groups

Patient Advocacy Groups play a crucial role in improving education and awareness of rare conditions such as Turner syndrome. In Box 40.1, Arlene Smyth describes how the Turner Syndrome Support Society (TSSS) UK was developed and the invaluable resources they provide for patients and health care professionals.

Box 40.1 Case Study and Resources Provided by the Turner Syndrome Support Society (TSSS) UK (Published with Consent)

Sadly, one of the most common calls for supporting the Turner Syndrome Support Society [UK] [TSSS] is the late diagnosis of girls with Turner syndrome [TS] many girls are not diagnosed until they are 15–21 years old. This is a very difficult age for any girl to cope with. For girls with TS, a late diagnosis is devastating to be told that you may be infertile and that you need to choose what is most important to you "height or pubertal development" is very difficult. Parents are left feeling frustrated and guilty as many of them sought advices from their GPs and were told that she is just a late developer and thus missed out on vital timely treatment.

Parents and health care professionals need to know about normal pubertal development to act if there are no signs of breast bud development by 12 or 13 at the latest. There is a health reason and they should be referred to a Paediatric Endocrinologist. The vast majority of girls with TS are beautiful normal looking girls who are shorter than their peers and have no signs of puberty or their puberty started and then stopped. Many of the documented features are not seen in all girls, please see "Diagnosing Turner Syndrome" and other information leaflets available www.tss.org.uk.

The Turner Syndrome Support [UK] was set up to support those affected by Turner syndrome. When my daughter was diagnosed at birth with TS. I wanted her to have friends and I wanted to meet other families too. Initially, it was just friendship and support, then I started to learn more about Turner syndrome and realise what a complex condition it was. I was lucky and met many amazing girls and women

with TS. They were kind and opened up to us about how difficult life could be, in turn that allowed us to come up with strategies to help and support each other.

The TSSS has grown and developed over the years. We have worked with health care professionals to help inform girls and women with TS so they can access the best possible medical care. Ensuring they understand the reason for taking their treatments and the long-term benefits to them. We produce some of the best information on Turner syndrome all checked and approved by our Clinical Advisory Board for accuracy. We have a wonderful relationship with our members we host Open Days, Social Events, and annual conference. We have a large social media presence and regional friendship groups ran by our volunteers.

Being diagnosed with a rare condition in its self is isolating, frightening, and you have so many unanswered questions. Not always about the medical issues but often about behaviour, feelings coping with TS. By helping and supporting families, we provide a service that compliments the excellent care available to those with TS once diagnosed. Together we can help them be the best they can be. This is a quote from one of our teen members who was diagnosed at 12 years old. She was asked what the TSSS meant to her. "The people I have met a long away have changed my life in ways I could not have imagined. I am proud to say I am part of the best family in the world, the TSSS Family a bond so close it can never break. That is what the TSSS means to me".

We are proud to work closely with patients, their families, HCP, and others such as teachers. Our website contains a wealth of information free to download. We have a close bond with other TS groups throughout the world and worked collaboratively on writing guidelines and attending conferences.

Arlene Smyth, Executive Officer at the TSSS Office

Turner Syndrome Support Society [UK]

12 Simpson Court, 11 South Ave, Clydebank Business Park, Clydebank G81 2NR, West Dunbartonshire Tel 0141 952 8006, Helpline 0300 111 7520 Mobile if urgent 07947 554587

www.tss.org.uk

Registered Charity NOS ENG 1080507 SCO 37932

The recently published *patient* directed advice and guidelines to complement the specialist medical publication is invaluable (https://tss.org.uk/downloads/patient_family_guidelines.pdf) and the Turner Syndrome Support Society (TSSS) UK and counterparts in other countries provide a very helpful resource and support. Moreover, the TSSS developed in collaboration with the author and other health care professionals a cardiac alert card (Fig. 40.7) for girls and women with TS to carry in their wallet to alert them and the emergency services, doctors, and nurses of the symptoms, investigations, and urgent management if clinical features of heart dissection develop.

40.15 Conclusion

Turner syndrome is the commonest karyotype abnormality affecting women, and associated with a broad spectrum of clinical abnormalities which present different challenges throughout a woman's life from birth to older age. Successful management requires increased ascertainment and earlier diagnosis of the condition, continuity of follow-up from childhood into and throughout adulthood, lifelong monitoring and the treatment where required of the various complications that arise in addition to the provision of appropriate social and psychological support throughout a woman's life. In the future,

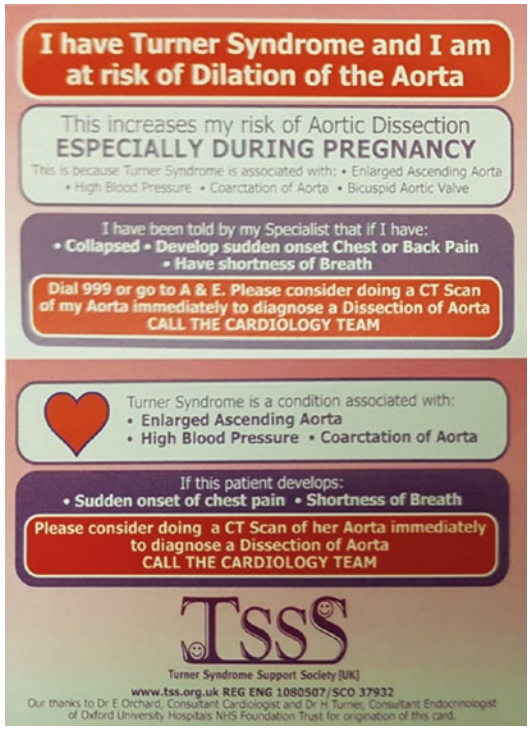


Fig. 40.7 Cardiac alert card for girls and women with TS. Used with permission from the Turner Syndrome Support Society [UK], available from https://tss.org.uk/information/healthcare

the increased use of a multidisciplinary team approach and developments in genetic understanding may help target appropriate follow-up in those at particular risk. Developments in treatment of fertility such as cryopreservation and improvements in cardiac imaging or treatment may lead to increased options for pregnancy and a reduction in the increased morbidity and mortality in women with TS.

Acknowledgments With special thanks to Arlene Smyth, Executive Officer, Turner Syndrome Support Society [UK] www.tss.org.uk for her contribution to this chapter with a case study and information on the Patient Advocacy Group.

References

Allen DB. Safety of human growth hormone therapy: current topics. J Pediatr. 1996;128(5 Pt 2):S8–13.

Alvarez-Nava F, Lanes R, Quintero JM, Miras M, Fideleff H, Mericq V, et al. Effect of the parental origin of the X-chromosome on the clinical features, associated complications, the two-year-response to growth hormone (rhGH) and the biochemical profile in patients with turner syndrome. Int J Pediatr Endocrinol. 2013;2013(1):10.

Atton G, Gordon K, Brice G, Keeley V, Riches K, Ostergaard P, et al. The lymphatic phenotype in Turner syndrome: an evaluation of nineteen patients and literature review. Eur J Hum Genet. 2015;23(12):1634–9.

Bakalov VK, Gutin L, Cheng CM, Zhou J, Sheth P, Shah K, et al. Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. J Autoimmun. 2012;38(4):315–21.

Bannink EM, van der Palen RL, Mulder PG, de Muinck Keizer-Schrama SM. Long-term follow-up of GH-treated girls with Turner syndrome: BMI, blood pressure, body proportions. Horm Res. 2009a;71(6):336–42.

Bannink EM, van der Palen RL, Mulder PG, de Muinck Keizer-Schrama SM. Long-term follow-up of GH-treated girls with Turner syndrome: metabolic consequences. Horm Res. 2009b;71(6):343–9.

Baxter L, Bryant J, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev. 2007;(1):CD003887.

Becker B, Jospe N, Goldsmith LA. Melanocytic nevi in Turner syndrome. Pediatr Dermatol. 1994;11(2):120–4.

Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab. 2010;95(1):167–77.

Birkebaek NH, Cruger D, Hansen J, Nielsen J, Bruun-Petersen G. Fertility and pregnancy outcome in Danish women with Turner syndrome. Clin Genet. 2002;61(1):35–9.

Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in turner syndrome. J Clin Endocrinol Metab. 2008;93(2):344–51.

Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92(1):10–25.

Bondy C. Pregnancy and cardiovascular risk for women with Turner syndrome. Womens Health (Lond). 2014;10(4):469–76.

Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92(1):10–25.

Bondy CA, Ceniceros I, Van PL, Bakalov VK, Rosing DR. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. Pediatrics. 2006a;118(4):e1220–5.

Bondy CA, Ceniceros I, Lange E, Bakalov VK. Declining estrogen use in young women with Turner syndrome. Arch Intern Med. 2006b;166(12):1322.

Bondy C, Bakalov VK, Cheng C, Olivieri L, Rosing DR, Arai AE. Bicuspid aortic valve and aortic coarctation

are linked to deletion of the X chromosome short arm in Turner syndrome. J Med Genet. 2013;50(10):662–5.
Bonnevie K. Embryoligical analysis of gene manifestation in Little and Bagg's abnormal mouse tribe. J Exp Zool. 1934;67:443–520.
Bosze P, Toth A, Torok M. Hormone replacement and the risk of breast cancer in Turner's syndrome. N Engl J Med. 2006;355(24):2599–600.
Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Mullerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update. 2014;20(5):688–701.
Calcaterra V, Gamba G, Montani N, de Silvestri A, Terulla V, Lanati G, et al. Thrombophilic screening in Turner syndrome. J Endocrinol Investig. 2011;34(9):676–9.
Cameron-Pimblett A, King TFJ, La-Rosa C, Conway GS. Hypothyroidism is a risk factor for acquiring diabetes in women with Turner Syndrome. Endocr Abstr. 2017;50:OC3.2. https://doi.org/10.1530/endoabs.50.OC3.2.
Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–5.
Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. Circulation. 2012;126(18):2220–6.
Carrascosa A, Gussinye M, Terradas P, Yeste D, Audi L, Vicens-Calvet E. Spontaneous, but not induced, puberty permits adequate bone mass acquisition in adolescent Turner syndrome patients. J Bone Miner Res. 2000;15(10):2005–10.
Cave CB, Bryant J, Milne R. Recombinant growth hormone in children and adolescents with Turner syndrome. Cochrane Database Syst Rev. 2003;(3):CD003887.
Chrousos GA, Ross JL, Chrousos G, Chu FC, Kenigsberg D, Cutler G Jr, et al. Ocular findings in Turner syndrome. A prospective study. Ophthalmology. 1984;91(8):926–8.
Conway GS, Band M, Doyle J, Davies MC. How do you monitor the patient with Turner's syndrome in adulthood? Clin Endocrinol. 2010;73(6):696–9.
Culen C, Ertl DA, Schubert K, Bartha-Doering L, Haeusler G. Care of girls and women with Turner syndrome: beyond growth and hormones. Endocr Connect. 2017;6(4):R39–51.
Davenport ML, Punyasavatsut N, Gunther D, Savendahl L, Stewart PW. Turner syndrome: a pattern of early growth failure. Acta Paediatr Suppl. 1999;88(433):118–21.
Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. 2007;92(9):3406–16.
Davenport ML, Roush J, Liu C, Zagar AJ, Eugster E, Travers S, et al. Growth hormone treatment does not affect incidences of middle ear disease or hearing loss in infants and toddlers with Turner syndrome. Horm Res Paediatr. 2010;74(1):23–32.
dos Santos AP, Andrade JG, Piveta CS, de Paulo J, Guerra G Jr, de Mello MP, et al. Screening of Y chromosome microdeletions in 46,XY partial gonadal dysgenesis and in patients with a 45,X/46,XY karyotype or its variants. BMC Med Genet. 2013;14:115.
Elsheikh M, Wass JA, Conway GS. Autoimmune thyroid syndrome in women with Turner's syndrome—the association with karyotype. Clin Endocrinol. 2001a;55(2):223–6.
Elsheikh M, Hodgson HJ, Wass JA, Conway GS. Hormone replacement therapy may improve hepatic function in women with Turner's syndrome. Clin Endocrinol. 2001b;55(2):227–31.
Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. Endocr Rev. 2002;23(1):120–40.
Fjermestad KW, Naess EE, Bahr D, Gravholt CH. A 6-year Follow-up survey of health status in middle-aged women with Turner syndrome. Clin Endocrinol. 2016;85(3):423–9.
Flynn MT, Ekstrom L, De Arce M, Costigan C, Hoey HM. Prevalence of renal malformation in Turner syndrome. Pediatr Nephrol. 1996;10(4):498–500.
Frias JL, Davenport ML, Committee on Genetics and Section on Endocrinology. Health supervision for children with Turner syndrome. Pediatrics. 2003;111(3):692–702.
Gibbs P, Brady BM, Gonzalez R, Robinson WA. Nevi and melanoma: lessons from Turner's syndrome. Dermatology. 2001;202(1):1–3.
Granger A, Zurada A, Zurada-Zielinska A, Gielecki J, Loukas M. Anatomy of turner syndrome. Clin Anat. 2016;29(5):638–42.
Gravholt CH, Poulsen HE, Ott P, Christiansen JS, Vilstrup H. Quantitative liver functions in Turner syndrome with and without hormone replacement therapy. Eur J Endocrinol. 2007;156(6):679–86.
Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1–G70.
Gunther DF, Eugster E, Zagar AJ, Bryant CG, Davenport ML, Quigley CA. Ascertainment bias in Turner syndrome: new insights from girls who were diagnosed incidentally in prenatal life. Pediatrics. 2004;114(3):640–4.
Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. Fertil Steril. 2011;95(7):2251–6.
Hart SJ, Davenport ML, Hooper SR, Belger A. Visuospatial executive function in Turner syndrome: functional

MRI and neurocognitive findings. Brain. 2006;129(Pt 5):1125–36.

Hewitt JK, Jayasinghe Y, Amor DJ, Gillam LH, Warne GL, Grover S, et al. Fertility in Turner syndrome. Clin Endocrinol. 2013;79(5):606–14.

Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121(13):e266–369.

Hong DS, Reiss AL. Cognition and behavior in Turner syndrome: a brief review. Pediatr Endocrinol Rev. 2012;9(Suppl 2):710–2.

Hook EB, Warburton D. Turner syndrome revisited: review of new data supports the hypothesis that all viable 45,X cases are cryptic mosaics with a rescue cell line, implying an origin by mitotic loss. Hum Genet. 2014;133(4):417–24.

Hughes IP, Choong CS, Harris M, Ambler GR, Cutfield WS, Hofman PL, et al. Growth hormone treatment for Turner syndrome in Australia reveals that younger age and increased dose interact to improve response. Clin Endocrinol. 2011;74(4):473–80.

Invernizzi P, Miozzo M, Selmi C, Persani L, Battezzati PM, Zuin M, et al. X chromosome monosomy: a common mechanism for autoimmune diseases. J Immunol. 2005;175(1):575–8.

Jacobs P, Dalton P, James R, Mosse K, Power M, Robinson D, et al. Turner syndrome: a cytogenetic and molecular study. Ann Hum Genet. 1997;61(Pt 6):471–83.

Kanaka-Gantenbein C. Hormone replacement treatment in Turner syndrome. Pediatr Endocrinol Rev. 2006;3(Suppl 1):214–8.

Kaplowitz PB, Chernausek SD, Horn JA. Fingernail angle in girls with Ullrich-Turner syndrome. Am J Med Genet. 1993;46(5):570–3.

Lanes R, Gunczler P, Esaa S, Martinis R, Villaroel O, Weisinger JR. Decreased bone mass despite long-term estrogen replacement therapy in young women with Turner's syndrome and previously normal bone density. Fertil Steril. 1999;72(5):896–9.

Lim DB, Gault EJ, Kubba H, Morrissey MS, Wynne DM, Donaldson MD. Cholesteatoma has a high prevalence in Turner syndrome, highlighting the need for earlier diagnosis and the potential benefits of otoscopy training for paediatricians. Acta Paediatr. 2014;103(7):e282–7.

Linglart A, Cabrol S, Berlier P, Stuckens C, Wagner K, de Kerdanet M, et al. Growth hormone treatment before the age of 4 years prevents short stature in young girls with Turner syndrome. Eur J Endocrinol. 2011;164(6):891–7.

Lowenstein EJ, Kim KH, Glick SA. Turner's syndrome in dermatology. J Am Acad Dermatol. 2004;50(5):767–76.

Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child. 1985;60(10):932–5.

Maraschio P, Tupler R, Barbierato L, Dainotti E, Larizza D, Bernardi F, et al. An analysis of Xq deletions. Hum Genet. 1996;97(3):375–81.

Marild K, Stordal K, Hagman A, Ludvigsson JF. Turner Syndrome and celiac disease: a case-control study. Pediatrics. 2016;137(2):e20152232.

Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. Circulation. 2007;116(15):1663–70.

Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome—integrating cardiology, genetics, and endocrinology. Endocr Rev. 2012;33(5):677–714.

Nathwani NC, Unwin R, Brook CG, Hindmarsh PC. The influence of renal and cardiovascular abnormalities on blood pressure in Turner syndrome. Clin Endocrinol. 2000;52(3):371–7.

Noto R, Maneatis T, Frane J, Alexander K, Lippe B, Davis DA. Intracranial hypertension in pediatric patients treated with recombinant human growth hormone: data from 25 years of the Genentech National Cooperative Growth Study. J Pediatr Endocrinol Metab. 2011;24(9–10):627–31.

Oktay K, Bedoschi G, Berkowitz K, Bronson R, Kashani B, McGovern P, et al. Fertility preservation in women with Turner Syndrome: a comprehensive review and practical guidelines. J Pediatr Adolesc Gynecol. 2016;29(5):409–16.

Pasquino AM, Passeri F, Pucarelli I, Segni M, Municchi G. Spontaneous pubertal development in Turner's syndrome. Italian Study Group for Turner's Syndrome. J Clin Endocrinol Metab. 1997;82(6):1810–3.

Pessach IM, Notarangelo LD. X-linked primary immunodeficiencies as a bridge to better understanding X-chromosome related autoimmunity. J Autoimmun. 2009;33(1):17–24.

Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. J Clin Endocrinol Metab. 2012;97(6):E994–1003.

Quilter CR, Karcanias AC, Bagga MR, Duncan S, Murray A, Conway GS, et al. Analysis of X chromosome genomic DNA sequence copy number variation associated with premature ovarian failure (POF). Hum Reprod. 2010;25(8):2139–50.

Ranke MB, Lindberg A, Ferrandez Longas A, Darendeliler F, Albertsson-Wikland K, Dunger D, et al. Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. Pediatr Res. 2007;61(1):105–10.

Rivkees SA. Ending the late diagnosis of Turner syndrome through a novel high-throughput assay. Pediatr Endocrinol Rev. 2012;9(Suppl 2):698–700.

Rivkees SA, Hager K, Hosono S, Wise A, Li P, Rinder HM, et al. A highly sensitive, high-throughput assay for the detection of Turner syndrome. J Clin Endocrinol Metab. 2011;96(3):699–705.

Rosenfeld RG, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF, et al. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. J Pediatr. 1998;132(2):319–24.

Ross J, Lee PA, Gut R, Germak J. Impact of age and duration of growth hormone therapy in children with Turner syndrome. Horm Res Paediatr. 2011a;76(6):392–9.

Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, et al. Growth hormone plus childhood low-dose estrogen in Turner's syndrome. N Engl J Med. 2011b;364(13):1230–42.

Roulot D. Liver involvement in Turner syndrome. Liver Int. 2013;33(1):24–30.

Sachdev V, Matura LA, Sidenko S, Ho VB, Arai AE, Rosing DR, et al. Aortic valve disease in Turner syndrome. J Am Coll Cardiol. 2008;51(19):1904–9.

Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, et al. Recommendations for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metab. 2001;86(7):3061–9.

Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA, United Kingdom Clinical Cytogenetics Group. Mortality in women with turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab. 2008;93(12):4735–42.

Sheanon NM, Backeljauw PF. Effect of oxandrolone therapy on adult height in Turner syndrome patients treated with growth hormone: a meta-analysis. Int J Pediatr Endocrinol. 2015;2015(1):18.

Skuse DH, James RS, Bishop DV, Coppin B, Dalton P, Aamodt-Leeper G, et al. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. Nature. 1997;387(6634):705–8.

Stephure DK, Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab. 2005;90(6):3360–6.

Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91(10):3897–902.

Sutton EJ, Young J, McInerney-Leo A, Bondy CA, Gollust SE, Biesecker BB. Truth-telling and Turner Syndrome: the importance of diagnostic disclosure. J Pediatr. 2006;148(1):102–7.

Taboada M, Santen R, Lima J, Hossain J, Singh R, Klein KO, et al. Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome. J Clin Endocrinol Metab. 2011;96(11):3502–10.

Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein KO, Singh R, et al. Metabolic effects of oral versus transdermal 17beta-estradiol (E(2)): a randomized clinical trial in girls with Turner syndrome. J Clin Endocrinol Metab. 2013;98(7):2716–24.

Tuffli GA, Johanson A, Rundle AC, Allen DB. Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. J Clin Endocrinol Metab. 1995;80(4):1416–22.

Turner H. A syndrome of infantilism, congenital webbed neck and cubitus valgus. Endocrinology. 1938;23:566–78.

Turtle EJ, Sule AA, Webb DJ, Bath LE. Aortic dissection in children and adolescents with Turner syndrome: risk factors and management recommendations. Arch Dis Child. 2015;100(7):662–6.

Ullrich O. Uber typische kombinationsbilder multipler abartungen. Z Kinderheilkunde Berlin. 1930;49:271–6.

van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, et al. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab. 2003;88(3):1119–25.

Vrablik M, Fait T, Kovar J, Poledne R, Ceska R. Oral but not transdermal estrogen replacement therapy changes the composition of plasma lipoproteins. Metabolism. 2008;57(8):1088–92.

Wihlborg CE, Babyn PS, Schneider R. The association between Turner's syndrome and juvenile rheumatoid arthritis. Pediatr Radiol. 1999;29(9):676–81.

Wikiera B, Mulak M, Koltowska-Haggstrom M, Noczynska A. The presence of eye defects in patients with Turner syndrome is irrespective of their karyotype. Clin Endocrinol. 2015;83(6):842–8.

Wilkins L, Fleischmann W. Ovarian agenesis: pathology, associated clinical symptoms and the bearing on the theories of sex differentiation. J Clin Endocrinol. 1944;39:204.

Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54.

Wyatt D. Melanocytic nevi in children treated with growth hormone. Pediatrics. 1999;104(4 Pt 2):1045–50.

Zvulunov A, Wyatt DT, Laud PW, Esterly NB. Influence of genetic and environmental factors on melanocytic naevi: a lesson from Turner's syndrome. Br J Dermatol. 1998;138(6):993–7.

Key Reading

1. Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92:10–25.
2. Conway GS, Band M, Doyle J, Davies MC. How do you monitor the patient with Turner's syndrome in adulthood? Clin Endocrinol (Oxf). 2010;73:696–9.
3. Culen C, Ertl DA, Schubert K, Bartha-Doering L, Haeusler G. Care of girls and women with Turner syndrome: beyond growth and hormones. Endocr Connect. 2017;6:R39–51.
4. Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. Endocr Rev. 2002;23:120–40.
5. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Soderstrom-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF, International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1–G70.
6. Bondy C. Pregnancy and cardiovascular risk for women with Turner syndrome. Womens Health (Lond). 2014;10:469–76.
7. Hewitt JK, Jayasinghe Y, Amor DJ, Gillam LH, Warne GL, Grover S, Zacharin MR. Fertility in Turner syndrome. Clin Endocrinol (Oxf). 2013;79:606–14.

41 Premature Ovarian Insufficiency, Menopause, and Hormone Replacement Therapy

Gerard S. Conway

Contents

41.1 **Introduction** 804

41.2 **The Menopause** 805

41.3 **Premature Ovarian Insufficiency** 806
41.3.1 Clinical Evaluation and Diagnosis of POI 806
41.3.2 Aetiology of POI 807

41.4 **Hormone Replacement Therapy** 809

41.5 **Fertility Options for Women with POI** 810
41.5.1 Spontaneous Fertility in POI 811
41.5.2 Ovum Donation 811
41.5.3 Embryo Cryopreservation 811
41.5.4 Oocyte Cryopreservation 811
41.5.5 Ovarian Tissue Cryopreservation 812

41.6 **Nursing Considerations in the Care of Patients with POI** 812

41.7 **Conclusions** 814

References 814

Abstract

Menopause and the years preceding it are associated with a wide variety of symptoms that are often missed in a routine consultation. Informed choice regarding hormone replacement therapy and lifestyle options can alleviate much of the burden of the menopause when this change in life has a major impact on well-being. Premature ovarian insufficiency is one of the most difficult conditions in reproductive medicine. It occurs in 1% of women. The impact of the diagnosis can dissipate with time assisted by full evaluation and discussion of the implications of POI. The role of the nurse includes assessment of symptoms, discussion of implications for fertility as well as

G. S. Conway (✉)
Institute for Women's Health, University College London, London, UK
e-mail: g.conway@ucl.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_41

assisted fertility treatment options and then to give guidance through choices of sex steroid replacement. Ongoing education is required in order to adapt the level of information and types of treatment according to life circumstances. Women with ovarian insufficiency frequently feel isolated or that there is insufficient time in a clinic visit for full discussion. Nursing input can overcome some of these limitations.

Keywords
Autoimmunity · Oestrogen and androgen treatments · Late effects of cancer · Ovum donation

Abbreviations

AMH	Antimullerian hormone
APS	Autoimmune polyglandular syndromes
BMI	Body mass index
COCP	Combined oral contraceptive pill
DXA	Dual X-ray absorptiometry
Fra-X	Fragile X
FSH	Follicle-stimulating hormone
HRT	Hormone replacement therapy
LH	Luteinising hormone
LOR	Low ovarian reserve
POI	Premature ovarian insufficiency
TS	Turner Syndrome

Key Terms

- **Premature ovarian failure:** A term describing ovarian insufficiency now considered obsolete.
- **Primary amenorrhoea:** Failure for menstruation to occur in adolescence.
- **Secondary amenorrhoea:** Absence of periods for greater than 6 months occurring after menarche.
- **Hypergonadotrophic Hypogonadism:** The finding of each deficiency in the presence of raised concentrations of LH and FSH.
- **Gonadal dysgenesis**: Early onset ovarian insufficiency causing primary amenorrhoea usually with a genetic cause such as Turner Syndrome.
- **Low ovarian reserve**: Women with regular cycles but raised FSH and low AMH usually in the context of infertility.
- **Early menopause**: Menopause before the age of 45.

Key Points

- Menopause usually occurs at the age of 51 and premature ovarian insufficiency (POI) is defined as hypergonadotrophic hypogonadism before the age of 40.
- Ovarian insufficiency requires consideration of fertility options, sex hormone replacement therapy, and psychological support. Nursing assessment should include an evaluation of the priorities in each of these domains at every clinic visit.
- Ovarian insufficiency has wide-ranging effects on quality-of-life and relationships requiring counselling and help with decision-making as well as support at the time of an often traumatic diagnosis.
- There are a number of options for sex steroid replacement comprising oestrogen, progestogen, and androgens. Assessment of optimal individualised hormone replacement treatment is based on quality of life taking careful note of details in history including mood and sexual function.

41.1 Introduction

The ovary is a unique organ in the body with a defined lifespan of approximately 50 years. The life expectancy of the ovary is determined by optimal germ cell development in utero and factors affecting programmed cell death throughout life. The peak germ cell number occurs at 6 months

gestation with >700,000 eggs. Once this maximum number has been achieved, the body is no longer able to make new oocytes and the total number gradually decline. It is estimated that nearly 50% of germ cells have been destroyed by the age of menarche, and by the onset of menopause, only 1000 remain. Throughout life, therefore, germ cell apoptosis takes place at a rate of approximately 25–150 lost per day. As the number of germ cell falls, a critical point is reached when periods stop with subsequent reduction in circulating oestrogen, and thus lesser extent testosterone, concentrations.

The menopause is defined by the last menstrual period and occurs at an average age of 50.7 years in the western world (van Noord et al. 1997). Premature Ovarian Insufficiency (POI) is defined as amenorrhoea with raised FSH before the age of 40. POI occurs in approximately 1% of females and becomes increasingly rare in younger age groups. For instance, in presence of normal karyotype, 1:1000 of women at 30 has POI, and 1:10,000 at 20 and 1:100,000 of women will present with gonadal failure and primary amenorrhoea (Fig. 41.1). POI accounts for 20–50% of females presenting with primary amenorrhoea and 10% of those with secondary amenorrhoea (Master-Hunter and Heiman 2006).

The term premature ovarian insufficiency is preferred to premature ovarian failure because it is an all-encompassing term that accounts for the variable course and occasional remission (Welt 2008a). The term hypergonadotrophic hypogonadism is also used to emphasise ovarian origin, whereby the raised concentrations of LH and FSH contrast from low gonadotrophins in hypothalamic or pituitary causes of hypogonadism. Gonadal dysgenesis refers to hypergonadotrophic hypogonadism with a known genetic cause such as an abnormal 46XY or 45X karyotype and implies that ovarian development was halted at an early stage of embryonic development. In the case of Turner Syndrome, it is thought that early ovarian development is usually normal, but that the chromosome anomaly leads to rapid germ cell apoptosis (Reynaud et al. 2004).

41.2 The Menopause

Menopause describes the end of natural reproductive life when periods stop. The process can be abrupt, but in many cases symptoms precede amenorrhoea by months or even years. The age of menopause varies between 45 and 60 with daughters tending to follow mothers in many

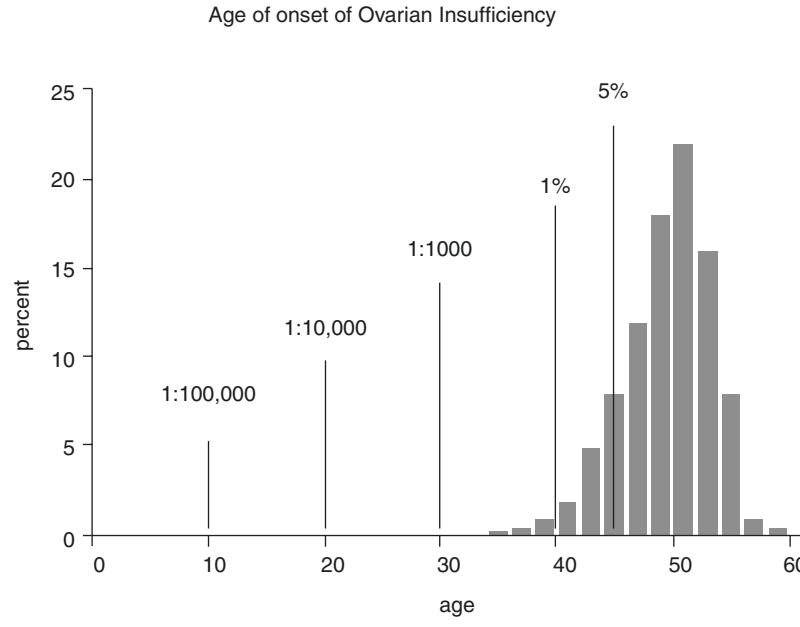


Fig. 41.1 A graph of the distribution of the age of onset of amenorrhoea according to the lifespan of the ovary

families (Davis et al. 2015). The interval between periods usually shortens as the menopause approaches from an average of 28 days often to 21 days. The diagnosis of menopause may not be obvious in women taking hormone treatments for period control or who have had a hysterectomy. In addition, nonspecific symptoms such as joint and muscle stiffness, loss of memory and concentration, or simply low mood can occur in the absence of classical symptoms. Oestrogen deficiency should be considered as a possibility for anyone experiencing new onset of symptoms after the age of 40. The diagnosis of menopause is mainly based on history and, for the majority of women, no diagnostic test is required. A measurement of FSH can be unreliable as it may not correlate with symptoms of the premenopause.

The majority of women experience some symptoms of the menopause which often gradually diminish over several years (Monteleone et al. 2018). In a proportion of women, disabling symptoms can be lifelong requiring indefinite treatment with HRT. Treatment of the menopause is individualised and may include lifestyle, hormone-based treatments, counselling, and treatments to improve sexual function. A great deal can be achieved with detailed information and advice. A discussion regarding the spectrum of symptoms that are associated with oestrogen deficiency can be reassuring and will ensure that no hidden symptom is left untreated. Symptoms relating to change of mood, libido, sexual function, and urogenital dysfunction may need to be sought by direct questioning.

The risks and benefits of hormone replacement therapy require discussion as this treatment is not essential and nonpharmaceutical alternatives are available. Studies which highlighted the risks of HRT between 2002 and 2004 resulted in a decline in the use of HRT (Sassarini and Lumsden 2015). Subsequent assessments, however, have shown that the risks of HRT may have been overestimated. In addition, the risk of stroke can be eliminated by the use of transdermal oestrogen instead of oral oestrogen, which formed the basis of most of the early HRT studies.

41.3 Premature Ovarian Insufficiency

41.3.1 Clinical Evaluation and Diagnosis of POI

The clinical presentation of POI varies depending on the age of presentation (Conway et al. 1996; Nelson 2009). Very early onset in adolescence leads to pubertal delay puberty and primary amenorrhoea. After menarche, the presentation is with symptoms of oestrogen deficiency and secondary amenorrhoea or as part of a work up for irregular periods or infertility. In addition, POI can be part of clinical syndromes that can be genetic, such as Turner Syndrome, or autoimmune.

The formal diagnosis of POI is based on the presentation of amenorrhoea with finding of elevated serum FSH concentrations (FSH > 25 IU/L) on at least two occasions separated by 4 weeks (Webber et al. 2016). The requirement for two samples takes into account the fact that ovarian function can fluctuate and end raised FSH and can be a transient phenomenon. In addition, because the diagnosis has such severe implications, certainty of the diagnosis is required. While it is the usual expectation that the condition will be permanent, some women follow an unpredictable course of relapse and remission particularly in the first year after diagnosis (Bachelot et al. 2017). There is a commonly quoted pregnancy rate of approximately 1–5% in women with POI and it is, therefore, important to inform women with POI of this phenomenon so that they use contraception when appropriate. Because of this background fertility, case reports of effective treatment of POI must be viewed with caution. Fluctuating ovarian function probably accounts for many cases where the older term ‘resistant ovary syndrome’ was applied and it is now understood that ovarian biopsy is not predictive of remission and should no longer be included as part of the work up of POI (Webber et al. 2016). Antimullerian hormone has found a place as a diagnostic marker of low ovarian reserve, but once the FSH concentration is raised, AMH offers little extra information (Visser et al. 2012).

A careful family history can identify other affected female members in as many as 30% of cases (van Kasteren et al. 1999a), and in this situation, more genetic screening is indicated and genetic counselling for relatives may be appropriate. A karyotype should be performed in anyone with a positive family history because small chromosome deletions can be inherited. Fragile X (Fra-X) premutation analysis should be offered to all women with POI because of its value in detecting a new pedigree for the prevention of fragile X syndrome (Conway 2010; Mila et al. 2018).

Oestrogen receptors are widely distributed throughout the body and the effects of oestrogen deficiency are diverse. While the classical symptoms of hot flushes, sleep disturbance, and vagina dryness are obvious, more subtle changes in mood and musculoskeletal pain are often unrecognised as part of this symptom spectrum. A careful history listing any change in well-being, no matter how minor, that coincides or precedes amenorrhoea will provide a useful guide to optimising hormone replacement therapy.

The major medical issues for health surveillance in women with POI revolve around the quality of life and bone protection offered by hormone replacement therapy (HRT). Oestrogen deficiency is a risk for osteoporosis and DXA scans should be performed at intervals to assist in the correct dosing of HRT. Options for reproduction include oocyte donation, but adoption should not be overlooked. Women also require personal and emotional support to deal with impact of diagnosis on their health and relationships. Long-term follow-up is essential to monitor HRT and to consider emerging associated autoimmune pathology.

41.3.2 Aetiology of POI

Ovarian insufficiency is the final outcome of many pathogenic mechanisms. Table 41.1 shows the main categories of pathogenic mechanisms that lead to ovarian insufficiency. Despite diagnostic advances, particularly in the identification of genetic associations, the cause of POI remains unknown in the majority of cases (Nelson 2009).

Table 41.1 Summary of pathogenic mechanisms causing premature ovarian insufficiency

Genetic	Chromosomal and genetic abnormalities causing abnormal ovarian development or accelerated apoptosis. Single gene defects—mutations in genes vital for ovarian development or function
Autoimmune	Autoimmune ovarian damage is usually presumed because of the association with other organ-specific autoimmune conditions. Thyroid and adrenal autoimmunity is common. Ovarian autoantibodies are rarely positive
Metabolic	In galactosaemia, abnormal metabolites are thought to mediate ovarian damage
Iatrogenic	Ovarian damage following pelvic surgery and radiotherapy of chemotherapy during treatment of cancer
Environmental factors	Viral infections and toxins such as pesticides are presumed. Smoking results in younger age of natural menopause

41.3.2.1 Genetic Causes of POI

A genetic aetiology for POI is suggested not only by a positive family history, but also if there are features of an associated syndrome. Cytogenetic chromosome anomalies occur in about 2% of cases with the majority involving the X chromosome (Davison et al. 1999; Baronchelli et al. 2011; Desai and Rajkovic 2017).

X chromosome defects and Turner's Syndrome: Defects of the X chromosome associated with POI include complete or partial deletion of one X (Turner syndrome), trisomy X, or X-autosome translocations. In the case of Turner Syndrome variants, there is a great deal of variability in severity of the condition and this corresponds approximately with genotype and the amount of X chromosome disruption. Ovarian histology can vary from streak ovaries to those with well-preserved structure and numerous follicles. Those with monosomy X (45X) tend to be the most severely affected, while those with partial deletions of the X chromosome or mosaic 45X/46XX karyotype often lack the typical phenotypic features of the syndrome, but may present with only ovarian insufficiency and secondary

amenorrhoea. Among women with Turner Syndrome, the prevalence of ovarian failure is between 80 and 90% with most experiencing primary amenorrhoea and complete pubertal delay (Cameron-Pimblett et al. 2017).

X chromosome deletions appear to segregate into two specific regions: POI1 at Xq26-qter and POI2 Xq13.3--Xq21.1 (Baronchelli et al. 2012). There are various proposed mechanisms by which X chromosome defects cause POI. Genes responsible for germ cell development located along the critical region may be interrupted, although break point genes that determine ovarian function have not been convincingly identified. It seems most likely that structural rearrangements of the X chromosome do not affect single genes, but rather disrupt normal pairing at meiosis, leading to meiotic arrest and subsequent atresia. It must also be noted, however, that some X chromosome break points are not associated with POI (Baronchelli et al. 2012).

Single gene defects causing POI: A growing number of genes have been linked to ovarian insufficiency, although the strength of evidence linking each anomaly with POI is variable (Desai and Rajkovic 2017; Ferrarini et al. 2013). The most clinically useful genetic association is that between carriers of the Fra-X premutation and ovarian failure. Fra-X premutations occur in 3% of women with sporadic POI and 15% of those with the familial form and this genetic test is the only one advised in the UK as part of routine work up of POI (Conway et al. 1998). In general, the phenotype of this subgroup of women with POI is indistinguishable from others, although a minority are reported to a progressive intention tremor. The pathway by which Fra-X premutations damage ovarian function is unclear as this type of expansion of exon 1 of the gene is not thought to effect protein transcription, even though the protein is expressed within the ovary.

41.3.2.2 Autoimmune Causes of POI

Autoimmune mechanisms may be involved in pathogenesis of up to 30% of cases of POI (Welt 2008b; Wilson 2011). POI has been reported to be associated with various endocrine (thyroid, adrenal, hypoparathyroidism, diabetes mellitus, and hypophysitis) and non-endocrine (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune haemolytic anaemia, pernicious anaemia, SLE, rheumatoid arthritis, Crohn's disease, Sjogren's syndrome, myasthenia gravis, primary biliary cirrhosis, and chronic active hepatitis) autoimmune disorders (La Marca et al. 2010). In many cases, non-ovarian autoimmune involvement exists only at subclinical level (Wilson 2011). POI may be part of the autoimmune polyglandular syndromes (APS) when accompanied by other autoimmune endocrinopathies. POI is more common with APS types I and III than with APS type II. The single most common autoimmune association is with hypothyroidism which occurs in 10% of women with POI.

Various pathways of autoimmune ovarian damage have been described, but a reliable ovarian specific autoimmune marker is still lacking. Several putative pathogenic autoantibodies have been explored (Melner and Feltus 1999). Anti-ovarian antibodies detected by routine *immunofluorescence* have been reported in several studies of women with POI, but their specificity and pathogenic roles are questionable. The incidence of anti-ovarian antibodies in POI in different studies has been reported to vary from 4 to 69% (Wheatcroft et al. 1997). Other candidate autoantibodies include those directed against steroidogenic enzymes (such as 3ß-hydroxysteroid dehydrogenase), gonadotropins and their receptors, the corpus luteum, zona pellucida, and oocyte. None of these, however, have been validated as a diagnostic marker of autoimmune ovarian failure. Therefore, in the clinical work up of POI, screening for an autoimmune aetiology is usually only possible by seeking coexisting autoimmune diseases.

Women with idiopathic POI show an increased number of activated T cells in peripheral blood. Similar findings have been described in other autoimmune endocrinopathies, such as recent onset Graves' disease, type 1 diabetes mellitus, and Addison's disease. However, postmenopausal women also show raised numbers of activated peripheral T cells and oestrogen substitution has been shown to lower the number of activated

peripheral T cells in women with POI. Therefore, it is difficult to be certain whether the raised numbers of activated blood T cells is the cause or the result of ovarian failure in this situation (La Marca et al. 2010).

41.3.2.3 POI Resulting from Cancer Treatments

As the number of survivors of childhood cancer increases across the world, iatrogenic POI develops in a greater proportion of women with this condition. Both chemotherapy, alkylating agents in particular, and radiotherapy used in the treatment of cancer or benign diseases are damaging to the ovary (Wallace et al. 2005; Morgan et al. 2012). The return of ovarian function after cancer treatment is commonly observed although difficult to predict. For women estimated to be at high risk of POI, oophorectomy or oocyte harvesting for cryopreservation may be considered (Wallace et al. 2012).

41.3.2.4 Miscellaneous Causes of POI

Viral oophoritis is a possible occult aetiology that could theoretically account for the many cases of idiopathic POI. There is, however, little direct evidence of viral ovarian damage beyond case reports such as mumps oophoritis (Morrison et al. 1975). Cigarette smoking is known to be associated with earlier age of natural menopause, but whether environmental effects are sufficiently strong to cause POI is not known. The available data regarding effects of endocrine disruptors, heavy metals, solvents, pesticides, plastics, and industrial chemicals on female reproduction are equivocal (Sharara et al. 1998).

41.4 Hormone Replacement Therapy

Box 41.1 presents an overview of the management and treatment of POI. Physiological replacement of ovarian steroid hormones until the age of normal menopause at 50 is generally accepted as routine for women with POI, although there is little risk/benefit data for this young population. The principle of HRT use in young women differs only slightly from that in older women with the main treatment goal being optimal quality of life. Young women may require a higher oestrogen dose than that used in an older age group. Also, expectations for sexual function

Box 41.1 An Overview of the Management of POI

Education and counselling

- Return of ovarian function may occur in 5–10% of women with POI, but it is difficult to predict when and if this may happen.
- Adoption and oocyte donation are the only realistic options for fertility, although cryopreservation of ovarian tissue is possible for those at risk of developing POI.
- Access to follow-up counselling is important as issues return with life events such as a close friend or family member becoming pregnant.

Investigations:

- Thyroid function tests, vitamin B12 and ferritin to cover associated autoimmune conditions.
- Autoantibody screen including thyroid and adrenal antibodies.
- Karyotype for early-onset POI and genetic screen for FRAXA premutation.
- Pelvic ultrasound and ovarian biopsy are not recommended.

Treatment:

- Oestrogen and progesterone replacement is usually indicated as individualised.
- Education is required regarding risks and benefits of oestrogen preparations—oral, transdermal, and vaginal.
- Inform on media HRT scares and relevance to young women.
- Consider vaginal oestrogen and testosterone supplements.

can be higher commonly requiring consideration for vaginal oestrogen and androgen replacement. An HRT regimen should be based on the individual preferences of each patient who should be encouraged to undertake a trial and error approach through the wide variety of product available.

Management of oestrogen replacement for young women presenting with primary amenorrhoea requires liaison with paediatric endocrinologists with experience in the induction of puberty in order to optimise breast and uterine development. For instance, a popular strategy is to maximise the time between the introduction of oestrogen and starting progesterone and withdrawal bleeding is thought to benefit breast development. Conversely, the common practice of starting a low dose-combined oral contraceptive in this circumstance may not offer the best outcome of uterine development.

Among ***oral oestrogen*** choices, oestradiol esters and 17 beta-oestradiol provide the mainstay of treatments (Lobo 2017). Conjugated equine oestrogens are used less frequently than in the past because of a greater risk of hypertension and thrombosis compared to oestradiol (Swica et al. 2018; Smith et al. 2014). Some young women with POF find the ***combined oral contraceptive pills*** (COCP) a more acceptable option for oestrogen replacement, but careful assessment of the pill-free week is advised. The pill-free week amounts to 3 months of oestrogen deficiency each year, which may coincide with symptoms of oestrogen deficiency or bone loss. In choosing a type of COCP, those with lower dose ethinylestradiol and second-generation progestins have the lowest risk to thrombosis (Hugon-Rodin et al. 2014). ***Transdermal oestrogen*** avoids first-pass liver metabolism and involves noninvasive self-administration and attainment of therapeutic hormone levels with low daily doses (Henzl and Loomba 2003). This route of oestrogen administration also appears to be free of an excess risk of thrombosis. ***Subcutaneous oestrogen*** replacement involves placement of 25–50 mg oestradiol pellets usually in the lower abdomen or buttocks in a minor office procedure, which is not currently available in some countries including the UK. ***Topical vaginal oestrogen*** may be used as an adjunct to systemic oestrogen. Creams, pessaries, tablets, and vaginal ring appear to be equally effective for control of symptoms (Faubion et al. 2017).

Once the choice of oestrogen has been made, separate consideration can be given to the ***progestin*** in women with an intact uterus. Progestins vary from the more potent such as norethisterone to the weaker such as dydrogesterone. Trial and error will allow the user to find the most suitable progesterone preparation. The route may be oral, transdermal, vaginal, or uterine. With the ***oral*** and ***transdermal*** routes, there is a choice between continuous or sequential (for 10–14 days each month) delivery. Sequential regimen ensures monthly menstrual bleed. Continuous regimen avoids menstrual flow, but breakthrough bleeding may be more common in young women compared to an older age group in whom there is greater uterine atrophy. ***Uterine delivery*** with the levonogestrel intrauterine device (Mirena) has the advantage of avoiding the adverse effects of oral progestins highlighted in the studies of older women (Marjoribanks et al. 2017).

Androgen replacement is useful in some instances when fatigue and loss of libido persist despite optimised oestrogen replacement (Wierman et al. 2014). Transdermal testosterone administration and dehydroepiandrosterone treatment are two of the options for androgen replacement in these women.

41.5 Fertility Options for Women with POI

Different fertility options will be appropriate for each individual with POI. It is important that discussions on this topic from a professional with experience in the field are made available not only soon after diagnosis, but at intervals throughout follow-up as the technology and opportunities in this field are continually developing. There are a number of psychological issues and ethical dilemmas that women face when considering fertility treatment options and it is very important to

discuss this with a specialist healthcare professional. Please refer to chapters on assisted fertility and psychological considerations in Part VI of this textbook for more details.

41.5.1 Spontaneous Fertility in POI

Women with POI have a 5–10% chance of spontaneous conception at some time after diagnosis, as in some cases hormone levels and disease activity fluctuate and return to biochemical normality; this is often transient and the likelihood of recovery of ovulation is not possible to predict. Pregnancy loss in those who conceive is reported at 20%, which is similar to that of the normal population. Several medical therapies have been tried to induce ovulation in women with POI; however, in a systematic review, all were reported to be equally ineffective (van Kasteren et al. 1999a). In particular, glucocorticoids have been considered for those with autoimmune markers, and although promising in early case reports, a controlled trial failed to show benefit (van Kasteren et al. 1999b).

41.5.2 Ovum Donation

Assisted conception with donated oocytes has been used to achieve pregnancy in women with POI for over 20 years and remains the only realistic fertility treatment for the majority of women with established POI (Luisi et al. 2015). The availability of donated oocytes varies from country to country and this option is not acceptable for some ethnic groups. Donated oocytes, fertilised with partner's sperm, are observed on the usually way for the integrity of the embryo. The best embryo is chosen for implantation with the recipient having been prepared with increasing doses of oral estradiol. Because of the lack of a corpus luteum, progesterone support is required which can be administered orally, virginally, or by injection. Endometrial preparation is established in earlier dummy cycles.

41.5.3 Embryo Cryopreservation

Cryopreservation of embryos is a long established technique as part of in vitro fertilization, but it will apply to only a small number of women with normal ovarian function who can anticipate imminent ovarian failure but have sufficient time to allow for controlled ovarian hyperstimulation (Wallace et al. 2005). This circumstance might arise in some cases of malignancy or in someone who is known to be at risk of ovarian failure such as those with X chromosome anomalies or Fra-X premutation who may wish to delay starting a family for some years. Donor sperm could be used for those without a partner.

41.5.4 Oocyte Cryopreservation

Cryopreservation of oocytes has become popular since the advent of vitrification, which improved the freezing process for such a large cell. Vitrification involves rapid cooling in high concentrations of penetrating cryoprotectants, which avoids formation of intracellular ice and resulting damage during cooling and warming. In vitro maturation of oocytes, where immature oocytes are retrieved from unstimulated ovaries, has also emerged as a safe and effective treatment for women with cancer who are undergoing gonadotoxic therapy.

Oocyte cryopreservation also requires controlled ovarian stimulation, but in contrast to preservation of embryos, no sperm is required. In practice, this option is only applicable to women with normal ovarian function and who are old enough for oocyte harvesting. The success rate for achieving pregnancy is likely to be lower than that for embryo cryopreservation because oocyte survival and subsequent fertilisation are impaired. This option has been used for women with Turner Syndrome who retain some ovarian function (El-Shawarby et al. 2010), but so far the overall success rate is not known for this subgroup compared to the more common application in women diagnosed with cancer.

41.5.5 Ovarian Tissue Cryopreservation

The use of ovarian tissue cryopreservation for later use has been explored in young women undergoing anticancer treatment. Cryopreservation of one ovary or strips of ovarian cortical tissue has resulted in the birth of over 12 children according to a review in 2012 (Wallace et al. 2012). This procedure has the advantage of not requiring sperm and being appropriate for prepubescent girls accepting that a laparoscopy is required. The cryopreserved tissue can be reimplanted into the pelvis with ovulation and pregnancy occurring spontaneously or after IVF. Once again, it is too early to be certain of the overall success rate of this procedure, which is only undertaken in specialist oncology centres.

41.6 Nursing Considerations in the Care of Patients with POI

POI can be a devastating condition, especially when women are diagnosed at a very early age. The nurse has a crucial role in providing holistic care and taking into consideration many aspects of patient's life as well as their treatment and management of their condition. Many women with POI require multidisciplinary approach in their care and nurses are key to coordinating and providing a seamless care across settings and disciplines. The case study in Box 41.2 describes the complexities of the condition and the emotional distress patients with POI have to face at the time of diagnosis and throughout life.

Box 41.2 Patient Case Study and Key Learning Points

I'm 20 years old and I was diagnosed with Premature Ovarian Insufficiency (POI) at the age of 16 back in December 2014. I was only 16, so it wasn't something that I thought about when I didn't progress through puberty. I never even heard of the condition until I was diagnosed! So, what happened with me was that I noticed I had never had a period and thought my body shape was not normal for a girl of my age at the time. My mum and I decided to go to my GP who then referred me to the gynaecological unit where I underwent various tests. Then, a few weeks later, the doctor simply sat us down and told us straight—"Your ovaries are not working." For me, I wasn't shocked. To me, it just sounded something unusual that I would clearly have to live with and get on with. My mum, on the other hand, was very concerned as mums would be. She cried when we got home, and I just said to her, "It's okay mum! It's not terrible! I'm like Monica from Friends!!" However, for her it was awful because earlier on that year my sister lost one of her ovaries due to a cyst, which was such a hard time for her and mum. Looking at it that way, one daughter was potentially at risk of not conceiving, whereas the other daughter couldn't, so no wonder my mum was in heartache! It all happened in 1 year to both of her girls.

2015 was the toughest year I've faced as I struggled immensely with anxiety. To this day, I still struggle a bit about my health, but not as much as I did then. I was doing my A-Levels which brought so much stress, and on top of that, I had many hospital appointments following on from my condition. I do look back at that year and think, "How did I manage?" One bad day, especially, was my 17th birthday and I was coming home from London and I remember getting on a train and just felt so shaky, sweaty, dizzy, and was having a panic attack. I told my mum that we needed to get off the train and I just cried in her arms on a bench at the station. That was the worst it got for me! I had had minor panic attacks in bed where I would sweat and shake, but having one in public made it all more concerning. This was all

brought on mainly because I was worrying about my health every second of everyday!

So, I decided to do something about it! I started yoga (today, I just do meditation, I find the physical stuff not that relaxing can I just say?! Dance instead!) which really helped! Massively! I wanted to care for myself and help myself get better in my own way. I didn't see a therapist because, honestly, I didn't think I was bad enough and understood that it was just something I needed to tackle myself. But self-help books do put you on the right track!

I could natter all day, but I really do hope this little segment of my story and experiences help other teenagers out there. **What I want my story to do is raise awareness about teen ovarian failure and the mental health that comes along with that.** It is a shock and understandably so and I want other teenagers to know that they are not alone. I want to start meeting other girls and share our experiences together, so we can learn from each other and help each other. That is my main aim for the future. After all, this condition is for life, so why not make a positive out of it?!

Key learning points:

- Having a life-changing diagnosis of POI during adolescence can be devastating for the patient and requires very careful handling and disclosing of information.
- It is important to take into consideration the home environment and other factors that may influence the outcome of accepting and coping with the diagnosis. Parents also need to be supported in this journey and not excluded from care planning and shared decision-making.
- Most patients will not require regular visits and follow-ups, but it is crucial to plan for adequate support during transition periods such as going to university or very stressful periods such as taking exams, starting a relationship, or planning for a family.
- Patients find peer support exceptionally beneficial at learning about and coping with their condition and improving their self-management and adherence to medication. Providing them with access to peer groups or patient advocacy groups can be very beneficial for patient and their families.

Patient advocacy groups play a crucial (Box 41.3) role in raising awareness of the condition and providing peer support for patients. They are also a highly valuable resource of information for patients and their families and it is important to maintain a close working relationship with the clinical teams.

Box 41.3 The Role of Daisy Network, Patient Advocacy Group, in POI

The Daisy Network is the only UK-registered charity dedicated to providing free information and support to women with Premature Ovarian Insufficiency (POI). It is run solely by volunteers. Our aim is to provide up-to-date medical information about POI and treatment options available to sufferers and to provide a support network of people to talk to for those newly diagnosed, in addition to continually raising awareness of the condition among doctors and the broader medical community.

The Daisy Network	Visit us on: https://www.daisynetwork.org.uk/
PO BOX 71432	Contact us on: info@daisynetwork.org.uk
London SW6 9HJ	Twitter and Instagram: @thedaisynet

41.7 Conclusions

The lifespan of the ovary is occasionally interrupted by pathological processes, some known but many unknown. Premature ovarian insufficiency can be a devastating diagnosis for a teenager or for someone who has yet to start a family. Knowledge of the pathogenesis of the condition as well as treatment options in terms of hormones and assisted fertility is a important skill for a nurse practitioner in endocrinology, paediatrics, and reproductive medicine.

Acknowledgments Special thanks to Marie Gerval, Co-Chair, The Daisy Network (www.daisynetwork.org.uk) for the contribution to this chapter with a case study and information on the Patient Advocacy Group.

References

Bachelot A, Nicolas C, Bidet M, Dulon J, Leban M, Golmard JL, et al. Long-term outcome of ovarian function in women with intermittent premature ovarian insufficiency. Clin Endocrinol (Oxf). 2017;86:223–8.

Baronchelli S, Conconi D, Panzeri E, Bentivegna A, Redaelli S, Lissoni S, et al. Cytogenetics of premature ovarian failure: an investigation on 269 affected women. J Biomed Biotechnol. 2011;2011:370195.

Baronchelli S, Villa N, Redaelli S, Lissoni S, Saccheri F, Panzeri E, et al. Investigating the role of X chromosome breakpoints in premature ovarian failure. Mol Cytogenet. 2012;5:32.

Cameron-Pimblett A, La Rosa C, King TFJ, Davies MC, Conway GS. The Turner syndrome life course project: karyotype-phenotype analyses across the lifespan. Clin Endocrinol (Oxf). 2017;87:532–8.

Conway GS. Premature ovarian failure and FMR1 gene mutations: an update. Ann Endocrinol (Paris). 2010;71:215–7.

Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;65:337–41.

Conway GS, Payne NN, Webb J, Murray A, Jacobs PA. Fragile X premutation screening in women with premature ovarian failure. Hum Reprod. 1998;13:1184–7.

Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Rees M, et al. Menopause. Nat Rev Dis Primers. 2015;1:15004.

Davison RM, Davis CJ, Conway GS. The X chromosome and ovarian failure. Clin Endocrinol (Oxf). 1999;51:673–9.

Desai S, Rajkovic A. Genetics of reproductive aging from gonadal dysgenesis through menopause. Semin Reprod Med. 2017;35:147–59.

El-Shawarby SA, Sharif F, Conway G, Serhal P, Davies M. Oocyte cryopreservation after controlled ovarian hyperstimulation in mosaic Turner syndrome: another fertility preservation option in a dedicated UK clinic. BJOG. 2010;117:234–7.

Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. Mayo Clin Proc. 2017;92:1842–9.

Ferrarini E, Russo L, Fruzzetti F, Agretti P, De Marco G, Dimida A, et al. Clinical characteristics and genetic analysis in women with premature ovarian insufficiency. Maturitas. 2013;74:61–7.

Henzl MR, Loomba PK. Transdermal delivery of sex steroids for hormone replacement therapy and contraception. A review of principles and practice. J Reprod Med. 2003;48:525–40.

Hugon-Rodin J, Gompel A, Plu-Bureau G. Epidemiology of hormonal contraceptives-related venous thromboembolism. Eur J Endocrinol. 2014;171:R221–30.

La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A. Primary ovarian insufficiency: autoimmune causes. Curr Opin Obstet Gynecol. 2010;22:277–82.

Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017;13:220–31.

Luisi S, Orlandini C, Regini C, Pizzo A, Vellucci F, Petraglia F. Premature ovarian insufficiency: from pathogenesis to clinical management. J Endocrinol Invest. 2015;38:597–603.

Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2017;1:CD004143.

Master-Hunter T, Heiman DL. Amenorrhea: evaluation and treatment. Am Fam Physician. 2006;73:1374–82.

Melner MH, Feltus FA. Autoimmune premature ovarian failure—endocrine aspects of a T cell disease. Endocrinology. 1999;140:3401–3.

Mila M, Alvarez-Mora MI, Madrigal I, Rodriguez-Revenga L. Fragile X syndrome: an overview and update of the FMR1 gene. Clin Genet. 2018;93:197–205.

Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause—global prevalence, physiology and implications. Nat Rev Endocrinol. 2018;14:199–215.

Morgan S, Anderson RA, Gourley C, Wallace WH, Spears N. How do chemotherapeutic agents damage the ovary? Hum Reprod Update. 2012;18:525–35.

Morrison JC, Givens JR, Wiser WL, Fish SA. Mumps oophoritis: a cause of premature menopause. Fertil Steril. 1975;26:655–9.

Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360:606–14.

Reynaud K, Cortvrindt R, Verlinde F, De Schepper J, Bourgain C, Smitz J. Number of ovarian follicles in human fetuses with the 45,X karyotype. Fertil Steril. 2004;81:1112–9.

Sassarini J, Lumsden MA. Oestrogen replacement in postmenopausal women. Age Ageing. 2015;44:551–8.

Sharara FI, Seifer DB, Flaws JA. Environmental toxicants and female reproduction. Fertil Steril. 1998;70:613–22.

Smith NL, Blondon M, Wiggins KL, Harrington LB, van Hylckama Vlieg A, Floyd JS, et al. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. JAMA Intern Med. 2014;174:25–31.

Swica Y, Warren MP, Manson JE, Aragaki AK, Bassuk SS, Shimbo D, et al. Effects of oral conjugated equine estrogens with or without medroxyprogesterone acetate on incident hypertension in the Women's Health Initiative hormone therapy trials. Menopause. 2018;25(7):753–61.

van Kasteren YM, Hundscheid RD, Smits AP, Cremers FP, van Zonneveld P, Braat DD. Familial idiopathic premature ovarian failure: an overrated and underestimated genetic disease? Hum Reprod. 1999a;14:2455–9.

van Kasteren YM, Braat DD, Hemrika DJ, Lambalk CB, Rekers-Mombarg LT, von Blomberg BM, et al. Corticosteroids do not influence ovarian responsiveness to gonadotropins in patients with premature ovarian failure: a randomized, placebo-controlled trial. Fertil Steril. 1999b;71:90–5.

van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. Fertil Steril. 1997;68:95–102.

Visser JA, Schipper I, Laven JS, Themmen AP. Anti-Mullerian hormone: an ovarian reserve marker in primary ovarian insufficiency. Nat Rev Endocrinol. 2012;8(6):331–41.

Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6:209–18.

Wallace WH, Kelsey TW, Anderson RA. Ovarian cryopreservation: experimental or established and a cure for the menopause? Reprod Biomed Online. 2012;25:93–5.

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926–37.

Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. Clin Endocrinol (Oxf). 2008a;68:499–509.

Welt CK. Autoimmune oophoritis in the adolescent. Ann N Y Acad Sci. 2008b;1135:118–22.

Wheatcroft NJ, Salt C, Milford-Ward A, Cooke ID, Weetman AP. Identification of ovarian antibodies by immunofluorescence, enzyme-linked immunosorbent assay or immunoblotting in premature ovarian failure. Hum Reprod. 1997;12:2617–22.

Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:3489–510.

Wilson C. Autoimmunity: autoimmune Addison disease and premature ovarian failure. Nat Rev Endocrinol. 2011;7:498.

Key Reading

1. Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926–37.
2. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1–G70.
3. Rossetti R, Ferrari I, Bonomi M, Persani L. Genetics of primary ovarian insufficiency. Clin Genet. 2017;91:183–98.
4. Desai S, Rajkovic A. Genetics of reproductive aging from gonadal dysgenesis through menopause. Semin Reprod Med. 2017;35:147–59.
5. Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017;13:220–31.
6. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril. 2016;106:1588–99.
7. Luisi S, Orlandini C, Regini C, Pizzo A, Vellucci F, Petraglia F. Premature ovarian insufficiency: from pathogenesis to clinical management. J Endocrinol Invest. 2015;38:597–603.

The Endocrine System and Pregnancy

42

Margaret Eckert-Norton and Saundra Hendricks

Contents

42.1 **Introduction** 819

42.2 **Normal Glucose Metabolism During Pregnancy** 820

42.3 **Type 1 Diabetes** 820

42.4 **Type 2 Diabetes** 820

42.5 **Preconception Planning** 821

42.6 **Gestational Diabetes** 821

42.7 **Management of Diabetes During Pregnancy** 822
42.7.1 Additional Surveillance 823
42.7.2 Medical Nutrition Therapy 823
42.7.3 Insulin Therapy 823
42.7.4 Multiple Daily Injections (MDI) 823
42.7.5 Continuous Subcutaneous Insulin Infusion (CSII) 824
42.7.6 Intrapartum with CSII 824
42.7.7 Oral Diabetes Agents 825

42.8 **Maternal and Foetal Complications of Diabetes in Pregnancy** 825

42.9 **The Thyroid Gland and Pregnancy** 825
42.9.1 Review of Thyroid Physiology 826
42.9.2 Hypothyroidism 826
42.9.3 Gestational Transient Thyrotoxicosis 827
42.9.4 Hyperthyroidism 827
42.9.5 Post-partum Thyroiditis 829
42.9.6 Thyroid Nodules in Pregnancy and Thyroid Cancer 829
42.9.7 Screening for Thyroid Disorders During Pregnancy 829

M. Eckert-Norton
St. Joseph's College and SUNY Downstate,
Brooklyn, NY, USA
e-mail: meckert-norton@sjcny.edu;
margaret.eckert-norton@downstate.edu

S. Hendricks (✉)
Department of Medicine, Center of Bioenergetics,
Houston Methodist Hospital, Houston, TX, USA
e-mail: sjhendricks@houstonmethodist.org

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_42

42.9.8 Summary of Thyroid Disorders During Pregnancy and Nursing Considerations 830
42.10 **Other Endocrine Considerations During Pregnancy** 830
42.11 **Hypothalamic-Pituitary-Adrenal Axis** 830
42.12 **Parathyroids and Maintaining Calcium Balance** 831
42.13 **Placenta as an Endocrine Organ** 831
42.14 **Endocrine Disruptors in Human Reproduction and Health** 831
42.15 **Precautionary Principle and Implications for Nursing Practice** 832
42.16 **Conclusions** 833
References 834

Abstract

Healthy endocrine function is vital for fertility, normal foetal growth and development, labour and delivery, and postnatal breast feeding. In disease states such as diabetes, attention must be given to preconception planning and management of concomitant issues through a pregnancy. Both hypoglycaemia and hyperglycaemia can be teratogenic, resulting in poor maternal and/or foetal outcomes.

Likewise, maternal thyroid function must be maintained in the euthyroid range to avoid significant foetal neural damage from hyper- or hypothyroidism. Monitoring and adjustments of thyroid replacement at each trimester are recommended to parallel increasing foetal requirements.

Pituitary dysfunction may become apparent during pregnancy as the gland enlarges. Prolactin levels will normally rise in response to rising oestrogen levels, but may also stimulate the growth of a prolactinoma. Hypothalamic-pituitary-adrenal dysfunction is uncommon, but may result for other dysfunctions.

Successful pregnancy outcomes require pre-pregnancy patient counselling, planning, and ongoing monitoring of patient responses. This continues through pregnancy and the post-partum period.

Keywords

Pregnancy · Diabetes type 2 · Thyroid function · HPA axis · Parathyroid disease

Abbreviations

CSI	Continuous subcutaneous insulin infusion
DM1	Type I diabetes
DM2	Type 2 diabetes
GDM	Gestational diabetes
HA1c	Haemoglobin A1c
hCG	Human chorionic gonadotropin
MDI	Multiple daily injections
MM	Methimazole
Mnt	Medical nutrition
PPT	Post-partum thyroiditis
PTU	Propylthiouracil
RAI	Radioactive iodine
SMBG	Self-monitoring of blood glucose
T3	Tri-iodothyronine
T4	Thyroxine
TRH	Thyroid-releasing hormone
TSH	Thyroid-stimulating hormone
TSI	Thyroid-stimulating immunoglobin
μg	Micrograms

Key Terms

- **Pre-gestational Diabetes:** Maternal hyperglycaemia secondary to inadequate insulin and/or resistance to insulin action prior to pregnancy.
- **Gestational Diabetes:** Maternal blood glucose elevation of variable degree with onset or recognition during pregnancy.
- **Teratogen:** Any agent that causes an abnormality following foetal exposure during pregnancy.

- **Human Chorionic Gonadotropin (HCG):** A placental hormone that stimulates production of progesterone from the corpus luteum, supporting the placenta during the early stages of pregnancy.
- **Foetal Immunological Privilege:** Physiological condition in pregnancy in which the foetus is protected from attack from the maternal immune system.
- **Post-partum Thyroiditis (PPT):** Inflammation of the maternal thyroid gland occurring during the first few months after the birth of a baby.
- **Progesterone:** A hormone secreted by the corpus luteum and the placenta that triggers the uterine lining to thicken to accept a fertilized egg. Progesterone decreases uterine contractions, stimulates blood supply to the endometrium, and suppresses further ovulation during pregnancy.
- **Endocrine Disrupting Chemicals (EDCs):** These are chemicals and compounds that may interfere with the endocrine system producing adverse developmental, reproductive, neurological, and/or immune effects in humans and other organisms.
- **Precautionary Principle:** A foundational concept of environmental regulation in many countries emphasizing that if threats of serious or irreversible damage to the environment exist, the lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to preserve the environment and protect the health of living organisms.

Key Points

- Uncontrolled diabetes pre-pregnancy and during pregnancy can have serious adverse effects on both mother and developing foetus that can be minimized with optimal blood sugar level treatment and control.
- Aggressive screening of women at risk for thyroid disorders in the prenatal period and through each trimester of pregnancy is essential to ensure normal foetal development.
- The pituitary gland enlarges during pregnancy; prolactin level increases and may impact the hypothalamic-pituitary-adrenal axis function.
- Peptide hormones produced by the placenta, hypothalamus, and the pituitary such as: gonadotropin-releasing hormone, corticotrophin-releasing hormone and growth hormone-releasing hCG, growth hormone, are important for sustaining pregnancy and regulating growth and development.
- Endocrine disruptors have been linked to reproductive dysfunction in men and women and the generational development of some diseases.

42.1 Introduction

This chapter presents current concepts related to the nursing care of pregnant woman with disorders of the endocrine system. While the emphasis is placed on the most commonly encountered clinical issues, other, less common, though clinically relevant, issues are also discussed. The significant role of the placenta as an active endocrine organ is reviewed.

Emerging data regarding exposure to endocrine-disrupting compounds and the impact of these compounds on maternal-foetal health outcomes is explored.

The most commonly occurring forms of diabetes are categorized into three major types: Type 1 diabetes, Type 2 diabetes, and Gestational diabetes. Each of these types of diabetes has distinct clinical presentations and management varies widely. There are potential complications for the pregnant woman and her baby that result from poor control of diabetes of any type. The following section discusses normal glucose metabolism in pregnancy and each of the three common types of diabetes as they relate to the pregnant woman and developing foetus.

42.2 Normal Glucose Metabolism During Pregnancy

Glucose is the primary foeto-placental fuel and its transport across the placenta is in proportion to the maternal glucose level. In order to adapt to the challenge of meeting the glucose needs of both the mother and the growing foetus, the maternal metabolism undergoes adaptations throughout pregnancy. The primary purpose of these adaptations is to prepare for the accelerated foetal growth in the last trimester when approximately 70% of foetal growth occurs. During early gestation, maternal nutrient and fat stores increase with minimal changes in insulin sensitivity, in order to prepare for the nutritional demands of late gestation and lactation.

By late gestation, insulin sensitivity decreases (increased insulin resistance) with a twofold increase in mean circulating insulin and 30% increase in hepatic glucose production from the maternal liver. The resulting increases in maternal blood glucose and fatty acids provide fuel for the developing foetus. Due to high foeto-placental fuel demands, maternal fasting glucose falls in spite of the increased hepatic glucose production (Lain and Catalano 2007). If foetal glucose demands cannot be met due to maternal malnutrition or illness, the foetus can utilize alternate fuels from breakdown of maternal fatty acids (Feldt-Rasmussen and Mathiesen 2011). Because maternal insulin does not cross the placenta, early foetal insulin production is vital for foetal utilization of fuels. Both the ambient maternal glucose level and glucose spikes stimulate foetal insulin production (Feldt-Rasmussen and Mathiesen 2011). Other specific types of diabetes exist due to causes such as cystic fibrosis, HIV/AIDS, medications, and organ transplantation. As these are relatively rare, for the purposes of this chapter, we will focus on the first three classifications: Type 1 diabetes, Type 2 diabetes, and Gestational diabetes.

42.3 Type 1 Diabetes

Type 1 diabetes (formally called juvenile diabetes) accounts for 5–10% of individuals with diabetes. It can occur at any age and is caused by cellular-mediated autoimmune destruction of pancreatic beta cells, the cells that produce insulin. The destructive process takes months, but eventually results in insulinopenia (the decreased or absent insulin levels). The signs and symptoms can be sudden and dramatic at diagnosis. Signs and symptoms include: extreme thirst, frequent urination, and weight loss. Treatment is aimed at achieving optimal glucose levels by replacing the hormone insulin that the pancreas can no longer produce.

People with type 1 diabetes require insulin replacement for survival (Guthrie and Guthrie 2004).

42.4 Type 2 Diabetes

Type 2 diabetes is caused by a loss of balance between insulin sensitivity and insulin secretion. Unlike type 1 diabetes, in type 2 diabetes the pancreas produces insulin, but peripheral tissues lose sensitivity to insulin action, a process known as insulin resistance. Early in the disease process, insulin levels are often elevated with normal glucose levels. Over a period of months or years, the beta cells cannot produce enough insulin to maintain normoglycaemia and hyperglycaemia ensues. Predisposing factors for Type 2 diabetes include obesity, sedentary lifestyle, family history, puberty, ethnicity, and advancing age. Unlike Type 1 diabetes, the onset of Type 2 diabetes is insidious and the diagnosis can be delayed for years after the onset of hyperglycaemia, setting the stage for long-term complications.

Ninety to ninety-five percent of people with diabetes have Type 2 diabetes (CDC 2011). Type 2 diabetes occurs across a wide range of ages (adolescence through advanced maturity) and disproportionately affects ethnic minorities in the U.S. Worldwide prevalence of 8.5% (WHO 2017). It is currently estimated that 12.7% of adults of African descent have Type 2 diabetes as compared to 7.4% in whites, and prevalence rates have more than doubled over in the 10 years previous to 2011, but has decreased a little in recent years (CDC 2017). Rates of Type 2 diabetes are rapidly increasing in youth who are of Latino, Native American, or Asian/Pacific Island descent. According to the

National Institutes of Diabetes and Digestive and Kidney Disease (NIDDK) in 2017, 11.7% of all women age 20 years and older have diabetes. This explosion of type 2 diabetes has resulted in a higher than expected rate of pre-gestational diabetes in women of childbearing age.

In the past, pre-gestational diabetes was usually assumed to be Type 1 diabetes. In recent years, the increasing rate of obesity and Type 2 diabetes in adolescents has resulted in an increase in the number of pregnancies complicated by pre-gestational Type 2 diabetes. Over time, as the recommendations for earlier testing are widely adopted, the number of preexisting diabetes pregnancies will climb. In any case, no matter the cause of the maternal hyperglycaemia, the resulting foetal hyperglycaemia is a potent teratogen, an agent that causes foetal malformation.

42.5 Preconception Planning

Initiating meticulous metabolic management prior to conception is critical to the successful outcome of diabetic pregnancies. The importance of preconception planning and counselling cannot be overstated in this high-risk population of women with preexisting diabetes (Type 1 or Type 2). When pregnancy is planned, many non-insulin therapies including blood pressure and cholesterol-lowering medications may need to be stopped or changed. The Endocrine Society Guidelines recommend that blood pressure control of <130/80 be achieved and angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blockers be stopped prior to withdrawing contraception (Blumer et al. 2013).

Pre-pregnancy counselling must include guidance regarding effective contraception and instruction and support to normalize glucose to as near normal as possible while avoiding significant hypoglycaemia. Even before the pregnancy is detected, maternal hyperglycaemia can contribute to congenital malformations in the cardiac and central nervous system. The risk for these malformations and foetal demise increases with any increase in maternal glycaemia during the first 6–8 weeks of gestation. For this reason, counselling regarding avoidance of unplanned pregnancy should begin during puberty and continue into adulthood for women with diabetes or who are in a high-risk population for developing diabetes (ADA 2018). Additionally, maternal risks of developing new or progression of existing eye and renal complications are increased during pregnancy in women with pre-gestational diabetes. Eye and renal examinations should begin prior to conception with close follow-up during pregnancy and for 1 year post-partum. Optimally, treatments for preexisting eye, renal, neuropathic, and cardiovascular disease begin prior to conception (Blumer et al. 2013).

42.6 Gestational Diabetes

It is estimated that 2–10% pregnancies are affected by gestational diabetes (GDM). Hyperglycaemia in pregnancy has been associated with high birth weight above the 90th percentile, increased rates of caesarean sections, neonatal hypoglycaemia, and foetal hyperinsulinaemia. Mothers have a higher risk for pre-eclampsia, preterm delivery. The impact on the neonate could include: shoulder dystocia, hyperbilirubinaemia, and may trigger the need for neonatal intensive care admission.

GDM has been defined as any degree of glucose intolerance first identified during pregnancy without regard to undetected pre-gestational hyperglycaemia (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). This long-held definition of gestational diabetes (GDM) has come under scrutiny as more women of childbearing age are diagnosed with Type 2 diabetes prior to pregnancy. In 2009, the "Hyperglycaemia and Adverse Pregnancy Outcomes" (HAPO) trial results were published. The HAPO was a large, multinational study that determined increased glucose levels during pregnancy; even levels that were below diagnostic criteria for diabetes were associated with adverse outcomes (Lapolla et al. 2011; Metzger et al. 2009). In other words, there is no safe level of hyperglycaemia during pregnancy.

With this new data from the HAPO Study, consensus panels with representatives from ten member organizations, including the American

Diabetes Association (ADA), convened to study and review the HAPO results and develop new diagnostic criteria for GDM. Due to the increasing incidence of obesity and pre-gestational diabetes in young women, new screening criteria were developed that included screening for hyperglycaemia at the first prenatal visit for women in high-risk groups. For women not previously diagnosed with diabetes, the ADA supports the new diagnostic procedures at 24–28 weeks gestation and the following diagnostic criteria:

- Performance of a 75-g oral glucose tolerance test (OGTT).
- Obtain plasma glucose measurements at fasting, 1 and 2 h
- The OGTT should be performed in the morning after an overnight fast of at least 8 h.
- The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:
  - Preprandial blood glucose ≤95 mg/dL (5.3 mmol/L)
  - Fasting blood glucose target of ≤90 mg/dL (5.0 mmol/L)
  - 1 h after the start of a meal ≤140 mg/dL (7.8 mmol/L)
  - 2 h after the start of a meal ≤120 mg/dL (6.7 mmol/L)
  - HbA1C ≤7% (ideally ≤6.5%) (Blumer et al. 2013)

The diagnosis of GDM has long-term importance for the mother after delivery. Within the first 2 months post-partum, 5–10% of women with GDM develop Type 2 diabetes and over the next 10–20 years this risk increases to 35–60% (CDC 2011). This fate may be avoided through lifestyle changes that include weight loss through exercise and healthy food choices and the use of certain glucose lowering medications. The Diabetes Prevention Program (DPP) showed these interventions could lower the risk for Type 2 diabetes by 50% or more and these individuals continued to have reduced risk 10 years later (Knowler and Hamman 2009).

42.7 Management of Diabetes During Pregnancy

Management of diabetes during pregnancy is aimed at achieving normal foetal growth and development by maintaining near normal glucose levels. Diabetes self-management education (DSME) has well-established evidence for improved outcomes and cost-effectiveness when provided in age-appropriate and culturally informed manner (ADA 2018). Diabetes self-management education usually includes content related to self-monitoring of blood glucose (SMBG), rationale for maintaining optimal glucose control, medical nutritional therapy (MNT), exercise, and medication. Although emerging evidence indicates that some oral glucose lowering agents may be safe during pregnancy, these data are not sufficient to ensure the safety of oral agents during pregnancy (ADA 2018). Therefore, insulin remains the cornerstone of pharmacological interventions for diabetes during pregnancy.

Self-monitoring of blood glucose (SMBG) via finger-stick blood samples and a glucose meter is the most widely used method of monitoring maternal glycaemia. The Endocrine Society guidelines (Blumer et al. 2013) recommendations for GDM glycaemic goals are:

- Fasting blood glucose levels less preprandial blood glucose ≤95 mg/dL (5.3 mmol/L)
- 1-h postprandial blood glucose levels less than 140 mg/dL
- 2-h postprandial blood glucose levels less than 120–127 mg/dL.

For women with preexisting Type 1 or Type 2 diabetes who become pregnant, the ADA (2018) recommends the following glucose targets if these targets can be reached without excessive hypoglycaemia:

- Pre-meal, bedtime, and overnight glucose: 60–99 mg/dL (3.3–5.4 mmol/L)
- Peak postprandial glucose: 100–129 mg/dL (5.4–7.1 mmol/L)
- HbA1C ≤7% (ideally ≤6.5%)

Frequent finger-stick SMBG is crucial to achieving glycaemic targets. It is typical that a pregnant woman with diabetes will measure blood glucose up to 6–10 times daily. Continuous glucose monitoring (CGM) may be used to supplement finger-stick glucoses, especially during the first trimester, where hypoglycaemia may be problematic in Type 1 diabetes. Although CGM can be useful in persons prone to hypoglycaemia, CGM measures interstitial glucose levels and correlation between interstitial and traditional blood glucose readings has not been established (Hoeks et al. 2011).

HA1c is a lab value that estimates the percentage of red blood cells that are marked as a result of elevated blood glucose (glycosylation). Normal values can vary by assay, but are usually 4–6%.

42.7.1 Additional Surveillance

In addition to glucose monitoring, urine ketones should be monitored during illness, and at any time, the capillary glucose exceeds 200 mg/dL. The presence of urine ketones may be an indicator of metabolic derangement and should be reported promptly (Kitzmiller et al. 2008). Since maternal hyperglycaemia causes foetal abdominal adiposity, ultrasound surveillance of foetal abdominal girth starting in the second trimester or early third trimester and repeated every 2–4 weeks can provide useful information in combination with SMBG (Metzger et al. 2007).

42.7.2 Medical Nutrition Therapy

Medical Nutrition Therapy (MNT) is essential to reaching metabolic targets. A registered dietitian or other professionals with experience in managing GDM should design a plan to provide adequate nutrients and caloric intake without inducing weight loss or excessive weight gain. For overweight or obese women, a modest caloric and carbohydrate reduction may be appropriate (Metzger et al. 2007).

As with gestational diabetes, MNT is crucial to optimizing metabolic management in women with pre-gestational diabetes (Type1 or Type2 diabetes). The tailored meal plan should be based on pregravid body mass index and individual gestational weight gain goals. To be successful, the food plan must be mindful of personal food preferences, ethnic and financial considerations as well as macro- and micronutrient composition. Keeping a detailed food diary is useful for the pregnant woman to make adjustments in her food intake and for her health care team to make therapeutic modifications in her food plan (Kitzmiller et al. 2008).

42.7.3 Insulin Therapy

For women with Type 1 diabetes, insulin and healthy lifestyle are the only therapeutic options available to them from the time that the diagnosis of diabetes is established. Before and during pregnancy, the insulin regimen should be intensified to a basal and preprandial regimen if this is not her pregravid regimen. Some women with Type 2 diabetes may require intensive insulin therapy to achieve optimal blood glucose control during pregnancy. This intensive regimen can be accomplished most commonly with multiple daily injections (MDI) or, in some cases, continuous subcutaneous insulin infusion (CSII) utilizing an insulin pump.

42.7.4 Multiple Daily Injections (MDI)

In MDI therapy, insulin is given in a basal/bolus manner. Basal insulin, long-acting insulin, is administered once or twice daily and the dose is expected to increase as the pregnancy progresses. Fast-acting insulin is used for pre-meal insulin and the doses are adjusted on a meal-by-meal basis depending on the carbohydrate content of the meal and a calculated insulin sensitivity ratio, or how many mg/dL a unit of insulin will drop the glucose. Some women may require 4–6 injections daily to reach and maintain normoglycaemia. As the pregnancy progresses, these formulas will change and will require constant surveillance

and adjustments (Kitzmiller et al. 2008). Since glucose fluctuations are the norm during pregnancy, any pregnant woman who takes insulin must be prepared for both hypoglycaemia and hyperglycaemia. Hypoglycaemia is most troublesome early in pregnancy, but can occur at any time. Anyone on intensive insulin therapy, MDI or CSII, should always carry a sugar source, preferably glucose tablets or gels that deliver a more predictable glucose load than soda or candy. Glucagon emergency kits should always be available for trained family, friends, and coworkers to administer in the event of a hypoglycaemic emergency. A medical alert bracelet should be worn by anyone taking insulin, especially those on an intensive regimen that predisposes one to hypoglycaemia. On the opposite end of the glucose curve is hyperglycaemia. The only treatment for hyperglycaemia is insulin and must be (International Association of Diabetes and Pregnancy Study Groups Consensus Pane, 2010).

42.7.5 Continuous Subcutaneous Insulin Infusion (CSII)

CSII, or external insulin pump therapy, is a therapeutic option that has been utilized primarily in Type 1 diabetes, but can be an effective therapy in Type 2 diabetes. Although CSII was first used in pregnancy in 1978, there is a paucity of research data about its use in this high-risk population. Although many patients and expert practitioners prefer insulin pump therapy, it has not been shown to be superior to multiple daily injections during pregnancy (Castorino et al. 2012).

In the simplest of terms, an insulin pump is an external device that runs on batteries with electronic controls, miniature processing module, and a disposable reservoir for insulin. The insulin is delivered to the patient through a disposable subcutaneous cannula that may have tubing connecting the pump to the cannula. There are pumps available that attach directly to the skin without the use of tubing. The abdomen is usually the best site for cannula placement, but as the gravid abdomen becomes distended the cannula can be inserted into the lower flank, the upper outer buttocks, or outer thigh. The insulin, reservoir, tubing, and cannula are replaced every 2–3 days. Rapid onset insulin analogues are used in the insulin pump. As with MDI therapy, the pump is programmed to deliver the insulin both slowly as background insulin (called basal insulin) and in a burst of insulin before meals (called bolus insulin doses). Basal insulin rates can be programmed to mimic the individual's circadian insulin requirements and adjusted as necessary. Bolus insulin is delivered before meals based on a two-part formula that is programmed into the pump. The first part is the carbohydrate ratio, or how many grams of carbohydrate 1 unit of insulin cover. The second part of the formula is the sensitivity factor, or how many mg/dL will 1 unit of insulin drop the glucose. These ratios are personalized and programmed into the pump and the individual "tells" the pump how many grams of carbohydrate she will be eating and what her glucose value is. Many glucose-measuring devices communicate with the pump, so this information may not need to be entered manually. In the event of a pump malfunction, insulin injections must be available (Bernasko 2012).

With both MDI and those using CSII, women must always be prepared for hypoglycaemia and hyperglycaemia. A sugar source and glucagon emergency kit must always be available.

42.7.6 Intrapartum with CSII

The mother may choose to continue CSII during labour and delivery. This decision should be made during pregnancy and discussed with and supported by the team caring for her. The labouring mother may be distracted or medicated and not able to manage her insulin pump. She must arrange to have assistance from an experienced person to monitor her glucose and operate the insulin pump during this potentially stressful time. If CSII is not continued or abandoned, a continuous IV insulin drip can be started to control glucose during the intrapartum period. The lowest basal rate in the final days of the pregnancy is usually sufficient to keep maternal glucoses between 70 and 140 mg/dL to prevent

newborn hypoglycaemia. Maternal glucose levels should be checked every hour during the intrapartum period so that appropriate therapeutic adjustments can be made (Bernasko 2012).

42.7.7 Oral Diabetes Agents

The recommended therapy for women with pregestational Type 2 diabetes who become pregnant and those diagnosed with gestational diabetes is not as straightforward as with Type 1 diabetes. At the time of this writing, the current American Diabetes Association (ADA) recommendations are that any oral agents are to be stopped and intensive insulin therapy initiated as soon as possible. There is concern about transplacental passage of medication during organogenesis and foetal development (Kitzmiller et al. 2008).

An open label study for women with gestational diabetes treated with metformin versus insulin found that neonatal complications were similar in the two groups and the women in the metformin group would choose their treatment again (Rowan et al. 2008). In a meta-analysis study that examined the benefits and risks of oral diabetic agents versus insulin in gestational diabetes, "No substantial maternal or neonatal outcome differences were found with the use of glyburide or metformin compared with the use of insulin in women with GDM" (Nicholson et al. 2009: 193). In contrast, another trial that examined the outcomes of women with GDM treated with glyburide compared to insulin therapy had the opposite outcome. The glyburide-treated mother's neonates were more likely to be macrosomic and admitted to the ICU than those whose mothers were treated with insulin (Cheng et al. 2012). In a trial that compared efficacy of metformin with glyburide in gestational found that the failure rate of metformin-treated group was 2.1 times that of the glyburide-treated group. Glyburide was found to be more efficacious than metformin, but the safety issues were not addressed (Moore et al. 2010). Again, as safety data are inconclusive, insulin remains the drug of choice when required for treating hyperglycaemia in pregnancy.

42.8 Maternal and Foetal Complications of Diabetes in Pregnancy

There are immediate and long-term foetal and maternal consequences of diabetes during pregnancy. During pregnancy, near normal glycaemia is essential for both mother and foetus. "The relationship of maternal glucose to pregnancy outcome is a continuum, and ideal results are achieved when maternal glucose concentrations are within normal limits, but not too low" (Kitzmiller et al. 2008: 1062). Maternal hyperglycaemia, especially during the first few weeks after conception, possibly before the pregnancy, has been recognized as a significant risk for spontaneous abortions and congenital malformations. Hyperglycaemia after 12 weeks gestation promotes foetal hyperinsulinaemia, excess foetal growth, and adiposity (Ray et al. 2001). Excess adiposity often causes macrosomia which is present in 27–62% of infants born to diabetic mothers, especially common when maternal glucose were elevated. Macrosomia is associated with neonatal complications of birth trauma, hypoglycaemia, caesarean delivery, hypocalcaemia as well as long-term risk of obesity, insulin resistance, and diabetes (Kitzmiller et al. 2008). Other maternal risks of uncontrolled or poorly controlled diabetes include preterm labour, pregnancy-induced hypertension, polyhydramnios, infections, and seizures (Castorino et al. 2012).

It is important to the nursing care of women with diabetes during pregnancy to recognize that although uncontrolled diabetes can have serious adverse effects on both mother and developing foetus, maintaining optimal blood sugar levels can minimize these adverse outcomes.

42.9 The Thyroid Gland and Pregnancy

Thyroid disorders are common, especially in women, and the management issues during pregnancy are complex. Abnormalities in thyroid hormone production can have devastating effects

during pregnancy. The reported prevalence of thyroid disorders during pregnancy ranges from 2 to 3% for hypothyroidism and 0.4–1.7% for hyperthyroidism (Glinoer and Spencer 2010; Yazbeck and Sullivan 2012). Hypothyroidism is characterized by abnormally low levels of hormones produced by the thyroid and associated elevated thyroid-stimulating hormone (TSH). Hypothyroidism has been linked to many adverse outcomes in pregnancy including: premature birth, pre-eclampsia, abruption, post-partum haemorrhage, impaired foetal neuropsychological development, and low birth weight (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012). Hyperthyroidism is characterized by abnormally high levels of thyroid hormones and associated suppression of TSH. Hyperthyroidism is also linked to adverse pregnancy outcomes including: spontaneous abortion, intrauterine growth restriction, thyroid storm in the mother, and increased perinatal mortality (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012).

42.9.1 Review of Thyroid Physiology

There is an intimate connection between the hypothalamic-pituitary hormones and thyroid hormone production. The thyroid hormones, triiodothyronine (T3) and thyroxine (T4), are secreted as part of a classic negative feedback loop with TSH and thyroid-releasing hormone (TRH). TSH is produced in the pituitary via TRH signalling from the hypothalamus. TRH signals the production of TSH, which in turns signals the thyroid to synthesize and release T3 and T4. T3 and T4 require iodine trapping in the thyroglobulin of the thyroid gland for the production of these hormones. When signalled by TSH, a series of chemical reactions takes place in the thyroid synthesizing T3 and T4 from the iodine-rich thyroglobulin. T3 and T4 are then released; some of the hormone remains free hormone, but most is bound to circulating proteins for distribution. The free hormone completes the feedback loop to the HPA, decreasing TRH and TSH production. T3 is the more metabolically active hormone. T3 is converted from T4 at distal sites when needed (See thyroid chapter) (Springer et al. 2017).

During pregnancy, three important physiological events occur that are important to thyroid function. First, increased oestrogen levels increase the production of binding proteins. This increases the amount of thyroid hormone which is bound and decreases the available free hormone. This stimulates the hypothalamus and pituitary to increase TRH /TSH. Secondly, human chorionic gonadotropin (hCG) and TSH are chemically identical in some areas. With the surge in hCG in early pregnancy, TSH effects are mimicked and production of thyroid hormones increased. Third, the placenta transfers some maternal T3 and T4 to the foetus in early pregnancy to support foetal growth and development. In the second and third trimesters, the placenta participates in the chemical conversion of T4 to T3 (a process called deiodination) and supports foetal thyroid hormone activity (Springer et al. 2017).

42.9.2 Hypothyroidism

As discussed above, hypothyroidism is characterized by insufficient production of T3 and T4. Thyroid hormone production depends on adequate availability of iodine. If iodine is nutritionally deficient, thyroid hormone production will be compromised. Worldwide, maternal iodine deficiency is still a leading cause of preventable intellectual compromise in infants (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012; Zimmerman 2009). Iodine deficiency can induce enlargement of the thyroid gland, a condition known as goitre. With iodine replacement, the goitre can regress and the thyroid returns to normal size. In some cases, however, the goitre persists and may compress surrounding tissues so that surgery may be indicated. Dietary sources of iodine include saltwater fish, shellfish, seaweed, some bread products, and iodized salt (Lutz and Przytulski 2006). However, many women do not eat shellfish for religious reasons and to avoid mercury exposure from seafood. Many women are also allergic to shellfish.

Curiously, sea salt does not contain any iodine. Iodized salt has been available in the United States since 1924. Although the United States has readily available supplies of iodized salt, internationally, particularly in southeast Asia and parts of Europe, iodized salt is not readily available. Many women in the United States avoid salt to minimize the risk of hypertension, an important consideration in pregnancy as well. Women of childbearing age require 150 μg of iodine daily. During pregnancy, daily intake of iodine should be 250 μg, but not exceed 500 μg (American Thyroid Association [ATA] 2011; Fitzpatrick and Russell 2010; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012). The amount of iodine contained in prenatal vitamins is variable. Nurses need to be aware of the nutritional content of the prenatal vitamins pregnant women are taking.

Today, the leading cause of hypothyroidism in the United States is autoimmune disease. Hashimoto's thyroiditis accounts for about 95% of cases (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012). Signs and symptoms of overt hypothyroidism include: fatigue, constipation, cold intolerance, hair thinning, vocal changes, and slowed cognitive activity. Many women with hypothyroidism offer no complaints and there is overlap between common problems during pregnancy and symptoms of hypothyroidism. It is the goal of treatment to avoid clinical hypothyroidism as determined by elevated TSH level.

As thyroid hormone deficit can have adverse effects very early in pregnancy, women on treatment for hypothyroidism should have preconception counselling about thyroid hormone requirements during pregnancy. Levothyroxine (Lt4) tablets are the recommended treatment for replacing thyroid hormone. Women who are being treated for hypothyroidism with Lt4 prior to pregnancy should increase their dose by approximately 30% to mimic the physiological increase during normal pregnancy (Stagnaro-Green et al. 2011). This dose adjustment can be accomplished by taking two extra tablets per week (nine tablets instead of seven) when a menstrual cycle is missed or pregnancy test is positive (Fitzpatrick and Russell 2010; Stagnaro-Green et al. 2011). To assure consistent absorption, Lt4 tablets should be taken on an empty stomach and separated from other medications, including prenatal vitamins by at least 4 h (Carson 2009; Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012).

42.9.3 Gestational Transient Thyrotoxicosis

As discussed above, hCG is structurally similar to TSH and can physiologically mimic TSH activity, stimulating the thyroid gland and increasing thyroid hormone production. In response to elevated hCG levels in early pregnancy, approximately 1–3% of women will develop transient signs and symptoms of hyperthyroidism. This is referred to as gestational transient thyrotoxicosis (GTT). GTT is often associated with hyperemesis gravidarum. Multiple gestation, hydatiform mole, and choriocarcinoma increase the risk of developing GTT. The thyroid gland typically remains normal size in this condition. GTT usually resolves by about 18 weeks gestation and only supportive therapies are required, though some women will need to be hospitalized for fluid and electrolyte management if the hyperemesis is severe. Should symptoms persist beyond 18 weeks, if goitre or eye changes occur or if autoimmune disease is present, the mother should be screened for overt hyperthyroidism (Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012).

42.9.4 Hyperthyroidism

Hyperthyroidism is characterized by an excess of thyroid hormone. Thyroid function tests indicating relative suppression of TSH and increased levels of free T3 and T4 are consistent with hyperthyroidism. Signs and symptoms include: resting tachycardia, hypertension, tremor, enlarged thyroid gland, and ocular changes including proptosis, lid lag, and stare. Less specific symptoms include: nausea and vomiting, increased appetite, weight loss, heat intolerance,

hyperdefecation (frequent bowel movement throughout the day), fatigue, insomnia, and new onset irritability or anxious mood. Uncontrolled hyperthyroidism is associated with spontaneous abortion, some congenital anomalies, preterm birth, low birth weight, abruption, neonatal thyroid disorder, and perinatal mortality. For the mother, uncontrolled hyperthyroidism is associated with pre-eclampsia and thyroid storm (Fitzpatrick and Russell 2010). Thyroid storm is a medical emergency and can be fatal. Thyroid storm is characterized by fever, hypoglycaemia, sudden changes in mental status, hypertension, resting tachycardia, enlarged thyroid gland, and exophthalamos. Thyroid storm can result in multi-organ failure and death. This rare but serious condition can be stabilized when recognized and treated early (Chong et al. 2010).

Grave's disease accounts for 85–95% of hyperthyroidism in pregnancy (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012). Grave's disease is an autoimmune disorder occurring in about 0.5% of the general population. Autoantibody formation results in thyroid overstimulation, enlarging the thyroid gland and increasing thyroid hormone production. The diagnosis is based on clinical presentation, thyroid function tests, and often the measurement of thyroid-stimulating immunoglobin (TSI) and/or TSH-receptor antibody (TRAb). All women with known Grave's disease should have preconception counselling and evaluation to ensure optimal thyroid function. Although many women can be stabilized on oral medication, some women may require surgery to achieve metabolic stability. In non-pregnant women, radioactive iodine (RAI) for thyroid ablation may also be a therapeutic option. It is critical that women who have been treated with RAI avoid pregnancy for at least 6 months to provide sufficient time to manage the hypothyroid state that will be induced. Because of possible teratogenic effects of RAI, it is absolutely contraindicated in pregnancy and lactation (De Groot et al. 2012; Fitzpatrick and Russell 2010; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012). In Grave's disease during pregnancy, autoantibodies can cross the placenta and may cause foetal hyperthyroidism and even goitre (Fitzpatrick and Russell 2010; Yazbeck and Sullivan 2012). Maternal symptoms, as discussed above, can include: resting tachycardia, hypertension, tremor, goitre, and ocular changes. Reflecting physiologic changes in maternal immune system, preexisting Grave's disease is more likely to exacerbate in the first trimester and in the post-partum period. Improvement is often seen during the second and third trimesters, during which medication is reduced and sometimes even discontinued. Grave's disease can also occur for the first time during pregnancy. Nurses and other clinicians need to be vigilant about evolving signs and symptoms that may indicate Graves hyperthyroidism, particularly in women with other autoimmune processes such as Type I diabetes.

Grave's disease during pregnancy is treated with anti-thyroid drugs of the thionamide class. Two drugs are most commonly used to treat the disorder: propylthiouracil (PTU) and methimazole (MMI). Both medications work by inhibiting production of T4. Additionally, PTU blocks conversion of T4 to T3. MMI is more potent mg/mg than PTU and has a longer half-life. MMI is generally a once daily medication, whereas PTU is usually taken three times daily. Both PTU and MMI are associated with agranulocytosis occurring in approximately 0.1% of persons treated with these medications. There has been conflicting evidence regarding the association of MMI with foetal anomalies. For this reason, PTU is the preferred treatment in the first trimester. PTU is associated with liver failure that can occur any time during treatment. Therefore, the ATA recommends initial treatment with PTU in the first trimester and clinician consideration of switching to MMI for the second and third trimesters (Stagnaro-Green et al. 2011). As anti-thyroid drugs cross the placenta, the foetal exposure to autoantibodies will also be treated with maternal medication. Foetal ultrasonography is used to assess heart rate, growth, and development.

However, overtreatment with thionamides can cause foetal hypothyroidism which can have serious adverse effects on foetal development. Minimizing excessive exposure to anti-thyroid medication is critical. The goal of medical ther-

apy is to maintain freeT4 levels in the upper limits of the normal range with as low a dose of medication as possible (De Groot et al. 2012; Fitzpatrick and Russell 2010; Galofre and Davies 2009; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012). Beta blockers such as propanolol can be used as adjunctive treatment for hypertension, tremor, and tachycardia. However, long-term treatment (greater than 2–6 weeks) with beta blockers is associated with foetal complications including hypoglycaemia, bradycardia, and intrauterine growth restriction (Fitzpatrick and Russell 2010; Galofre and Davies 2009; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012).

42.9.5 Post-partum Thyroiditis

Post-partum thyroiditis (PPT) is another autoimmune process that may induce transient hyperthyroidism followed by transient hypothyroidism and resolution to normal thyroid function within 12 months after delivery. Not all women presenting with PPT will experience all stages of this disorder. The average prevalence of PPT in parous women is 7.5–8.1%. Up to 70% women who have had PPT in the past will develop it after subsequent pregnancies. Women with Type I diabetes have a PPT prevalence of 25% (Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012). Beta blockade is used to treat hyperthyroid symptoms which are typically mild. Anti-thyroid medication is not warranted and is not effective in PPT. Thyroid replacement with levothyroxine (LT4) can be initiated if the hypothyroid stage lasts longer than 6 months or if symptoms become severe, the woman is breast feeding, or if another pregnancy is desired (Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012).

42.9.6 Thyroid Nodules in Pregnancy and Thyroid Cancer

Thyroid nodules are relatively common, occurring in about 1–2% of young women. Most nodules are benign, some are functional (secrete thyroid hormone), some nonfunctional, and rarely some nodules are cancerous. The prevalence of thyroid cancer in pregnancy is estimated to be approximately 14/100,000 pregnant women. All thyroid nodules need to be evaluated by ultrasound and TSH measurement (Fitzpatrick and Russell 2010; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012). If a woman is found to have a nodule with atypical echo pattern on ultrasound or if the nodule is growing or larger than 10 mm, she should be referred for a fine needle aspiration (FNA) biopsy. FNA is an office procedure and is considered safe during pregnancy. If the nodule is not suspicious on ultrasound, FNA can be delayed until after delivery. Radionuclide scans and RAI commonly used for diagnosis and treatment in non-pregnant women are absolutely contraindicated during pregnancy. Outcomes for well-differentiated thyroid cancer (DTC) in pregnancy are excellent. There is 10 year survival of 99%, not different from age-matched non-pregnant women. Surgical intervention for DTC can often be delayed until after delivery. If undifferentiated cancer is detected, the tumour is large or rapidly growing, or the cancer is in advanced stages, surgery can be done during pregnancy with the second trimester considered to be the safest time (Fitzpatrick and Russell 2010; Stagnaro-Green et al. 2011; Yazbeck and Sullivan 2012).

42.9.7 Screening for Thyroid Disorders During Pregnancy

According to The Endocrine Society's [TES] Clinical Guidelines in 2007 and the 2011 American Thyroid Association Guidelines for Diagnosis and Management of Thyroid Diseases during Pregnancy and Post-partum, there is insufficient evidence to justify universal screening of all pregnant women for thyroid dysfunction. Although thyroid disorders have many serious adverse effects on pregnancy outcome, evidence based on cost-effectiveness of screening and interventions is inconsistent. Therefore, aggressive case finding of women at risk for thyroid disorders based on

specific criteria is recommended (De Groot et al. 2012; Stagnaro-Green et al. 2011). Nurses need to actively assist with or perform screening pregnant women who are at risk for thyroid disease. According to the American Thyroid Association (2011), the following groups of women should be screened by TSH measurement:

1. History of thyroid dysfunction or previous thyroid surgery
2. Age > 30 years
3. Symptoms of thyroid disorder or presence of a goitre (enlarged thyroid gland)
4. Women with known thyroid antibodies
5. Women with Type 1 diabetes or other autoimmune diseases
6. History of miscarriage or preterm delivery
7. History of head or neck radiation
8. Family History of thyroid dysfunction
9. Morbid obesity (BMI $\geq$ 40 kg/m^2)
10. Use of amiodarone, or lithium or recent administration of iodine contrast media
11. Infertility
12. Residing in an area of known moderate to severe iodine insufficiency (Stagnaro-Green et al. 2011)

42.9.8 Summary of Thyroid Disorders During Pregnancy and Nursing Considerations

The goal of nursing care of pregnant women with thyroid disorders is to support optimal thyroid function throughout the entire gestational period and post-partum. Optimal thyroid function is supported by adequate iodine intake, pregestational counselling and evaluation, aggressive screening of women at risk for thyroid disorders, and nursing interventions to facilitate adherence to medically prescribed treatment regimens. Thyroid function is assessed by clinical presentation and laboratory measurement of thyroid hormone production. Understanding thyroid physiology is foundational to professional nursing care and serves as the basis for advocacy, education, and counselling for women with thyroid disorders during pregnancy.

42.10 Other Endocrine Considerations During Pregnancy

Many endocrine disorders are related to autoimmune responses. Whenever preexisting autoimmune processes are present, endocrine disorders are more likely and must be monitored during pregnancy.

42.11 Hypothalamic-Pituitary-Adrenal Axis

The maternal pituitary gland increases markedly in size in response to increased oestrogen levels in pregnancy. A normal pituitary is approximately 6 mm size in non-pregnant women, but may enlarge to 12 mm by 1 week post-partum. This activity correlates with rising prolactin levels (Feldt-Rasmussen and Mathiesen 2011). Typically, the pituitary will return to normal size within 6 months after delivery. Cortisol, secreted from the adrenal glands, increases throughout pregnancy and surges during labour. Both the maternal hypothalamus and the placenta stimulate this increase in cortisol production through increase in adrenocorticotrophic-stimulating hormone (ACTH) from the pituitary and placental corticotrophin-releasing hormone (CRH). In the course of normal pregnancy, maternal free cortisol may increase threefold. In response to increased oestrogen, binding proteins are also increased, decreasing the amount of free cortisol that will cross the placenta (Feldt-Rasmussen and Mathiesen 2011; Smith et al. 2011) (See Chap. 12).

Of all neuroendocrine tumours, prolactinomas are by far the most common, accounting for about 40% of all pituitary tumours. The prevalence of prolactinomas in the general population is estimated to be 100 per million (Mann 2011). Prolactinomas most commonly occur in women of childbearing age. Galactorrhea and amenorrhea are common presenting symptoms. Treatment can include surgery, radiotherapy, and/or medication, depending on tumour size and presenting symptoms. The drugs most commonly

used for treatment are the dopamine-receptor agonists, bromocriptine and cabergoline. When treated with dopamine-receptor agonists, many women will respond favorably with restored fertility. Treatment may be stopped when pregnancy occurs, although bromocriptine has an excellent safety record during pregnancy and cabergoline data seem promising regarding safety during pregnancy (Molitch 2010) (See Chap. 19).

42.12 Parathyroids and Maintaining Calcium Balance

Maternal parathyroid hormone levels are relatively stable during pregnancy. In the first trimester, maternal absorption of calcitonin (vitamin D3) results in increased calcium absorption. The resulting increase in calcium may be stored in the maternal skeleton in preparation for increased demand for maternal calcium from the developing foetus later in pregnancy. This increase in calcium may also explain in part the increased risk for kidney stone in the pregnant women (Feldt-Rasmussen and Mathiesen 2011).

42.13 Placenta as an Endocrine Organ

The placenta allows both maternal and foetal circulation to be in close proximity to each, while preventing actual mixing of the two systems. During pregnancy, the respiratory, alimentary, and excretory needs of the developing foetus are addressed by the placenta. Throughout pregnancy, the placenta plays an important role in the synthesis of both steroid hormones (derived from LDL cholesterol) and peptide hormones (derived from protein precursors).

An example of placental steroid hormone synthesis is progesterone production. During gestation, progesterone secretion is predominantly associated with placental and decidual production. In conjunction with hCG and cortisol, progesterone inhibits the maternal immune system by diminishing T-lymphocyte activity, thus preventing rejection of the foetal tissue and conferring foetal immunological privilege. Progesterone is also a potent inhibitor of smooth muscle contractility and prevents contractions of the uterine myometrium until the onset of labour. Additionally, progesterone serves as a substrate for the production of foetal adrenal hormones such as cortisol and aldosterone (Feldt-Rasmussen and Mathiesen 2011).

Examples of placental peptide synthesis include hypothalaminc-like hormones (e.g. Gonandotropin-releasing hormone, corticotrophin-releasing hormone, and growth hormone-releasing hormone) and pituitary-like hormones such as hCG, growth hormone, and other growth factors including insulin-like growth factors (e.g. IgF1 and IgF2). These peptide hormones are important for sustaining pregnancy and regulating growth and development. It is of interest that there is no neuronal control of placental peptide hormones and the exact mechanism of feedback to regulate placental peptide hormones is unknown (Feldt-Rasmussen and Mathiesen 2011).

42.14 Endocrine Disruptors in Human Reproduction and Health

Over the last decade, there has been increasing awareness of the hazard posed by substances known as endocrine disruptors or endocrine disrupting chemicals/compounds (EDCs). According to The Endocrine Society's 2009 scientific statement, EDs are defined from a physiological perspective as "...a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to the environment" (Diamanti-Kandarakis et al. 2009: 2). EDCs are associated with multiple reproductive and developmental problems including, but not limited to: delayed conception, infertility, spontaneous abortion, still birth/neonatal death, preterm birth, congenital anomalies, low birth weight, developmental delays, and childhood cancers (Andersson et al.

2012; Chalupka and Chalupka 2010; Diamanti-Kandarakis et al. 2009).

Sources of EDs are diverse and prevalent including many commonly encountered substances such as some plastic bottles, metal food cans, detergents, computers, cell phones, flame retardants, food, toys, cosmetics, paints, varnishes, perfumes, soil, ground water, and pesticides (Chalupka and Chalupka 2010; Diamanti-Kandarakis et al. 2009; Gilden et al. 2010; National Institute of Environmental Health Sciences [NIEHS] Website 2012). Examples of just a few specific compounds that have been linked to endocrine disruption include:

- Bisphenol A (BPA) which is found in some food and drink containers, hard plastic bottles, and some baby products
- Glycol esters used in some paint, varnishes, and perfumes
- Pesticides used to protect food in both residential and commercial settings
- Phthalates added to some PVC plastics to soften them (plasticizers); also found in some cosmetics, perfumes, toys, and pharmaceuticals (Chalupka and Chalupka 2010)

The Endocrine Society identifies five important issues in endocrine disruption:

1. Age at exposure: periods of foetal and neonatal development increase susceptibility to EDCs.
2. Latency from exposure: repercussions of developmental exposure may not be evident until many years later (e.g. puberty, adulthood, or aging).
3. Importance of mixtures: if a population is exposed to environmental contamination multiple compounds may be involved, some of which will have additive or synergistic impact.
4. Non-traditional dose-response dynamics: very low doses of EDCs may have enormous impact, mid-range doses may have enormous impact in some cases, and in other cases high doses may have enormous impact. In still other cases, the substance may be benign or possibly beneficial in low doses and hazardous in higher doses (U-shaped dose-response curve).
5. Transgenerational, epigenetic effects: EDCs may have an impact on future generations via alterations in regulation of gene expression (Diamanti-Kandarakis et al. 2009).

Naturally occurring substances may also be endocrine disrupters. For example, soy baby formula contains plant-derived oestrogens known as phytoestrogens. Soy formula feeding by infant boys has been variably associated with changes in reproductive hormones, spermatogenesis, sperm capacitation, and fertility (Cederroth et al. 2010; Diamanti-Kandarakis et al. 2009). Therefore, there may be some link between these naturally occurring compounds and future reproductive issues in men. A dilemma regarding exposure to EDCs is evident in breast and bottle feeding. If a mother has exposure to EDCs, it is possible that her breast milk may contain concentrated amounts of the hazardous compound. For infants who are fed formula, in addition to the soy issue, the cans in which formula is packaged may contain plasticizers, a potential source of EDCs. The implication to be drawn from these observations is that there is a developmental basis for adult disease. This concept is fundamental to our understanding of the impact of EDCs in human health across the life span (Diamanti-Kandarakis et al. 2009).

42.15 Precautionary Principle and Implications for Nursing Practice

As explicated by the Science and Environmental Health Network (SEHN), the Precautionary Principle implies: “When the health of humans and the environment is at stake, it may not be necessary to wait for scientific certainty to take protective action” (SEHN Website 2012). The SEHN stresses the importance of action prior to deleterious health outcomes becoming widespread. The SEHN website offers four important strategies for implementing the Precautionary Principle. These strategies include:

> "Exploring alternatives to possibly harmful actions, especially clean technologies that eliminate waste and toxic substances; placing the burden of proof on the proponents of an activity rather than on the victims or potential victims of the activity; setting and working toward goals that protect health and the environment; and bringing democracy and transparency to decisions affecting health and the environment" (SEHN 2012, FAQ).

The Endocrine Society 2009 scientific statement endorses the Precautionary Principle in addressing the issues raised by EDCs. Among the recommendations for clinical practice suggested in the scientific statement, several are particularly relevant to nursing practice. Nurses need to advise their clients, particularly women of childbearing age, about potential exposure to EDCs and ways to minimize risks of exposure. All health care professionals need to be educated about the potential impact of EDCs across the lifespan. Health care professionals need to: develop, and have access to, clear concise and accurate health education materials to share with patients. Clinicians need to be vigilant about detecting potential cases of EDCs exposure when documenting client health history (Chalupka and Chalupka 2010; Diamanti-Kandarakis et al. 2009). Nurses are in a unique professional position to advocate for health policies related to endocrine disruptors, to develop community-specific educational tools, provide health counseling, and participate in case finding. The health of future generations may depend on what we as nurses do today.

42.16 Conclusions

Endocrine function is both altered by pregnancy and is vital to the developing foetus and successful neonatal outcomes. Optimal endocrine function is vital for fertility and normal foetal growth and development. Successful pregnancy outcomes require pre-pregnancy patient counselling, planning, and ongoing monitoring of patient responses. Counselling continues throughout pregnancy and the post-partum period. Additionally, abnormalities in the endocrine system can impact labour and delivery and postnatal breast feeding. Women with diabetes, before and/or during pregnancy, must be given preconception planning and careful management to avoid adverse pregnancy outcomes resulting from hypoglycaemia and hyperglycaemia. Optimal maternal thyroid function must be maintained to avoid significant foetal neural damage from hyper or hypothyroidism. Hypothalamic-pituitary-adrenal dysfunction is uncommon, but may present during gestation or post-partum. All families should be aware of EDCs and their potential impact on human health.

Clinical Application Exercise

Case Study 1

Sonia is a 32-year-old woman with Type I diabetes. She and her husband are school teachers. They have a daughter who is a healthy 3 year old. After her daughter was born, Sonia developed Grave's disease for which she is still taking medication. Sonia is now pregnant with their second baby.

Diabetes Management

1 unit of rapid-acting insulin is needed for each 15 g of carbohydrate and 1 unit of insulin will drop the glucose 20 mg/dL.

Using these ratios, if a woman was planning to consume 45 g of carbohydrates and her glucose was 140 mg/dL and she wanted to drop her glucose to 100 mg/dL:

1. How many units would she need to cover her carbohydrate in her meal?
2. How many additional units would she need to bring her glucose down to 100 mg/dL?
3. What will the total number of units or prepandial insulin that she needs to inject (or program her pump to deliver)?
4. If your patient is using MDI or CSII, how would you prepare her for hypoglycaemia and hyperglycaemia?
5. List the three categories of diabetes that most impact pregnancy.
6. Describe the relative degree of insulin resistance during early vs. late pregnancy.
7. List the IADPSG diagnostic criteria.
8. Discuss the short- and long-term complications to the offspring of pregnancies complicated by gestational diabetes.

9. Discuss the importance of preconception planning in pre-gestational diabetes for the foetus and for the mother.
10. Describe the components of an intensive insulin regimen.
11. Discuss the pros and cons of oral diabetes agents in pregnancy

Thyroid Management

1. Does the region in which you practice have a readily available source of iodine? Read the labels of food you commonly consume. Is your iodine intake about 250 μg?
2. Explain the classic feedback loop between TRH, TSH, T3, and T4
3. Describe the potential threats to healthy pregnancy outcomes that result from hypothyroidism.
4. Describe the potential threats to healthy pregnancy outcomes that result from hyperthyroidism.
5. Discuss the concept of foetal immunological privilege.

Other Considerations in Management

1. Explain the significance of endocrine disrupting compounds in human reproduction.
2. Apply the Precautionary Principle to nursing practice with women of childbearing age.

References

American Diabetes Association [ADA]. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care. 2018a;41(Suppl 1): S13–27.

American Diabetes Association [ADA]. Management of diabetes in pregnancy: standards of medical care in diabetes—2018. Diabetes Care. 2018b;41(Suppl 1): S137–43. https://doi.org/10.2337/dc18-S013.

American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1086–133. https://doi.org/10.1089/thy.2011.0087.

Andersson A, Bay K, Grigor K, Meyts E, Skakkebæk N. Special issue on the impact of endocrine disrupters on reproductive health. Int J Androl. 2012;35(3):215. https://doi.org/10.1111/j.1365-2605.2012.01274.x.

Bernasko J. Insulin pump therapy for pregnancy: a primer. J Matern Fetal Neonatal Med. 2012;25:552–7. https://doi.org/10.3109/14767058.2011.598586.

Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, Yogev Y. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol. 2013;98(11):4227–49. https://doi.org/10.1210/jc.2013-2465.

Carson M. Assessment and management of patients with hypothyroidism. Nurs Stand. 2009;23(18):48–56.

Castorino K, Paband R, Zisser H, Jovanovic L. Insulin pumps in pregnancy: using technology to achieve normoglycemia in women with diabetes. Curr Diab Rep. 2012;12:53–9. https://doi.org/10.1007/s11892-011-0242-7.

Cederroth CR, Auger J, Zimmermann C, Eustache F, Nef S. Soy, phyto-oestrogens and male reproductive function: a review. Int J Androl. 2010;33(2):304–16. https://doi.org/10.1111/j.1365-2605.2009.01011.x.

Centers for Disease Control [CDC] (2011). National Diabetes Fact Sheet 2017. Revised 2 July 2017. Retrieved 15 July 2018 from https://www.cdc.gov/media/releases/2017/p0718-diabetes.

Chalupka S, Chalupka A. The impact of environmental and occupational exposures on reproductive health. J Obstet Gynecol Neonatal Nurs. 2010;39(1):84–102. https://doi.org/10.1111/j.1552-6909.2009.01091.x.

Cheng YW, Block-Kurbisch I, Inturrisi M, Caughey AB. Treatment of gestational diabetes mellitus: glyburide compared to subcutaneous insulin therapy and associated perinatal outcomes. J Matern Fetal Neonatal Med. 2012;25:379–84.

Chong H, See K, Phua J. Thyroid storm with multiorgan failure. Thyroid. 2010;20(3):333–6.

De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin R, Eastman C, Lazarus J, Luton D, Mandel S, Mestman J, Rovet J, Sullivan S. Executive summary: management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2543–65.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Thomas Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30(4):293–342. http://www.endo-society.org/journals/scientificstatements/upload/edc_scientific_statement.pdf.

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183–97.

Feldt-Rasmussen U, Mathiesen E. Endocrine disorders in pregnancy: physiological and hormonal aspects of pregnancy. Best Pract Res Clin Endocrinol Metab. 2011;25(6):875–84.

Fitzpatrick D, Russell M. Diagnosis and management of thyroid disease in pregnancy. Obstet Gynecol Clin N Am. 2010;37(2):173–93.

Galofre J, Davies T. Autoimmune thyroid disease in pregnancy: a review. J Womens Health (Larchmt). 2009;18(11):1847–56. https://doi.org/10.1089/jwh.2008.1234.

Gilden R, Huffling K, Sattler B. Pesticides and health risks. J Obstet Gynecol Neonatal Nurs. 2010;39(1):103–10. https://doi.org/10.1111/j.1552-6909.2009.01092.x.

Glinoer D, Spencer C. Serum TSH determinations in pregnancy: how, when and why? Nat Rev Endocrinol. 2010;6(9):526–9.

Guthrie RA, Guthrie DW. Pathophysiology of diabetes mellitus. Crit Care Nurs Quart. 2004;27(2):113–25. EBSCOhost, ez.sjcny.edu/login? url=http://ez.sjcny.edu:2057/login.aspx?direct=true&db=rzh&AN=106766982&site=ehost-live&scope=site.

Hoeks LB, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabetic Med. 2011;28(4):386–94. EBSCOhost. https://doi.org/10.1111/j.1464-5491.2010.03177.x.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care. 2010;33:676–82. https://doi.org/10.2337/dc09-1848.

Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, et al. Managing preexisting diabetes for pregnancy. Diabetes Care. 2008;31:1060–79.

Knowler WC, Hamman RF. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374:1677–86.

Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50:938–48.

Lapolla AA, Dalfrà MG, Ragazzi EE, De Cata AP, Fedele DD. New international association of the diabetes and pregnancy study groups (IADPSG) recommendations for diagnosing gestational diabetes compared with former criteria: a retrospective study on pregnancy outcome. Diabet Med. 2011;28(9):1074–7. https://doi.org/10.1111/j.1464-5491.2011.03351.x.

Lutz C, Przytulski K. Nutrition and diet therapy: evidence-based applications. 4th ed. Philadelphia: F.A. Davis; 2006.

Mann W. Treatment for prolactinomas and hyperprolactinaemia: a lifetime approach. Eur J Clin Investig. 2011;41(3):334–42. https://doi.org/10.1111/j.1365-2362.2010.02399.x.

Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 2007;30:S251–60. https://doi.org/10.2337/dc07-s225.

Metzger BE, Lowe LP, Dyer AR, Trimble ER, Sheridan B, Hod M, et al. Hyperglycaemia and adverse pregnancy outcome (HAPO) study: associations with neonatal anthropometrics. Diabetes. 2009;58(2):453–9.

Molitch M. Prolactinomas and pregnancy. Clin Endocrinol. 2010;73(2):147–8.

Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes. Obstet Gynecol. 2010;115:55–9.

National Institute of Environmental Health Sciences [NIEHS] Website. 2012. http://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm.

Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes. Obstet Gynecol. 2009;113:193–205.

Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. QJM. 2001;94:435–44.

Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–15. http://www.NEJM.org

Science and Environmental Health Network Website. 2012. Retrieved 9/4 at http://www.sehn.org/ppfaqs.html.

Smith AK, Newport D, Ashe MP, Brennan PA, LaPrairie JL, Calamaras M, et al. Predictors of neonatal hypothalamic-pituitary-adrenal axis activity at delivery. Clin Endocrinol. 2011;75(1):90–5. https://doi.org/10.1111/j.1365-2265.2011.03998.x.

Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: from physiology to screening. Crit Rev Clin Lab Sci. 2017;54(2):102–16. https://doi.org/10.1080/10408363.2016.1269309. Epub 2017 Jan 19.

Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081–125.

World Health Organization Fact Sheet Diabetes. Reviewed November 2017. http://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed 15 July 2018.

Yazbeck C, Sullivan S. Thyroid disorders during pregnancy. Med Clin North Am. 2012;96(2):235–56.

Zimmerman MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. Am J Clin Nutr. 2009;89(Suppl):668S–72S.

Part VII

Male Endocrinology and Reproduction

Andrew A. Dwyer and Sofia Llahana

43 Anatomy and Physiology of the Hypothalamic-Pituitary-Gonadal (HPG) Axis

Andrew A. Dwyer and Richard Quinton

Contents

43.1 **The Hypothalamic-Pituitary-Gonadal (HPG) Axis** 841
43.1.1 Normal Development and Function of the HPG Axis 841
43.1.2 Abnormal Development 844

43.2 **Hormonal Control of the HPG Axis** 845
43.2.1 Gonadotrophins 846
43.2.2 Gonadal Sex Steroids 846
43.2.3 Other Gonadal Peptides 846

43.3 **Testicular Function** 847
43.3.1 Seminiferous Tubules 847
43.3.2 Interstitial Compartment 848

43.4 **Endocrine Aspects of Sexual Function** 848
43.4.1 Sexual Desire 849
43.4.2 Erectile Function 849
43.4.3 Sexual Dysfunction 850

43.5 **Conclusions** 850

References 851

Abstract

The hypothalamic-pituitary-gonadal (HPG) axis is central for human reproduction. This axis includes neuroendocrine networks that integrate wide ranging internal and external inputs to coordinate reproductive competence. Gonadotrophin-releasing hormone (GnRH) is the principal regulator of reproduction. GnRH controls gonadotrophin secretion and subsequently, gonadal (testicular) function. The HPG axis is activated during foetal life, neonatally and in puberty through adulthood. This developmental perspective is important as these peri-

A. A. Dwyer (✉)
William F. Connell School of Nursing, Chesnut Hill, MA, USA

Boston College, Chesnut Hill, MA, USA
e-mail: Andrew.dwyer@bc.edu

R. Quinton
Newcastle-upon-Tyne Hospitals Foundation NHS Trust (Royal Victoria Infirmary), Institute for Human Genetics, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, UK
e-mail: Richard.Quinton@nuth.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_43

ods contribute to the proper formation and development of sexual structures *in utero* as well as the development and function of the system enabling reproductive capacity in adulthood. The HPG axis remains silenced during childhood and neuroendocrine re-activation triggers pubertal onset. In early puberty, nocturnal sleep-entrained GnRH-induced gonadotrophin secretion stimulates testicular development and the initial rise in sex steroids resulting in the appearance of secondary sexual characteristics. Progressively, this pulsatile neuroendocrine activity extends through the day and is regulated by negative feedback. Puberty culminates in sexual maturation and the reproductive capacity of adult life. Sperm development occurs in the seminiferous tubules of the testes and requires testosterone and other testicular products for normal spermatogenesis. Effective HPG axis function is needed for normal sexual function and fertility and contributes to overall health and well-being. This chapter is a mini-review for endocrine nurses providing a summary of HPG axis development, function and regulation. This targeted summary is intended to serve as a basis for understanding key elements relating to male reproductive endocrine disorders such as hypogonadism, sexual dysfunction and infertility.

Keywords
Hypothalamus · Pituitary · Gonadotrophins
Testes · Spermatogenesis · Testosterone
Sexual function

Abbreviations

AMH	Anti-Müllerian hormone
CHH	Congenital hypogonadotrophic hypogonadism
DHEA	Dehydroepieandrostenedione
DHEAS	Dehydroepieandrostenedione sulphate
DHT	Dihydrotestosterone
DSD	Disorder of sex development
ED	Erectile dysfunction
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin-releasing hormone
hCG	Human chorionic gonadotrophin
HH	Hypogonadotrophic hypogonadism
HPG	Hypothalamic-pituitary-gonadal
IB	Inhibin B
INSL3	Insulin-like peptide 3
KS	Kallmann syndrome
LH	Luteinizing hormone
PDE5	Phosphodiesterase type 5
SC	Sertoli cell
SD	Standard deviation
SHBG	Sex hormone binding globulin
ST	Seminiferous tubule

Key Terms

- **Mini-puberty:** The postnatal surge in gonadotrophins during the first 6 months of neonatal life. In male infants levels rise following the first week of life, peaking at around 3 months then progressively decline. This surge is thought to be important fertility potential in adulthood.
- **Cryptorchidism (maldescended testes):** This refers to testes that are not descended into the scrotum and may be in the inguinal canal or abdomen. It may occur unilaterally or bilaterally and has negative consequences on fertility.
- **Orchiopexy (orchidopexy):** A surgical procedure to bring maldescended testis/testes into the scrotum. Earlier surgical correction (i.e. in the first year of life) may help improve future fertility potential.
- **Secondary sexual characteristics:** These are features that develop during puberty and are outward signs of the progression towards sexual maturation. In males, these characteristics are stimulated by rising androgen levels and include changes in body habitus (increased musculature), deepening of the voice, and development of body and facial hair.

- **Spermatogenesis:** The process by which spermatogonia become mature spermatozoa. This includes forming haploid gametes via mitosis and meiosis (spermatocytes) and the maturation process (spermiogenesis).
- **Mitosis:** This is a form of cell division wherein one parent cell is transformed into two cells with a full complement of identical sets of chromosomes—each within their own nucleus.
- **Meiosis:** A form of cell division wherein a parent cell produces four haploid gametes (cells with half of the number of chromosomes as the parent cell). It is an essential process for developing sperm for reproduction.
- **Tumescence:** A state in which the sexual organs become swollen and engorged with blood in response to physical, visual or emotional stimuli. In men, this is known as a penile erection. The reverse (detumescence) is when the erectile tissue returns to its flaccid state.

Key Points

- Reproduction is regulated by the hypothalamic-pituitary-gonadal (HPG) axis. Understanding how the axis functions is fundamental to identifying the cause(s) of male reproductive endocrine disorders.
- The HPG axis functions via stimulatory effects and negative feedback effects. Male reproductive endocrine disorders can occur at the level of the hypothalamus, pituitary and/or the testes.
- The HPG axis is active in foetal life, during the mini-puberty and at puberty into adulthood. Circulating LH, FSH and testosterone hormone levels reflect GnRH secretion during these periods.
- Early HPG axis activity can have long-reaching effects on the reproductive phenotype and fertility. Accordingly, careful history-taking is an essential component of endocrine evaluation.

43.1 The Hypothalamic-Pituitary-Gonadal (HPG) Axis

Reproductive capacity is central to species survival. In humans and other higher vertebrates, this essential function is regulated by the coordinated endocrine action of the hypothalamic-pituitary-gonadal (HPG) axis. Secretion of gonadotrophin-releasing hormone (GnRH) by a small population of specialized hypothalamic neurons (<2000) initiates the neuroendocrine activity of the HPG axis. Recent research has identified signals "upstream" of GnRH (Abreu and Kaiser 2016; Boehm et al. 2015) yet classically; GnRH has been considered the "pilot light" of reproduction (Balasubramanian et al. 2010). GnRH is secreted in a pulsatile manner, meaning that it is released in discrete bursts from the median eminence into the hypophyseal portal system (the network of vessels connecting the hypothalamus with the anterior pituitary). Once GnRH is delivered to the anterior pituitary (adenohypophysis), it stimulates the gonadotrophs to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH). These two hormones are collectively referred to as gonadotrophins. Whereas GnRH has a very short half-life and as yet cannot be measured outside of the hypophyseal portal circulation, LH and FSH enter the peripheral circulation and are readily measurable in venous blood. The gonadotrophins in turn stimulate sex steroid production and gametogenesis in the gonads. In males, LH is primarily responsible for stimulating specialized cells in the testes (Leydig cells) to produce testosterone. In contrast, FSH plays a major role in regulating the seminiferous tubule and spermatogenesis via its action on the Sertoli cells (Fig. 43.1).

43.1.1 Normal Development and Function of the HPG Axis

The proper formation and function of the hypothalamus, anterior pituitary and testes require multiple coordinated developmental events demanding

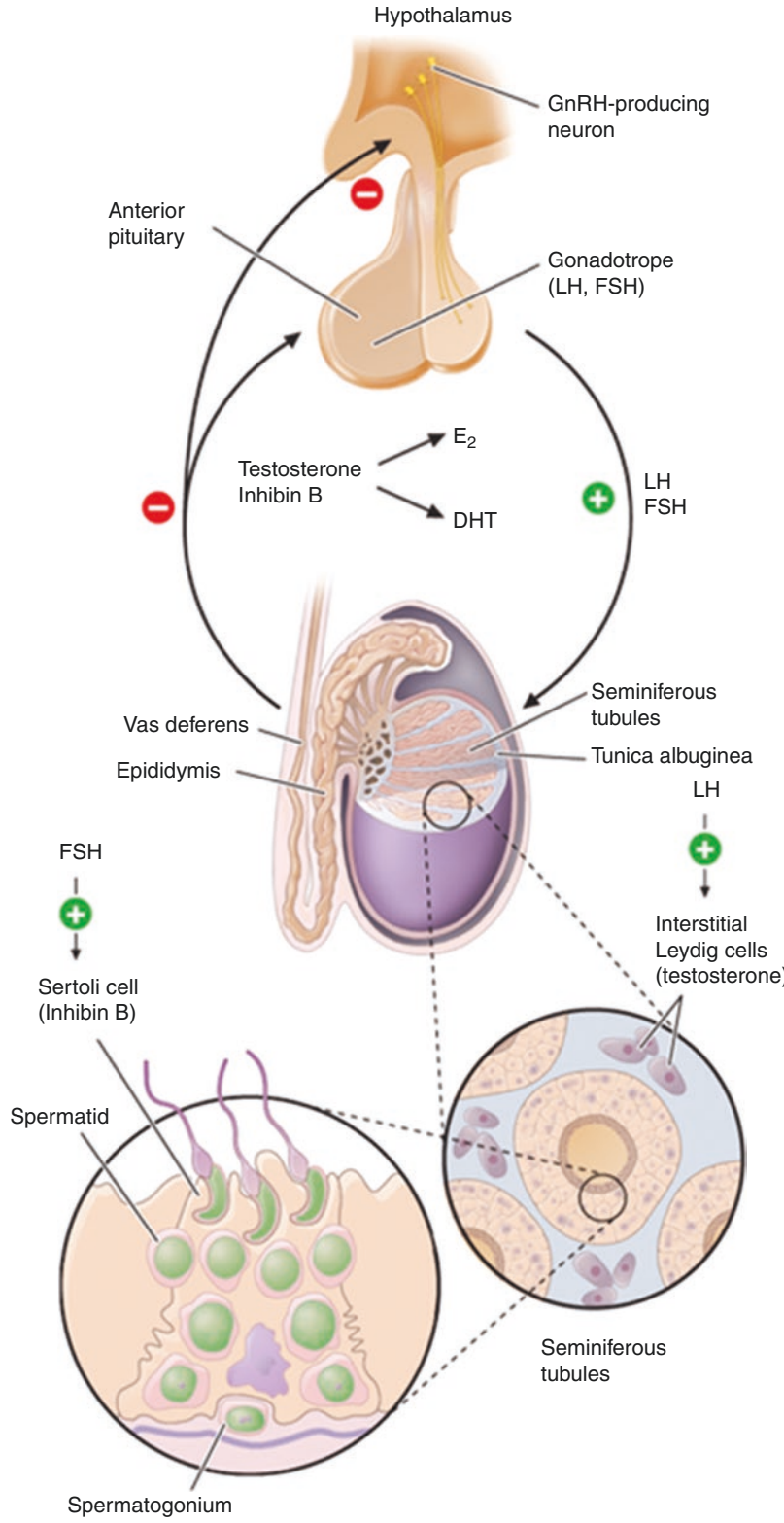


Fig. 43.1 The male hypothalamic-pituitary gonadal axis (used with permission from Bhasin S. and Jameson L.J. (2017) Disorders of the testes and male reproductive system, chapter 11. In: Jameson L.J. (Eds) Harrison's Endocrinology, 4th Edition. McGraw-Hill Education, pages 159–185.). Pulsatile secretion of GnRH from hypothalamic neurons triggers the release of LH and FSH from the pituitary and into the peripheral circulation. FSH supports spermatogenesis via stimulatory effect on the Sertoli cells in the seminiferous tubules. LH stimulates the Leydig cells in the interstitium to produce testosterone. Positive and negative feedback regulate the axis function

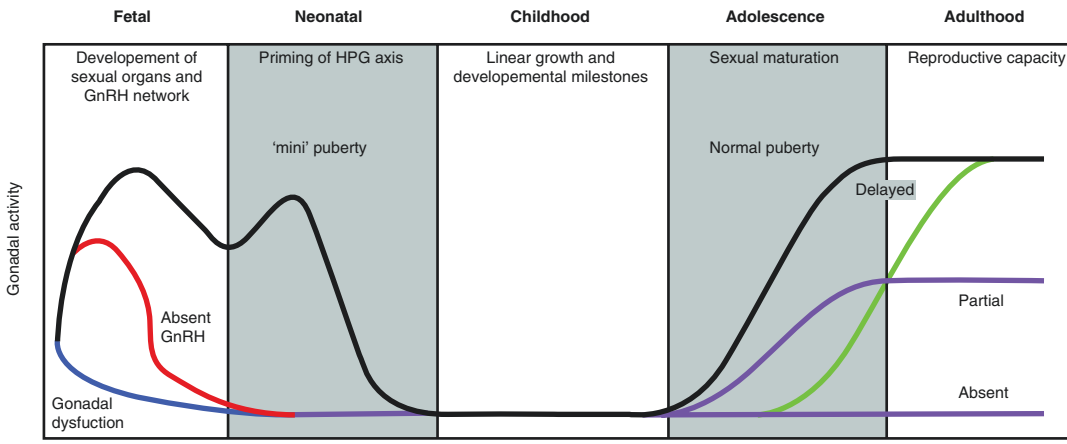


Fig. 43.2 Gonadal activation throughout development. Schematic depicting gonadal activation from foetal life through adulthood. Gonadal dysfunction (i.e. disorders of sexual development) in foetal life is depicted by the blue line while incomplete activation of the hypothalamic-pituitary-gonadal axis is shown in red (i.e. congenital hypogonadotrophic hypogonadism). The spectrum of pubertal development includes normal (grey), delayed (green), as well as partial/stalled and absent (purple)

spatiotemporal coordination under genetic and epigenetic control. Disruption of these crucial steps in development may manifest in endocrine dysfunction. Moreover, the HPG axis is active in three distinct waves during the lifespan (Fig. 43.2). Presently, the precise mechanisms controlling the activation, silencing and re-activation of the HPG axis remain largely unknown. However, recent genetic and physiologic investigations have begun to elucidate the molecular control of these processes and have identified critical signalling pathways essential for proper development and function.

43.1.1.1 Foetal and Neonatal Life

GnRH neurons are unlike other neurons in that they originate outside of the central nervous system. They primarily originate in the rudimentary nose (olfactory placode) and undergo a remarkable migration into the brain. Early in development they migrate along olfactory nerves across the base of the skull (cribriform plate) into the forebrain (arcuate nucleus). After aggregating, they begin secreting GnRH in a coordinated fashion from around 32 weeks gestation. GnRH is released from the terminal axons in the median eminence into the portal hypophyseal circulation (Boehm et al. 2015). It is notable that the activity of the HPG axis varies across development. During early foetal life, the axis is driven *in utero* by maternal hormones (i.e. human chorionic gonadotrophin, hCG) from around 7 weeks gestation and then is again active in a brief neonatal window referred to as mini-puberty (Grumbach 2005). Although gonadotrophin and testosterone levels are briefly low from birth until about 1 week of age LH, thereafter they begin to rise again, peaking between 1 and 3 months of life in neonate males (Kuiri-Hanninen et al. 2014). This HPG axis activation is significant as testosterone levels reach adult levels and it presents a unique opportunity to observe HPG function prior to puberty (Grumbach 2005). This surge in testosterone production is accompanied by rising levels of weaker androgens such as dehydroepieandrostenedione (DHEA) and its sulphated form (DHEAS) that may clinically manifest as "baby acne". However, these androgens do not result in sexual maturation or spermatogenesis as the androgen receptor is not yet expressed on the Sertoli cells; nor do they result in body hair growth as skin does not yet express 5AR enzyme to convert testosterone locally to DHT (Rey et al. 2013).

Events *in utero* and the subsequent mini-puberty during first 3 months of life in male infants may seem far removed from eventual adult reproductive capacity. However, these first two waves of HPG axis activity can significantly impact the reproductive phenotype and potential

for fertility in men (Dwyer et al. 2016). In particular early HPG activation (i.e. LH stimulated testosterone secretion) is important for normal testicular descent into the scrotum as well as further development of the penis. Accordingly, the earliest signs indicating possible deficient secretion or action of GnRH include cryptorchidism (maldescended testes) or micropenis (atypically small phallus). Notably, the hormonal surge of mini-puberty is a period of important yet clinically subtle testicular growth. This brief window of proliferation is crucial for increasing the number of Leydig cells as well as Sertoli and germ cells that are key for future spermatogenesis (Kuiri-Hanninen et al. 2014).

43.1.1.2 Childhood and Puberty

After 3 months of life, the axis is silenced and there is a relative period of quiescence during childhood prior to its re-activation in puberty. The exact mechanism(s) that control these changes are yet unknown and remain elusive. It is presumed that they are influenced by heritable (genetic) factors as well as environmental and epigenetic influences (Abreu and Kaiser 2016). There is a wide range of timing for pubertal onset. However the progression of signs is consistent across normal development. The first sign of pubertal onset in boys is increased testicular volume—typically observed between 11 and 12 years of age. This is followed by development of pubic hair (Tanner II), growth spurt (peak growth velocity), sperm in the first morning voided urine, achieving Tanner V pubic hair and a "spurt" in muscle strength. Importantly, outward signs of pubertal onset are the manifestation of the re-awakening of the HPG axis. This initially occurs with sleep-entrained GnRH pulses (Boyar et al. 1974). As frequent blood sampling to assess GnRH-induced LH secretion is not clinically feasible, a useful tool for approach for evaluating pubertal progression in male adolescents is using a Prader orchidometer to assess testicular volume as volume ≥4 mL indicates pubertal initiation (Boehm et al. 2015). Further, plotting testicular size using the puberty normogram enables a sensitive charting of pubertal development according to population-based norms (Joustra et al. 2015).

43.1.1.3 Adulthood

Puberty culminates in full reproductive capacity and the HPG axis has several important functions in adult life beyond reproduction. Importantly, normal function of the axis supports spermatogenesis and sex steroid production that have both androgenic and anabolic aspects. Testosterone is important for libido and sexual function and supports lean muscle mass. Further it has a stimulatory effect on erythropoiesis as well as bone health. Thus, normal HPG axis function is relevant for adult men long after reproductive goals have been attained. Similarly, disrupted HPG axis function can result in risk for developing health problems or overt pathology in any or all of these functions.

43.1.2 Abnormal Development

The coordinated development of the hypothalamus, pituitary and gonads means that when development does not progress normally (i.e. as a result of genetic mutations, environmental influences or toxic exposures) problems may manifest as either isolated deficiencies or as disorders affecting multiple levels of the HPG axis. Abnormal development may cause structural problems in the hypothalamus, pituitary and/or testes. Further, to exert their biologic action, hormones require a functional receptor. Therefore, changes in genes (mutations) encoding either the ligand (hormone) or the receptor can result in reproductive axis dysfunction (Boehm et al. 2015). Because the HPG axis is quiescent during much of childhood, some problems effecting of HPG axis development may not present until adolescence or early adulthood if the mini-puberty diagnostic window has been missed—as it usually is.

43.1.2.1 Hypothalamic Defects

For GnRH secretion to occur, GnRH neurons must migrate to the arcuate nucleus, form a network and release GnRH in a coordinated episodic (pulsatile) manner. Disruption of these steps may compromise effective GnRH-stimulated release of gonadotrophins from the anterior pituitary and without trophic stimulation from LH and FSH the

testes have impaired testosterone and sperm production. This is biochemically evident as hypogonadotrophic hypogonadism (HH). It is recognized that the vast majority of GnRH neurons derive from the embryonic nose (olfactory placode) and that the neurons migrate along olfactory nerves (Boehm et al. 2015). Thus, gene defects affecting craniofacial development, GnRH neuron fate specification and migration can result in the neurons never reaching their destination. Alternatively, if the signalling system upstream of the GnRH neurons is defective the GnRH neurons will not "switch on". The result of such developmental defects is isolated GnRH deficiency—congenital hypogonadotrophic hypogonadism (CHH). When it occurs with no sense of smell, it is termed Kallmann syndrome (KS). Importantly, in such cases it is clear that the defect is hypothalamic as these patients respond to pulsatile GnRH administration. In contrast, those patients with a pituitary defect typically cannot respond to exogenous GnRH. It is important to note that in addition to their hypothalamic defect, some patients with CHH/KS also have defects at the level of the pituitary and/or testes (Sykiotis et al. 2010).

43.1.2.2 Pituitary Defects

The anterior pituitary arises from the adenohypophyseal placode and is a combination of two ectodermal tissues: Rathke's pouch from the oral ectoderm (forming the anterior pituitary) and the infundibulum from neural ectoderm. Pituitary development is a complex process regulated by a number of genes, transcription factors and other signalling molecules (Bancalari et al. 2012). The anterior pituitary has five specific endocrine cell types (prolactins, somatotropes, thyrotropes, corticotropes and gonadotrophs); abnormal development may result in deficits in any or all of these hormones (i.e. panhypopituitarism). Indeed, patients with developmental defects such as combined pituitary hormone deficiency, and septo-optic dysplasia may exhibit reproductive defects. Indeed, genetic overlaps have been documented between these conditions and CHH/KS (Raivio et al. 2012). Similarly, gene defects encoding the pituitary gonadotroph receptor for GnRH (*GNRHR*) make the gonadotrophs less responsive to hypothalamic GnRH, thus presenting as HH (although in many cases this can be overcome with very high doses of exogenously administered GnRH) (Boehm et al. 2015).

43.1.2.3 Testicular Defects

At birth, hallmark signs of an inactive HPG axis include micropenis and cryptorchidism (maldescended testes) (Grumbach 2005). Micropenis is defined as stretched penis 2.5 standard deviations smaller than normal (i.e. ≤2.5 cm among term infants) (Hatipoglu and Kurtoglu 2013). Cryptorchidism may be unilateral or bilateral and typically classified in relation to the inguinal ring—either above (abdominal) or below (inguinal) (Ritzen et al. 2007). Just as mutations in *GNRHR* result in insufficient GnRH action at the level of the pituitary, mutations in gonadotrophin receptors (*LHR*, *FSHR*) render the testes unable to respond to high circulating gonadotrophin levels (Boehm et al. 2015). Klinefelter syndrome (47XXY) is a common chromosomal defect in males affecting approximately 1:600 males and is characterized by a testicular defect that often manifests in adolescence or adulthood (Groth et al. 2013). Disorders of sex development (DSD) may be indicated at birth by ambiguous genitalia and/or non-palpable gonads (Ahmed et al. 2016). DSD include a wide range of rare conditions of testicular defects including congenital anorchia, vanishing testes syndrome, dysgenetic gonads, persistent Müllerian duct syndrome, ovotestis and others. While not a testicular defect, complete or partial androgen insensitivity syndrome is a DSD resulting from mutations in the androgen receptor. These patients are genetically male (46XY) yet are infertile and phenotypically female as they cannot become virilized despite very high testosterone levels.

43.2 Hormonal Control of the HPG Axis

The reproductive functions of the testes include sex steroid production and gametogenesis. These are under neuroendocrine control from hormones secreted by hypothalamus (GnRH)

and the anterior pituitary (LH, FSH). Over the past decade research has identified factors, notably the kisspeptin/neurokinin B/dynorphin pathway, upstream of GnRH that contribute to the regulation of hypothalamic GnRH section (Skorupskaite et al. 2014).

43.2.1 Gonadotrophins

GnRH is the stimulus for the release of gonadotrophins into the peripheral circulation from the anterior pituitary. Importantly, LH and FSH trigger the production of sex steroids and other peptides (notably inhibin B) in the testes. These gonadal products in turn provide negative feedback regulating the neuroendocrine activity of the HPG axis. Gonadotrophin secretion may be regulated upstream (i.e. by decreased frequency or amount of GnRH secretion) or directly by direct inhibition of the pituitary gonadotophes. Testosterone produced by the interstitial Leydig cells slows GnRH pulse frequency at the level of the hypothalamus and dampens pituitary release of LH from the pituitary. Further, aromatized T in the form of oestradiol also plays an important role in negative feedback in men by reducing LH pulse amplitude and diminishing pituitary responsiveness to GnRH (Pitteloud et al. 2008). The control of FSH secretion is predominantly regulated by inhibin B secreted by testicular Sertoli cells (Boepple et al. 2008) and to a much lesser extent by sex steroids (oestradiol and testosterone). This negative feedback control of the HPG is a critical aspect that helps clinicians identify the level of a particular defect in the male reproductive axis differentiating primary (i.e. testicular) from secondary (neuroendocrine) defects (see Sect. X, Chap. XX).

43.2.2 Gonadal Sex Steroids

LH stimulates the interstitial Leydig cells to produce testosterone, the predominant sex steroid in men. The enzyme aromatase converts a portion of circulating testosterone into oestradiol (Neto et al. 2016). Aromatase is present in adipose tissue and as such, increased aromatase activity observed in states of obesity may become clinically evident as gynaecomastia (development of glandular breast tissue in men) resulting from increased oestradiol levels. Oestradiol exerts its effects (i.e. on the bone) by binding with the oestrogen receptor. Notably, recent evidence points to a threshold effect wherein men suffer declines in bone health when serum oestradiol levels drop below 10 pg/mL (36.7 pmol/L) or when serum T levels are less than 200 ng/dL (6.9 nmol/L) (Finkelstein et al. 2016). Another enzyme, 5-alpha reductase transforms testosterone to dihydrotestosterone (DHT) which is much more potent in binding to the androgen receptor. Importantly, DHT does not undergo aromatization. By and large, circulating testosterone is bound in the peripheral circulation. Approximately 44% is strongly bound to sex hormone binding globulin (SHBG) and unavailable, about 54% is weakly bound to albumin and only about 2% is freely circulating (Neto et al. 2016). Testosterone bound to SHBG is unavailable so conditions that increase circulating SHBG (such as ageing) decrease the amount of available testosterone. Overall androgen action results from the combined effects of available testosterone and its metabolites. These hormones are critical at different points in development, from sexual development in foetal life to the outward signs of puberty (i.e. virilization, deepening of the voice) and sexual maturation to benefits on bone health and lean muscle mass in adulthood (Table 43.1).

43.2.3 Other Gonadal Peptides

The testes secrete a number of different peptides, the function of which has not been completely elucidated. A complete description of all these products is beyond the scope of this chapter so we will focus on three: insulin-like peptide 3 (INSL3), anti-Müllerian hormone (AMH) and inhibin B (IB). In addition to producing T, Leydig cells also produce INSL3 during periods of HPG axis activation (Rey et al. 2013). The

Table 43.1 Androgenic and anabolic effects of testosterone (and its metabolites) through development

In utero	Mini-puberty	Puberty	Adulthood
• Foetal genitourinary tract differentiation • Masculinization of the genitalia • Testicular descent	• Penile and scrotal growth • *Brain masculinization*[a]	• 2° sexual characteristics • Penile growth • Erections, ejaculation • Libido • Somatic growth • Muscle bulk • Bone formation, epiphyseal fusion • Erythropoiesis • Prostate growth	• Libido • Sexual function • Lean muscle mass • Bone health • Prostate • Erythropoesis

[a]It is hypothesized that testosterone in neonatal life contributes to the so-called "masculinization" of the brain yet definitive evidence is lacking

precise physiologic role of INSL3 is unclear but it is important for normal testicular descent and has been used as a marker of interstitial function and Leydig cell activity. Similarly, the Sertoli cells (SCs) produce two important peptides, AMH and IB (Rey et al. 2013). AMH is critical for sexual differentiation while IB is a key regulator of FSH secretion. Early in testis differentiation (embryonic week 5), SCs secrete AMH resulting in regression of Müllerian ducts—thus preventing the formation of a uterus and fallopian tubes. In concert, androgens masculinize the external genitals and trigger differentiation of male genitourinary system as the Wolffian ducts become the epididymis, seminal vesicle and vas deferens. AMH remains high until the onset of puberty when rising T secretion stimulates SC maturation, down-regulating AMH (Rey et al. 2013). Because AMH is secreted by immature SCs, serum levels can be used as a distinctive surrogate marker of testes for infants with ambiguous external genitalia. IB is the predominant negative feedback regulator of FSH. As the seminiferous tubules account for the vast amount of testicular volume, it is well established that SC number correlates testicular size. Moreover, SCs support a species-specific, finite number of germ cells and so SC population correlates well with sperm output. Therefore, as a secreted product of SCs, serum IB levels have been used as a surrogate marker of SC population. Accordingly, serum measurements can also provide insight into spermatogenesis and cases of infertility.

43.3 Testicular Function

The two primary functions of the testes include spermatogenesis—the process of forming gametes for reproduction and sex steroid (androgen) production. These tasks occur in two different parts of the testes. Sperm is developed in the seminiferous tubules while testosterone production occurs between the tubules in the interstitial compartment.

43.3.1 Seminiferous Tubules

The seminiferous tubules (STs) are the site for spermatogenesis, a complex multistep process that is controlled by number of endocrine, paracrine and autocrine factors (Neto et al. 2016). The STs are veritable sperm factories that comprise two-thirds of the total testicular volume (the normal adult testis is 15–25 mL in volume). STs are the functional units of sperm production. They are tightly coiled and each individual tubule is approximately one metre in length (Neto et al. 2016). This means that the cumulative length of the tubules is approximately 250 m per testis—the equivalent of 2½ football fields. The structure of the tubule involves an exterior basement membrane lined with densely packed SCs followed by germ cells at varying stages of development progressing towards the lumen of the tubule.

The purpose of germ cells is to develop to spermatozoa and capable of transmitting genetic (and epigenetic) information to the next genera-

tion. They are the only type of human cell type capable of undergoing meiosis—dividing into two cells (gametes) with half of the number of chromosomes for reproduction. Notably, the process of spermatogenesis, from germ cell to sperm, is both complex and lengthy, demanding approximately 74 days (Neto et al. 2016). First, primordial germ cells (gonocytes) differentiate into two types of spermatogonia: inactive (A dark) and active (A pale). The A dark spermatogonia are reserves, they are stem cells that remain in a quiescent state awaiting activation. The A pale are proliferative. They may regenerate in a self-renewing manner or undergo mitosis to spermatogonium B. These subsequently undergo mitosis to produce primary spermatocytes (Fig. 43.1). Factors secreted by SCs determine whether A pale spermatogonia will either regenerate or differentiate. The self-renewing mechanism means that spermatogonia are the progenitors for all other germ cells and account for the entire sperm development throughout life. In brief, spermatogenesis involves three phases: mitosis, meiosis and spermiogenesis. The mitotic phase included initial proliferation from A pale to B spermatogonium then a second mitosis from B to primary spermatocyte. First meiosis marks the transition from primary to secondary spermatocyte and the second meiosis produces round spermatids. Spermiogenesis is the final phase and refers to the transformation of haploid germ cells (spermatids) to spermatozoa (Fig. 43.1, for a detailed review see Key Reading at the end of the chapter). Subsequently, the mature spermatozoa are released into the lumen of the ST.

This entire process of spermatogenesis takes approximately 74 days and is continually ongoing (Neto et al. 2016). It is estimated that a healthy adult male produces anywhere from 150–275 million spermatozoa per day. Spermatogenesis is not only dependent upon FSH stimulation but qualitatively and quantitatively normal sperm development demands androgen action—particularly for meiotic progression and maturation of the spermatids (gametes). STs are surrounded by peritubular myoid cells that together with the SCs form the blood–testis barrier. Peritubular myoid cells have properties akin to smooth muscle cells and help move testicular fluid secreted by SCs and spermatozoa from the tubules to the efferent ducts. These ducts form the epididymis where mature sperm are stored prior to ejaculation.

Spermatogenesis is a multistep process yet delivering sperm in the ejaculate requires additional products from male accessory sex organs. Indeed, the spermatozoa comprise a very small portion of the ejaculate, approximately 2–5%. In humans, the ejaculate is a mixture of secretions from the seminal vesicles (65–75%), the prostate (25–30%) and the bulbourethral glands (<1%).

43.3.2 Interstitial Compartment

The interstitial compartment of the testes represents only a small part of the entire testicular volume, yet its functional role is critical. The Leydig cells reside outside of the STs and are the primary source of testosterone production in males. Healthy adult males produce 3–10 mg of testosterone per day, accounting for >95% of the total circulating amount (Neto et al. 2016). As noted above testosterone is essential for sex development *in utero*, penile growth in mini-puberty, the development of secondary sex characteristics (virilization, deepening of the voice) in puberty as well as supporting lean muscle mass, erythropoiesis, bone health and libido/sexual function in adulthood. Notably, intra-testicular testosterone concentration is approximately 100-fold higher than peripheral circulation (Neto et al. 2016). This is important as such high concentrations are needed to support normal spermatogenesis.

43.4 Endocrine Aspects of Sexual Function

The seventeenth century mathematician, scientist and philosopher René Descartes proposed the famous "Cartesian" separation of the mind and body. Certainly, few would likely consider our modern view of sexuality as falling within such conceptual framework. However, for ease of presenting the topic, we propose that male sexual function can be broadly thought of as having two

central components: the sexual brain and the sexual body. The two are inherently connected. Indeed, male reproduction depends on coordinated endocrine hormonal factors and physiologic response that are influenced by psychosexual factors.

43.4.1 Sexual Desire

The concept of sexual desire can be expressed using a variety of terms. Sexual motivation, libido, sex drive, lust and sexual appetite address the same notion—albeit with slightly different connotations. All these terms relate to desire (including fantasy) for sexual activity. It has been proposed that gonadal sex steroid levels and external (visual) stimuli combine to create sexual incentives that are subsequently reinforced by sexual reward emotional pleasure and dopamine release (Georgiadis et al. 2012). Sexual desire is strongly linked with individual (psychological) attitudes towards sexuality, yet there are significant biological (organic) and endocrine influences. Testosterone has long been associated with virility. Importantly testosterone is a major hormonal contributor stimulating sexual desire while DHT and oestradiol play relatively small parts and weak adrenal androgens (DHEA, DHEAS) do not appear to contribute (Corona et al. 2016). There is a significant amount of evidence for this based on the fall in libido observed in studies involving men undergoing androgen deprivation therapy as well as male contraceptive studies. Similarly, a number of interventional studies have noted increased sexual desire concurrent with exogenous testosterone administration (Corona et al. 2016).

Prolactin also plays a suppressive role in sexual desire. Hyperprolactinaemia is associated with decreased libido yet the mechanism(s) is not entirely clear. It could be acting via prolactin-induced hypogonadism or via effects on the neurotransmitter dopamine which is important for sexual behaviour. Psychological stress has long been identified as having a negative effect on libido. Interestingly, there is a growing body of literature to suggest that stress may also negatively impact male fertility (spermatogenesis) via decreased testosterone production as well as by the inhibitory effects that cortisol has on the HPG axis (Nargund 2015). The sexual brain is influenced by a number of neurotransmitters and hormonal inputs that affect sexual desire—namely testosterone in males. Accordingly, a functioning HPG axis and eugonadal status (normal serum testosterone levels) contribute to maintaining healthy sexual desire in men.

43.4.2 Erectile Function

Broadly, erectile function refers to the ability to achieve and maintain an erection suitable for satisfactory sexual performance (Yafi et al. 2016). This function is essential for reproduction and includes two types of erections, reflex and psychogenic. The reflex erection is controlled by peripheral nerves and the lower spinal cord in response to tactile stimuli. The psychogenic aspect of erection involves the limbic system of the lower brain and is stimulated by erotic or emotional stimuli. The penis remains in a flaccid state as long as smooth muscle is contracted. A variety of inputs from the nervous system (adrenergic input via noradrenaline), the muscle itself (myogenic control) as well as circulating factors released from the endothelium (e.g. prostaglandins) regulate smooth muscle contraction. In the presence of sexual stimulation, erections occur when the smooth muscle relaxes. Blood flow fills the corpora cavernosa blocking venous outflow (veno-occlusion) creating a tumescence (erection). Release of nitric oxide from nonadrenergic noncholinergic nerve fibres stimulating increased cyclic GMP is critical in initiating this process of tumescence. This is reversed as phosphodiesterase type 5 (PDE5) works to break down (hydrolyse) cyclic GMP resulting in detumescence. The contribution of testosterone to erectile function appears to be through its modulating effects on smooth muscle. While studies indicate a threshold effect on erectile function (Corona et al. 2016), this does not seem to be an absolute requirement as some men are able to sustain near-normal sexual activity despite levels well below this cut-off (Yafi et al. 2016).

43.4.3 Sexual Dysfunction

Problems with sexual function may include problems with libido and desire or erectile dysfunction (ED) that caused by psychogenic, organic or endocrine factors. Among psychogenic factors stress, anxiety and depression are well-documented factors (Yafi et al. 2016). This can result in progressive loss of self-confidence and avoidance behaviour stemming from concerns about sexual performance that further exacerbate the situation and may strain intimate relationships. Importantly this is amenable to intervention and also important for the partner as there is a clear bi-directional component to sexuality, satisfaction and quality of life (Yafi et al. 2016). It is estimated that approximately 80% of ED results from an organic aetiology. Large population based studies have demonstrated strong associations between ED and age, overall health status and emotional well-being (Yafi et al. 2016). Indeed, ED has emerged as an indicator of cardiovascular health and endothelial dysfunction as reduced blood flow and arterial insufficiency/stenosis can underlie ED. Similarly, diabetes, dyslipidaemia and smoking promote atherosclerosis and can contribute to ED. Additional organic causes include neurogenic resulting from pelvic trauma or surgery.

A variety of endocrine factors contribute to sexual dysfunction. Low testosterone has been associated with decreased libido (hypoactive sexual desire), ED and delayed ejaculation (Buvat et al. 2010). This may stem from dysfunction within the HPG axis resulting in hypogonadism or indirectly as a result of axis suppression via elevated cortisol or prolactin levels (Corona et al. 2016). Stress and fasting can suppress the HPG axis as well yet it appears that men are much more resistant to such suppression compared to women who commonly develop hypothalamic amenorrhoea triggered by stress and caloric deficits. In contrast, men are susceptible to HPG axis suppression secondary to obesity, which has no evident counterpart in women. Serum T decreases with age, approximately 1% per year after age 40 and it is widely accepted that sexual dysfunction increases with age. However, there is a lack of convincing evidence that the hormonal changes associated with ageing are a direct, primary driver of changes in sexual function among otherwise healthy ageing men (Corona et al. 2013). Rather it seems that ill health (i.e. chronic disease, obesity) are much stronger contributors to sexual dysfunction (Yafi et al. 2016).

Questions about sexual function are common items in questionnaires developed to screen for testosterone deficiency. These instruments are often sensitive yet lack specificity, thus making a biochemical diagnosis essential (Dean et al. 2015; Bhasin et al. 2010). For details on diagnosing hypogonadism, please refer to Chap. 45. Notably, a recent meta-analysis indicated that T treatment is beneficial for improving libido and a variety of aspects of erectile function in men when serum T levels <12 nmol/L (345 ng/dL) (Corona et al. 2014). Importantly, the management of sexual dysfunction is based on the accurate identification of aetiology. By and large it involves an empirical, step-wise approach that may include lifestyle modifications and counselling (i.e. smoking cessation, weight loss, exercise, stress management, sex/couples therapy), medications (e.g. adjusting medications with ED as a side effect, hormone treatment, PDE5 inhibitors, intra-urethral prostaglandin suppositories) or surgical interventions (e.g. penile implants, penile revascularization) (Yafi et al. 2016).

43.5 Conclusions

Male reproduction capacity is orchestrated by the dynamic hypothalamic-pituitary-gonadal axis. The development of the axis occurs in three distinct waves that contribute to normal adult reproductive function. Neuroendocrine control of reproduction involves the hormonal interplay at the level of the hypothalamus and pituitary. GnRH-induced gonadotrophin secretion stimulates spermatogenesis and testosterone production (the dominant male sex steroid). The axis is controlled via intricate negative feedback loops and disruption of the axis can result in hypogonadism, sexual dysfunction and infertility. Understanding the basic structure and physiology

of the male reproductive endocrine system is a fundamental competency for endocrine nurses caring for patients in this domain.

References

Abreu AP, Kaiser UB. Pubertal development and regulation. Lancet Diabetes Endocrinol. 2016;4(3):254–64.

Ahmed SF, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin Endocrinol. 2016;84(5):771–88.

Balasubramanian R, Dwyer A, Seminara SB, Pitteloud N, Kaiser UB, Crowley WF Jr. Human GnRH deficiency: a unique disease model to unravel the ontogeny of GnRH neurons. Neuroendocrinology. 2010;92(2):81–99.

Bancalari RE, Gregory LC, McCabe MJ, Dattani MT. Pituitary gland development: an update. Endocr Dev. 2012;23:1–15.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.

Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547–64.

Boepple PA, Hayes FJ, Dwyer AA, Raivio T, Lee H, Crowley WF Jr, et al. Relative roles of inhibin B and sex steroids in the negative feedback regulation of follicle-stimulating hormone in men across the full spectrum of seminiferous epithelium function. J Clin Endocrinol Metab. 2008;93(5):1809–14.

Boyar RM, Rosenfeld RS, Kapen S, Finkelstein JW, Roffwarg HP, Weitzman ED, et al. Human puberty. Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. J Clin Invest. 1974;54(3):609–18.

Buvat J, Maggi M, Gooren L, Guay AT, Kaufman J, Morgentaler A, et al. Endocrine aspects of male sexual dysfunctions. J Sex Med. 2010;7(4 Pt 2):1627–56.

Corona G, Rastrelli G, Maseroli E, Forti G, Maggi M. Sexual function of the ageing male. Best Pract Res Clin Endocrinol Metab. 2013;27(4):581–601.

Corona G, Isidori AM, Buvat J, Aversa A, Rastrelli G, Hackett G, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med. 2014;11(6):1577–92.

Corona G, Isidori AM, Aversa A, Burnett AL, Maggi M. Endocrinologic control of men's sexual desire and arousal/erection. J Sex Med. 2016;13(3):317–37.

Dean JD, McMahon CG, Guay AT, Morgentaler A, Althof SE, Becher EF, et al. The International Society for Sexual Medicine's Process of Care for the Assessment and Management of Testosterone Deficiency in Adult Men. J Sex Med. 2015;12(8):1660–86.

Dwyer AA, Jayasena CN, Quinton R. Congenital hypogonadotropic hypogonadism: implications of absent minipuberty. Minerva Endocrinol. 2016;41(2):188–95.

Finkelstein JS, Lee H, Leder BZ, Burnett-Bowie SA, Goldstein DW, Hahn CW, et al. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. J Clin Invest. 2016;126(3):1114–25.

Georgiadis JR, Kringelbach ML, Pfaus JG. Sex for fun: a synthesis of human and animal neurobiology. Nat Rev Urol. 2012;9(9):486–98.

Groth KA, Skakkebaek A, Host C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30.

Grumbach MM. A window of opportunity: the diagnosis of gonadotropin deficiency in the male infant. J Clin Endocrinol Metab. 2005;90(5):3122–7.

Hatipoglu N, Kurtoglu S. Micropenis: etiology, diagnosis and treatment approaches. J Clin Res Pediatr Endocrinol. 2013;5(4):217–23.

Joustra SD, van der Plas EM, Goede J, Oostdijk W, Delemarre-van de Waal HA, Hack WW, et al. New reference charts for testicular volume in Dutch children and adolescents allow the calculation of standard deviation scores. Acta Paediatr. 2015;104(6):e271–8.

Kuiri-Hanninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Horm Res Paediatr. 2014;82(2):73–80.

Nargund VH. Effects of psychological stress on male fertility. Nat Rev Urol. 2015;12(7):373–82.

Neto FT, Bach PV, Najari BB, Li PS, Goldstein M. Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol. 2016;59:10–26.

Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, et al. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 2008;93(3):784–91.

Raivio T, Avbelj M, McCabe MJ, Romero CJ, Dwyer AA, Tommiska J, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab. 2012;97(4):E694–9.

Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P, Aszpis S, et al. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology. 2013;1(1):3–16.

Ritzen EM, Bergh A, Bjerknes R, Christiansen P, Cortes D, Haugen SE, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr. 2007;96(5):638–43.

Skorupskaite K, George JT, Anderson RA. The kisspeptin-GnRH pathway in human reproductive health and disease. Hum Reprod Update. 2014;20(4):485–500.

Sykiotis GP, Hoang XH, Avbelj M, Hayes FJ, Thambundit A, Dwyer A, et al. Congenital idiopathic hypogo-

nadotropic hypogonadism: evidence of defects in the hypothalamus, pituitary, and testes. J Clin Endocrinol Metab. 2010;95(6):3019–27.
Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. Nat Rev Dis Primers. 2016;2:16003.

Key Reading

1. Abreu AP, Kaiser UB. Pubertal development and regulation. Lancet Diabetes Endocrinol. 2016;4(3):254–64. https://doi.org/10.1016/S2213-8587(15)00418-0.
2. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, Dwyer AA, Giacobini P, Hardelin J-P, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, document YJE c. European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nat Rev. Endocrinol. 2015;11(9):547–64. https://doi.org/10.1038/nrendo.2015.112.
3. Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P, Aszpis S, Pacenza N, Stewart Usher J, Bergadá I, Campo SM. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology. 2013;1(1):3–16. https://doi.org/10.1111/j.2047-2927.2012.00008.x.
4. Neto FT, Bach PV, Najari BB, Li PS, Goldstein M. Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol. 2016. pii: S1084–9521(16)30104–5. https://doi.org/10.1016/j.semcdb.2016.04.009.
5. Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, Maggi M, Nelson CJ, Parish S, Salonia A, Tan R, Mulhall JP, Hellstrom WJ. Erectile dysfunction. Nat Rev Dis Primers. 2016;2:16003. https://doi.org/10.1038/nrdp.2016.3.

44 Classification of Hypothalamic-Pituitary-Gonadal (HPG) Axis Endocrine Disorders

Andrew A. Dwyer and Richard Quinton

Contents

44.1 **Introduction** 855

44.2 **Signs and Symptoms of Testosterone Deficiency** 856

44.3 **Testicular Disorders (Primary) Hypogonadism** 856
44.3.1 Cryptorchidism 857
44.3.2 Klinefelter Syndrome (KS) 858
44.3.3 Disorders of Sex Development (DSD) 860
44.3.4 Acquired Primary Hypogonadism 860

44.4 **Hypothalamic and Pituitary Disorders (Secondary) Hypogonadism** 861
44.4.1 Congenital Hypogonadotropic Hypogonadism 861
44.4.2 Syndromic Forms of Secondary Hypogonadism 861
44.4.3 Inactivating Mutations 862
44.4.4 Acquired Forms 863
44.4.5 Functional Causes 863

44.5 **Ageing and Testosterone Deficiency** 864

44.6 **Obesity-Related Testosterone Deficiency** 864

44.7 **Tumours** 865

44.8 **Iatrogenic** 865
44.8.1 Post Chemotherapy or Radiation Therapy 865

A. A. Dwyer (✉)
William F. Connell School of Nursing,
Chesnut Hill, MA, USA

Boston College, Chesnut Hill, MA, USA
e-mail: Andrew.dwyer@bc.edu

R. Quinton
Newcastle-upon-Tyne Hospitals Foundation NHS
Trust (Royal Victoria Infirmary), Institute for Human
Genetics, University of Newcastle-upon-Tyne,
Newcastle-upon-Tyne, UK
e-mail: Richard.Quinton@nuth.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_44

44.8.2 Medications 866
44.8.3 Androgen Deprivation Therapy 866
44.9 **Systemic Disease** 866
44.10 **Endocrine Disrupting Chemicals** 867
44.11 **Conclusions** 867
References 868

Abstract

The proper function of the hypothalamic-pituitary-gonadal (HPG) axis is needed for full pubertal development, normal androgen production and full reproductive capacity. Congenital or acquired disorders at any level of this system can produce characteristic signs and symptoms of testosterone (T) deficiency and disrupt fertility. Organic problems at the level of the hypothalamus and/or pituitary can be differentiated from testicular disorders by measurement of serum gonadotrophins (luteinizing hormone and follicle stimulating hormone). Primary hypogonadism results from testicular defects and is evidenced by elevated gonadotrophins, whereas secondary hypogonadism is central in origin and characterized by low (or abnormally normal) gonadotrophins. Epidemiologic studies have demonstrated a progressive decline in serum T with age. However, the increased rates of hypogonadism seen in advanced age primarily relate to obesity and chronic disease burden. Androgen deficiency may result from a wide range of causes including tumours, medications and systemic illness that directly affect the testes or suppress the HPG axis. Regardless of aetiology, untreated hypogonadism has significant negative consequences on health and quality of life. T deficiency not only contributes to poor bone health but is also linked to increased risk for metabolic problems such as the metabolic syndrome and diabetes and has been associated with all-cause cardiovascular mortality. Understanding the pathophysiology underlying hypogonadism is the foundation for appropriately assessing, diagnosing and treating androgen deficiency. This chapter is a mini-review for endocrine nurses providing a summary of disorders affecting the HPG axis with specific attention given to the nursing process in relation to testosterone deficiency.

Keywords

Hypogonadism · Androgen deficiency
Testosterone · Sexual dysfunction · Obesity
Testes

Abbreviations

AMH	Anti-Müllerian hormone
AOH	Adult-onset hypogonadism
AR	Androgen receptor
BBS	Bardet–Biedl syndrome
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CHH	Congenital hypogonadotropic hypogonadism
CPHD	Combined pituitary hormone deficiency
DSD	Disorder of sex development
ED	Erectile dysfunction
EDCs	Endocrine disrupting chemicals
EMAS	European Male Ageing Study
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin-releasing hormone
HIV	Human immunodeficiency virus
HPG	Hypothalamic-pituitary-gonadal
IB	Inhibin B
INSL3	Insulin-like peptide 3
LH	Luteinizing hormone
LOH	Late-onset hypogonadism
SHBG	Sex hormone binding globulin
SOD	Septo-optic dysplasia
SSRIs	Selective serotonin reuptake inhibitors
T	Testosterone
TDS	Testicular Dysgenesis Syndrome

Key Terms

- **Hypogonadism:**: The combination of repeated, unequivocally low serum testosterone levels combined with clinical signs and symptoms of androgen deficiency, typically within the framework of a recognized clinical syndrome.
- **Gynaecomastia:** The development of glandular breast tissue in men resulting from an imbalance of testosterone and oestradiol. Pseudogynaecomastia refers to the superficially similar appearance resulting from excess fat accumulation; in practice, many men exhibit a combination.
- **Sexual dysfunction:** The inability to engage in normal, pleasurable sexual activity resulting from diminished desire (libido), arousal difficulties (erectile dysfunction) and/or problems with orgasm (ejaculation).
- **Metabolic syndrome:** A condition comprising a constellation of risk factors that increase risk for cardiovascular disease and diabetes. Definitions vary across organizations yet key elements include insulin resistance, hypertension, abnormal lipid profile (i.e. elevated triglycerides, low high-density lipoprotein levels) and obesity (particularly central).
- **Late-onset hypogonadism:** This is clinically characterized by decreased sexual interest, morning erections and erectile dysfunction in the setting of serum testosterone levels below the normal adult range in older men. However, in practice, obesity and cumulative burden of ill health are more powerful predictors than biological age per se.

Key Points

- Disorders at the level of the hypothalamus or pituitary result in hypogonadotropic hypogonadism (secondary hypogonadism). Effective treatments are available for correcting testosterone deficiency and for inducing fertility in these classic forms of hypogonadism.
- Testicular defects can result in hypergonadotropic hypogonadism (primary hypogonadism). Primary hypogonadism is readily identified by elevated serum gonadotrophin levels. Testosterone treatment can ameliorate hypogonadism but fertility treatment for these disorders remains challenging.
- Apart from the small percentage of older men who exhibit some age-related testicular dysfunction, the increased prevalence of low testosterone levels in ageing men is largely due to obesity and other chronic health problems, causing suppression of gonadotrophin levels, rather than ageing per se. It remains unknown whether this phenomenon is adaptive, maladaptive or neutral in its effects.
- There is a bi-directional interaction between obesity and testosterone. Weight loss is highly effective way for obese men to simultaneously reduce their cardio-metabolic risk and increase their testosterone levels.
- Regardless of aetiology hypogonadism, sexual dysfunction and infertility can severely impact quality of life. Nursing assessment should include evaluation of psychological and interpersonal aspects.

44.1 Introduction

In men, hypogonadism is a state defined by insufficient testicular androgen (testosterone) production. Testosterone (T) deficiency may occur at any point from puberty through adult life. Hypogonadism is evidenced biochemically by low circulating serum T levels and clinically by a wide range of signs and symptoms of T deficiency (Table 44.1) (Bhasin et al. 2010). Hypogonadism can have consequences on health and well-being and contributes to male factor infertility. Among infertile couples, it is estimated that male factors contribute (fully or partially) to 20–70% of cases (Tournaye et al. n.d.). The prevalence of hypogonadism is rather difficult to pin down as

Table 44.1 Signs and symptoms suggestive of androgen (testosterone) deficiency

Clinically observable signs	Patient-reported symptoms
More specific:	
• Incomplete/delayed sexual development • Eunuchoidal proportions[a] • Gynaecomastia, breast tenderness/discomfort • Small testes (TV < 5 mL) or ↓ in volume • Oligospermia or azoospermia (infertility) • ↓ in height, ↓ BMD, or low-trauma fracture	• ↓ sexual desire (libido) • ↓ sexual activity • ↓ spontaneous erections • ↓ morning erections • Sexual dysfunction (erectile and/or orgasmic) • Hot flushes, ↑ in sweating • ↓ shaving or ↓ in body hair (axillary/pubic)
Less specific:	
• Mild anaemia (normochromic, normocytic[b]) • ↑ body mass index (BMI), ↑ body fat	• Fatigue, ↓ energy and motivation • Irritability, ↓ sense of wellbeing • Depressed mood, feeling down • Difficulty concentrating, impaired memory • Sleep disturbance/ insomnia • ↓ strength or muscle bulk • ↓ physical or work performance • ↑ frailty (impaired balance and coordination)

Bhasin et al. J Clin Endocrinol Metab 2010, Dean et al. J Sex Med 2015

[a]Altered body proportions in which armspan exceeds height by ≥7 cm. *TV* testicular volume, *BMD* bone mineral density

[b]Anaemia of chronic disease wherein the average red blood cell size and haemoglobin content are within normal limits

this depends on whether estimates are based on a diagnosis of a hypogonadism-related disease (i.e. congenital hypogonadotropic hypogonadism), as part of a clinical syndrome (i.e. diabetes) or based on a defined biochemical cut-off (i.e. serum T < 10 nmol/L). Epidemiologic data have identified an age-related decline in serum T, particularly the circulating free fraction, yet much of the increased hypogonadism with age results from concurrent health issues such as obesity, chronic disease, medications and frailty (Bhasin et al. 2010; Dean et al. 2015; Morgentaler et al. 2016; Khera et al. 2016).

44.2 Signs and Symptoms of Testosterone Deficiency

The 2010 Endocrine Society clinical Practice Guideline on testosterone therapy in men with androgen deficiency syndromes delineated two specific groups of signs and symptoms (Bhasin et al. 2010). The expert panel identified more specific signs and symptoms of hypogonadism as: incomplete/delayed sexual development, reduced sexual desire/libido, decreased spontaneous erections and erectile dysfunction, gynaecomastia, diminished facial/axillary/pubic hair, small testes (volume < 5 mL), infertility, low bone mineral density and hot flashes. These more specific signs and symptoms tend to be evident in young men with classic forms of hypogonadism. Less-specific signs and symptoms include decreased energy level, diminished motivation or initiative, feeling down or blue, difficulty concentrating, poor memory, disturbed sleep, anaemia, reduced muscle strength, increased body fat and diminished physical or work performance (Table 44.1). Notably, the correlation between signs, symptoms and serum T levels is weak as best—as underscored by a recent systematic review (Millar et al. 2016).

Indeed, the clinical presentation of hypogonadism greatly depends on age of onset, the severity of androgen deficiency, rapidity of onset and genetic and host factors. Herein, we will describe the classification of male endocrine disorders resulting from disruption of the hypothalamic-pituitary-gonadal (HPG) axis.

44.3 Testicular Disorders (Primary) Hypogonadism

A number of conditions cause insufficient testicular production of testosterone and Leydig cell dysfunction. Primary gonadal failure (hypogonadism) is characterized by elevated serum gonadotrophin levels in the setting of low T levels. Some testicular disorders underlying hypo-

Table 44.2 Causes of testosterone deficiency

Congenital disorders	Acquired disorders
Primary (1°) hypogonadism (hypergonadotropic) resulting from gonadal defects	
• Cryptorchidism Uncorrected maldescended testes (bilateral) • Chromosomal abnormalities Klinefelter syndrome (47XXY) • Disorders of sex development (DSD) 46XY gonadal dysgenesis Vanishing testes/testicular regression syndrome Steroid synthesis defects Partial/complete androgen resistance syndromes Swyer syndrome Noonan syndrome • Inactivating mutations LH receptor	• Gonadectomy • Trauma Bilateral trauma/torsion Orchiectomy • Infection/inflammation (bilateral) Mumps/viral orchitis Autoimmune polyglandular syndrome • Iatrogenic Chemotherapy (alkylating agents) Radiotherapy (pelvic irradiation) • Systemic disease HIV infection, sickle cell disease
Secondary (2°) hypogonadism (hypogonadotropic) resulting from hypothalamic-pituitary defects	
• Isolated GnRH deficiency Congenital hypogonadotropic hypogonadism Kallmann syndrome	• Tumours Pituitary adenoma (prolactinoma), craniopharyngioma, gliomas, germinomas, meningiomas, astrocytomas • Trauma/vascular Pituitary stalk dissection, pituitary apoplexy • Infiltrative disease Haemochromatosis, histiocytosis, sarcoidosis, granulomatous disease • Iatrogenic/medications Cranial irradiation, glucocorticoid therapy, high-dose corticosteroids, opioids, antipsychotics, androgen deprivation therapy, illicit drug use: marijuana, narcotics, anabolic androgenic steroids • Functional Critical illness, hyperprolactinaemia, stress, eating disorders, weight loss, excessive exercise, obesity • Systemic disease COPD, rheumatoid arthritis, chronic liver disease, chronic renal disease, diabetes
• Syndromic forms Combined pituitary hormone deficiency Septo-optic dysplasia CHARGE syndrome Bardet–Biedl syndrome Prader–Willi syndrome Congenital adrenal hypoplasia	
(*NR0B1*) • Inactivating mutations GnRH receptor Gonadotrophins	

HIV human immunodeficiency virus; *CHARGE* Coloboma, *H*eart defect, *A*tresia of nasal choanae, *R*etarded growth/development, *G*enital abnormalities and *E*ar abnormalities/deafness; *COPD* chronic obstructive pulmonary disease

gonadism are exceedingly rare such as congenital anorchia (e.g. vanishing testes, XY gonadal dysgenesis, Swyer syndrome) or Leydig cell hypoplasia secondary to inactivating mutations of the LH receptor (Salvi and Pralong 2010). Other contributors to primary hypogonadism, notably cryptorchidism and Klinefelter syndrome are much more common (Table 44.2).

44.3.1 Cryptorchidism

The lower temperature of the scrotum (compared to the abdomen) is critical for spermatogenesis. Thus, maldescended testes can have far reaching negative impact on fertility. Approximately 1–2% of males are born with cryptorchidism and the vast majority (80–90%) of cases are unilateral (Lee and Houk 2013). Importantly, testes remaining in the inguinal canal (or abdomen) have little or no function and if left uncorrected, men have increased risk of infertility, T deficiency (if bilateral) and testicular cancer. Thus, the current recommendation is that surgical correction of undescended testes be performed in the first year of life (Ritzen et al. 2007). In normal initial testicular descent between 10 and 15 weeks gestation in a process is largely driven by androgens and insulin-like peptide 3 (INSL3) as well as anti-

Müllerian hormone (AMH) (Lee and Houk 2013). As such, GnRH deficiency resulting in decreased LH-induced T secretion or gene mutations in *INSL3*, *AMH* or the androgen receptor (*AR*) can cause cryptorchidism. It is worthwhile noting that, even in cases of unilateral cryptorchidism, the contralateral testis is not completely normal suggesting that cryptorchidism is a bilateral disease (Chan et al. 2014). Similarly, so-called "retractile testes that intermittently move into the inguinal canal are not completely normal on histology. Current recommendations favour surveillance as opposed to orchiopexy (surgical correction), which is recommended for congenital undescended testes within the first year of life (Ritzen et al. 2007). Notably, there is growing concern that endocrine disrupting chemicals (EDCs) may be contributing to growing rates of cryptorchidism (Juul et al. 2014) which is discussed later in this chapter.

44.3.2 Klinefelter Syndrome (KS)

Klinefelter syndrome (47, XXY) is the most common form of male hypogonadism and the most frequent male chromosomal anomaly occurring in approximately 1:660 males (Groth et al. 2013). First described in 1942 by eminent endocrinologist Harry Klinefelter, the syndrome is clinically characterized by small testes, gonadal failure (hypergonadotropic hypogonadism), disrupted spermatogenesis (infertility), gynaecomastia and eunuchoidal proportions (armspan exceeds height by ≥7 cm). Importantly, few patients are diagnosed before puberty (<10%) and it is estimated that only about 25% of men with Klinefelter syndrome (KS) are ever diagnosed (Groth et al. 2013). While the reason for this remains unclear, it is thought that number of undiagnosed cases results from mosaic forms of KS with a milder clinical phenotype. Serum LH, FSH and inhibin B (IB) levels are typically normal until puberty at which point Leydig cells begin to hyalinize and testicular function declines (Groth et al. 2013). Testicular function progressively degenerates and testicular volume typically does not exceed 5–6 mL in KS. In light of the progressive decline in sperm, there has been recent growing interest in the possibility that early sperm extraction could potentially preserve fertility for these men (Aksglaede and Juul 2013). With access to modern assisted fertility techniques such as microdissection, testicular sperm extraction (TESE) combined with intracytoplasmic sperm injection (ICSI), men with KS are no longer categorically infertile. However, experience with and outcomes from these new techniques are limited and carry considerable ethical and emotional concerns particularly for adolescents. Professional genetic counselling is recommended for such case as well as discussion of prenatal diagnostic techniques.

Importantly, T replacement therapy is recommended once serum gonadotrophins begin to rise in early puberty, or at the very least, when serum T levels become hypogonadal (Groth et al. 2013). This can ensure full development of secondary sexual characteristics and help support bone health. Some reports have identified increased risk for mediastinal tumours, autoimmune disorders, vascular disease, thromboembolism and cancer in cohorts of patients with KS, some of which may relate to lifestyle issues. Strong evidence supports an increased risk for metabolic complications including obesity, the metabolic syndrome and type 2 diabetes. Accordingly, lifestyle coaching should be part of regular consultations along with ongoing monitoring of bone health (i.e. densitometry) and regular assessment of adherence to T replacement (Box 44.1).

Box 44.1 Nursing Process: Hypogonadism

1. Assess

Evaluate all aspects of patient health status, including aspects relating to health promotion, protection and disease prevention including signs and symptoms of testosterone deficiency (see Table 44.1).

- Take a detailed medical and family history including specific questions on pubertal timing. Perform a careful review of past and current medications.

- Examine clinically relevant signs with particular attention to degree of sexual maturation and testicular volume.
- Identify potential contributors to T deficiency such as chronic illness, medications or illicit drug use.
- Inquire about sexual function.

2. Diagnose

Work collaboratively to plan appropriate screening tests (and examinations) based on recommendations, i.e. patients presenting with infertility, sexual dysfunction, gynaecomastia diseases of the seller region, men taking medications effecting T biosynthesis or metabolism, men with HIV and weight loss, osteoporosis or low-trauma fracture.

- Identify patient knowledge deficits as areas for therapeutic education.
- Coordinate relevant radiologic examinations.
- Ensure appropriate, accurate reproductive hormone profiling, i.e. morning blood draw (between 08:00 and 12:00) in a fasting state.
- Collaborate with endocrine colleagues to determine if the patient warrants treatment based on evidence-based guidelines.
- Facilitate additional specialist referrals as needed (i.e. urology).

3. Plan

Interpret test results, recognize abnormal findings and help communicate results and implications to the patient/family.

- Prepare teaching points to address identified patient knowledge deficits.
- Review potential treatment modalities and gather materials to engage the patient in shared decision-making.
- Identify patient resources including websites, patient support groups, contacts for narcotics anonymous, weight loss programmes (nutrition and physical therapy consultations) or research studies/clinical trials as appropriate.
- Coordinate plan of care with the primary care provider to ensure continuity and collaboration if they will be overseeing treatment.

4. Implement

Initiate treatment and inform the patient of appropriate monitoring and follow-up.

- Teach proper medication administration technique with return demonstration as appropriate (i.e. sterile self-injection).
- Provide therapeutic education to ensure comprehension of the term effects of the diagnosis and key principles for management.
- Provide emotional support to patient/family based on condition-specific psychological issues and provide resource materials.
- Assess readiness for change in cases of substance abuse (rehabilitation) and obesity (initiating lifestyle modifications for weight loss).
- Reinforce the importance of therapeutic adherence for health and well-being.
- Provide prescriptions for medication and materials (i.e. syringes, needles, sharps container).
- Facilitate transition to primary care as is relevant to the plan of care.
- Plan and coordinate initial and subsequent follow-up appointments.

5. Evaluate

Assess the effectiveness of interventions and revise the plan of care as appropriate.

- Evaluate biochemical response to treatment (i.e. serum T level) paying particular attention to peak-trough pharmacokinetics based on treatment modality.
- Inquire about potential unwanted side effects of treatment.
- Monitor adherence to the treatment: Was treatment initiated? Were any doses missed either intentionally or unintentionally? Is the treatment ongoing?
- Assess actual and potential effects on patient-reported outcomes (i.e. energy level, sleep quality, sexual function).
- Inquire about sexual function and satisfaction and fertility plans or concerns.
- Monitor for other psychological comorbidities (i.e. anxiety, depression, body image concerns) and coping behaviours.
- Assess patient's ability to navigate the healthcare system including transition and financial concerns.
- Reformulate the plan of care as needed in collaboration with the healthcare team.

In addition to these health problems and the physical stigmata of KS, affected boys often have poor motor skills, behavioural problems and may exhibit neurocognitive deficits (Skakkebaek et al. 2015). While highly variable, patients with KSD may have problems with cognition and language acquisition (i.e. dyslexia), learning disabilities and difficulties with executive function. These difficulties often require speech-language therapy, special education programmes and/or psychological counselling. The combination of cognitive behavioural problems and hypogonadism can negatively affect quality of life and the effective adaptation to living with KS (Turriff et al. 2015). Impulsivity and anger-management issues may be inherent to the condition and are very unlikely to be caused or exacerbated by physiological testosterone replacement. Accordingly, comprehensive holistic nursing care includes assessment of psychosocial concerns, discussing these aspects with patients and families, identifying educational and coping resources, and making appropriate interprofessional referrals as needed (Box 44.1).

44.3.3 Disorders of Sex Development (DSD)

Disorders of sex development (DSD) include a wide range of conditions spanning a broad spectrum of phenotypic features and pathophysiology (Hughes et al. 2006). Most cases of DSD are identified at birth as atypical or ambiguous genitalia are the impetus for evaluation. Atypical genitalia (i.e. hypospadias, a condition when the urethra opens on the ventral side of the penis rather than at the tip) at birth can be common occurring in 1:300 births. However, truly ambiguous genitalia, most often caused by congenital adrenal hyperplasia (CAH), are quite rare and occur in roughly 1:5000 births (Hughes et al. 2006). In some cases, adolescents may present because of lack of pubertal development. There are a number of 46XY DSD wherein the gonads are in fact testes, yet serum T is pathologically low. Many of these conditions are autosomal recessive genetic disorders resulting in defective enzymes (comprehensively summarized in Hughes et al. 2006). Patients with DSD deserve care by an inter-professional team (i.e. endocrinology, radiology, surgery, psychology, psychiatry and nursing) (Hiort et al. 2014). These patients and families need psychological support and should be connected with available patient support groups (Brain et al. 2010). Nurses can play a key role in supporting patients and families, facilitating communication within the multidisciplinary team and providing patient-centred, coordinated care (Box 44.1).

44.3.4 Acquired Primary Hypogonadism

Acquired forms of primary hypogonadism (testicular failure) may result from trauma, infection/inflammation (i.e. mumps orchitis), iatrogenic or secondary to systemic disease (Table 44.2). One type of traumatic injury, testicular torsion, has an

incidence of 4.5 cases per 100,000 (Ross and Bhasin 2016). It occurs when the testes become twisted on the spermatic cord cutting off blood flow to the testes. If not corrected urgently (i.e. within 6–8 h), necrosis can permanently damage the testes resulting in infertility and T deficiency. Testicular inflammation (orchitis) may be secondary to viral infection. Among post-pubertal men, orchitis occurs in roughly a quarter of mumps infections (Ross and Bhasin 2016). Unilateral inflammation occurs in about two-thirds of cases and may result in diminished testicular size yet 75% maintain fertility. Bilateral cases are more severe as only a third of men recover spermatogenesis (Ross and Bhasin 2016).

44.4 Hypothalamic and Pituitary Disorders (Secondary) Hypogonadism

As reviewed in the previous chapter, testosterone production is contingent upon adequate gonadotrophin stimulation (i.e. luteinizing hormone, LH) of the Leydig cells. Hypogonadism resulting from inadequate gonadotrophin stimulation is biochemically evident in low (or inappropriately normal) serum gonadotrophin levels—thus hypogonadotropic hypogonadism. Secondary hypogonadism may be congenital (from birth) or acquired (Table 44.2). Hypogonadotropic hypogonadism may result from defects at the level of the hypothalamus (i.e. isolated GnRH deficiency), pituitary defects causing inadequate gonadotrophin release, genetic mutations resulting in inadequate action of GnRH/gonadotrophins as well as via functional suppression of the neuroendocrine axis (Boehm et al. 2015).

44.4.1 Congenital Hypogonadotropic Hypogonadism

Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder (1/4000–10,000) caused by isolated GnRH deficiency and clinically characterized by absent or incomplete puberty and infertility (Boehm et al. 2015). When CHH occurs with anosmia (lack of sense of smell), it is termed Kallmann syndrome. While sense of small and reproduction may appear to be unrelated functions, the embryonic origins of GnRH neurons in the olfactory placode provide the development link. More than 20 genes have been identified as underlying CHH and Kallmann syndrome either alone or in combination (Boehm et al. 2015; Stamou et al. 2015). Some gene mutations disrupt GnRH neuron development and migration—manifesting as Kallmann syndrome. Other mutations may disrupt GnRH homeostasis and secretion and clinically present as cases of normosmic CHH (Boehm et al. 2015). In some cases, mutations in the gene encoding the GnRH receptor (*GNRHR*) result in decreased GnRH action and CHH ensues (described below). CHH may occur with other associated phenotypes such as cryptorchidism with/without micropenis, renal agenesis, hearing loss, midline defects (cleft lip/palate) and skeletal anomalies. CHH is difficult to diagnose and many patients are diagnosed late with significant psychosocial impact (Dwyer et al. 2014). These patients are in need of psychological support and may benefit from peer-to-peer support (Box 44.1). Effective treatments are available for inducing secondary sexual characteristics and fertility in most cases (Boehm et al. 2015; Rastrelli et al. 2014). Spontaneous reversion of CHH is observed in about 10–15% of cases following treatment, but may not be sustained permanently and thus warrant ongoing monitoring (Dwyer et al. 2016).

44.4.2 Syndromic Forms of Secondary Hypogonadism

Developmental defects can result in hypothalamic-pituitary dysfunction and hypogonadotropic hypogonadism. Many problems present with a constellation of features and thus are referred to as syndromic forms. These cases are typically identified during childhood as anterior hormone deficiency, adrenal failure, obesity of neurologic aspects command attention far before absent puberty is clinically evident (Brioude

et al. 2010). Given the complexity of these cases, patients and families need purposeful planned transitional care to ensure continuity and ongoing support (Box 44.1).

44.4.2.1 Combined Pituitary Hormone Deficiency (CPHD) and Septo-Optic Dysplasia (SOD)

Patients with combined pituitary hormone deficiency (CPHD) often are identified early in childhood and treated for the respective pituitary hormone deficiencies, yet gonadotrophin deficiency may not become apparent until the failure of puberty to commence spontaneously. Importantly, these patients are responsive to treatment inducing secondary sexual characteristics and fertility (Mao et al. 2015). A number of genes have been identified to underlie this condition yet the majority of cases remain without an identified genetic cause (Castinetti et al. 2016). Septo-optic dysplasia (SOD) is a developmental brain malformation that may occur with pituitary hormone deficiency as well as severe visual impairment, neurocognitive disability and developmental disorders on the autism spectrum (Ryabets-Lienhard et al. 2016). Notably, genetic overlap has been reported between SOD, CPHD and Kallmann syndrome (Raivio et al. 2012).

44.4.2.2 CHARGE, Bardet–Biedl and Prader–Willi Syndromes

The constellation of coloboma (ocular malformation of the lens, iris or retina), congenital heart defects, choanal atresia (abnormal formation of the nasal cavity), retardation of growth and development, genital hypoplasia, and ear anomalies associated with deafness define CHARGE syndrome (Bergman et al. 2011). In addition to additional immunologic problems, patients with CHARGE syndrome may exhibit hypogonadotropic hypogonadism necessitating treatment. Approximately two-thirds of cases are explained by mutation Chromodomain-helicase-DNA-binding protein 7 (*CHD7*) (Bergman et al. 2011) a gene also involved in CHH and Kallmann syndrome (Boehm et al. 2015). Bardet–Biedl syndrome (BBS) is a recessive genetic disorder of the cellular cilia that may present with a wide range of clinical features (obesity, mental retardation, renal anomalies, polydactyly, retinal degeneration, hypogonadism, as well as cardiovascular, hepatic and metabolic problems (Khan et al. 2016). In addition to being clinically heterogeneous, BBS is genetically diverse with 19 identified loci and complex genetics (i.e. digenicity, oligogenicity) (Khan et al. 2016) akin to CHH and Kallmann syndrome (Boehm et al. 2015). Prader–Willi syndrome (PWS) is a rare genetic disorder (1/10,000–25,000) on chromosome 15 that causes physical, mental and social disability. During infancy, PWS is characterized by hypotonia and poor feeding (failure to thrive). Subsequently, additional features such as developmental delays, cognitive disability, short stature, hyperphagia, obesity and behavioural problems (i.e. obsessive food seeking) emerge (Angulo et al. 2015). Multiple endocrine deficiencies are not uncommon. Patients typically receive growth hormone and sex steroid treatment (Deal et al. 2013).

44.4.2.3 Congenital Adrenal Hypoplasia

A rare form of hypogonadotropic hypogonadism occurs in the setting of congenital adrenal hypoplasia. Mutations in Nuclear receptor subfamily 0, group B, member 1 (*NR0B1*, formerly *DAX1*) result in early adrenal failure and subsequently absent/incomplete puberty is the initial sign of hypogonadotropic hypogonadism (Jadhav et al. 2011).

44.4.3 Inactivating Mutations

Much like a lock and key, proper signalling requires both functional ligand and receptor. Mutations in genes encoding the ligands upstream of GnRH (*KISS1*, formerly *GPR54*), GnRH itself (*GNRH1*), LH (*LHβ*) and FSH (*FSHβ*) are exceedingly rare causes of secondary hypogonadism (Salvi and Pralong 2010; Boehm et al. 2015; Chan 2011). The receptors of these ligands (*KISS1R, GNRHR, LHR, FSHR*) belong to the G-protein coupled receptor super-family

and mutations are very rare (but for *GNRHR*). Mutations in *FSHR* cause disrupted albeit not complete infertility, and non-functioning LHR can result in hypospadias, micropenis and/or Leydig cell hypoplasia (i.e. 46XY disorder of sex development, DSD) (Salvi and Pralong 2010). Typically the serum levels of the mutated hormone are undetectable while the other gonadotrophin is elevated. Interestingly, mutations in GNRHR underlie approximately 4–5% of CHH cases and may be overcome by high doses of GnRH (Boehm et al. 2015) and have been identified in a number of CHH reversals (Dwyer et al. 2016).

44.4.4 Acquired Forms

Acquired hypogonadism refers to T deficiency in adult life subsequent to full pubertal development. T deficiency of neuroendocrine origin can result from trauma (i.e. skull fracture, pituitary stalk dissection), vascular events (i.e. pituitary apoplexy), infiltrative disorders (i.e. hemochromatosis) or from illicit drug use (i.e. marijuana, opiates or anabolic androgenic steroids) suppressing the HPG axis as well as iatrogenic caused or secondary to systemic disease (Ross and Bhasin 2016). Anabolic androgenic steroids are used without medical supervision to enhance athletic performance and appearance and the estimated lifetime prevalence of abuse is approximately 6% of men (Nieschlag and Vorona 2015). The extremely high circulating androgen levels suppress the HPG axis resulting in testicular atrophy and infertility. These consequences are reversible yet products are typically used in very high doses and as some products have an extended half-life, recovery of HPG axis function may take several months and in some cases up to a year or longer (Nieschlag and Vorona 2015).

Another form of acquired secondary hypogonadism occurs in men with adult-onset isolated GnRH deficiency. These men complete puberty then present in adulthood with decreased libido, poor sexual function and infertility secondary to a crash of their HPG axis (Nachtigall et al. 1997). Notably, detailed hormone profiling with blood draws every 10 min reveals pulsatile LH secretion patterns with frankly hypogonadal T levels. The men have no other apparent underlying cause of their hypogonadism and defect is identified as hypothalamic as these men respond to physiologic pulsatile GnRH replacement. Long-term follow-up studies suggest that the neuroendocrine defect is permanent as these men do not subsequently recover HPG axis function (Dwyer et al. 2010).

44.4.5 Functional Causes

Secondary hypogonadism can also result from physiologic causes. Such cases of functional hypogonadism are much more common in females, wherein physical, emotional or nutritional stressors can result in suppression of menses (functional hypothalamic amenorrhea) (Fourman and Fazeli 2015). Males appear to be much more resistant to hypothalamic suppression from either excessive exercise or energy deficits as only small series have been reported to date (Chavan et al. n.d.). Typically, such cases are restricted to patients with eating disorders (i.e. anorexia nervosa) or endurance athletes on highly very low-fat diets. A much more common form of functional hypogonadism results from hyperprolactinaemia suppressing hypothalamic GnRH secretion. Elevated serum prolactin levels may result from physiologic causes (e.g. stress, illness, sleep deprivation), pathophysiologic (i.e. prolactin-secreting tumour) or iatrogenic causes (i.e. medications) (Ajmal et al. 2014). Notably, dopamine negatively regulates prolactin while serotonin has a stimulatory effect on prolactin. Thus, antipsychotic medications that block dopamine action and anti-depressants (i.e. selective serotonin reuptake inhibitors, SSRIs) can cause elevated prolactin levels and may induce hypogonadism (Ajmal et al. 2014). Importantly, eugonadal function returns with the removal of the underlying cause of hyperprolactinaemia. A key component of identifying the root cause of hypogonadotropic hypogonadism is ruling out potential causes. This demands a detailed history taking with a careful medication review and biochemical assessment (Box 44.1).

44.5 Ageing and Testosterone Deficiency

Serum LH and FSH levels define hypo- and hypergonadotropic forms of hypogonadism. However, a certain percentage of men present in adulthood with low testosterone as well as signs and symptoms of hypogonadism (Table 44.1). These men often have elements of both presentations with both pituitary and testicular hyposecretion—thus mixed hypogonadism. This is characteristic of the presentation of many ageing men. There have been four key epidemiologic studies examining testosterone deficiency in ageing men (summarized in Dean et al. 2015): the Massachusetts Men's Aging Study (n > 1600, aged 40–70 years), Boston Area Community Health Survey (n > 1400, aged 30–79 years), Hypogonadism in men (n > 2100, aged >45 years) and the European Male Ageing Study (EMAS) (n > 3000, aged 40–79 years). These studies point to a progressive decline in serum T with age as well as alterations in sex hormone binding globulin (SHBG). Historically, a number of vague terms have been used to describe the age-related fall in serum T including male menopause, andropause, and androgen deficiency syndrome of the ageing male. Recently, more precise definitions have provided much-needed clarity to this phenomenon. EMAS was a multicentre European cohort study of years that defined "late-onset hypogonadism" (LOH) as at least three sexual symptoms (decreased sexual interest, morning erections and erectile dysfunction [ED]) in the setting of a total serum T level < 11 nmol/L (317 ng/dL) and free T < 220 pmol/L (Wu et al. 2010). Presently, a number of international organizations agree that LOH (the preferred European term) (Wang et al. 2008) and adult-onset hypogonadism (AOH, the term put forth by the Sexual Medicine Society of North America) (Khera et al. 2016) include both laboratory and symptom-based criteria.

Importantly, actual symptomatic testosterone deficiency occurs in a small minority of ageing men and is only in the range of 2–6% (Dean et al. 2015). Notably this can be largely attributed to comorbidities, and in particular obesity (described below) (Morgentaler et al. 2016). Moreover, EMAS investigators found that with age 2% of men had a primary hypogonadism and that approximately 10% had a compensated hypogonadism meaning that they were able to maintain normal serum T levels via increased pituitary LH secretion (Tajar et al. 2010). These men with primary and compensated hypogonadism were older than their eugonadal counterparts. Regardless of age, T therapy effectively resolves signs and symptoms of testosterone deficiency including libido and sexual function particularly when levels are <8 nmol/L (231 ng/dL) (Morgentaler et al. 2016). While older men are more prone to erythrocytosis and prostate problems than younger counterparts, these are not reasons for withholding T treatment if monitored appropriately (Aversa and Morgentaler 2015) (Box 44.1).

44.6 Obesity-Related Testosterone Deficiency

There are consistent data showing a negative correlation between obesity and T (free, albumin bound and total) regardless of age (Kelly and Jones 2015). Some have proposed that obesity is the most common cause of T deficiency in the developed world (Dean et al. 2015) as obesity is the single most powerful predictor (Tajar et al. 2010). Obese men with T deficiency often exhibit low-normal serum gonadotropins suggestive of a mixed cause. Importantly, it is reversible and studies using lifestyle modification (i.e. diet and exercise) or bariatric surgery show that the increase in serum T is proportional to the amount of weight loss (Kelly and Jones 2015). The relationship between T and fat (obesity) is bi-directional. For instance, T deficiency results in decreased lean muscle mass and increased fat mass, this increased fat mass spurs aromatase activity in the adipocytes, higher aromatase increases the conversion of T to oestradiol, thereby directly decreasing circulating T as well as indirectly via oestradiol-mediated suppression of GnRH secretion. This creates a vicious cycle. The exact mechanism has yet to be fully

elucidated. It is notable that the variety of contributing factors is diverse, ranging from excess aromatization to oestradiol and the subsequent suppressive effect of oestradiol on GnRH secretion to the inhibitory effects of leptin, adiponectin, and gut hormones ghrelin, peptide YY, the effects of pro-inflammatory adipocytokines (i.e. tumour necrosis factor alpha, interleukin 6) and physiologic stressors accompanying obesity (i.e. chronic disease, sleep apnoea, arthritis) (Kelly and Jones 2015).

It is widely known that obesity increases the risk for developing metabolic problems such as hypercholesterolemia and type 2 diabetes. Abdominal obesity (visceral) in particular is a major factor in the metabolic syndrome that includes a constellation of abnormalities (Alberti et al. 2009) that heighten metabolic and cardiovascular risk as well as all-cause mortality. Both large-scale studies and meta-analyses demonstrate that T deficiency is strongly linked with increased risk for developing obesity, the metabolic syndrome and type 2 diabetes (Khera et al. 2016). Therefore, it is prudent to take a two pronged approach to obesity-related hypogonadism: promote lifestyle modification to achieve weight loss and treat confirmed T deficiency. Nursing plays a key role in educating patients about health risks, identifying resources for enhancing self-management, coaching and guiding patients on lifestyle modification and evaluating adherence to treatment and providing positive reinforcement as patients work to meet their individual goals (Box 44.1).

44.7 Tumours

Tumours such as craniopharyngiomas, pituitary adenomas, gliomas, germinomas and meningiomas can cause secondary hypogonadism through different mechanisms. As space-occupying lesions, compression and destruction of the hypothalamic-pituitary region can impair GnRH-induced gonadotrophin secretion causing hypogonadism. Such lesions are more apt to perturb gonadotrophin secretion, and so these patients typically present with hypogonadism with normal adrenal and thyroid function. Alternatively, prolactin-secreting pituitary adenomas (prolactinomas) cause hyperprolactinaemia and suppress the neuroendocrine axis (Ross and Bhasin 2016). In adults, prolactinomas (pituitary adenomas) are the most frequent tumours causing hypogonadotropic hypogonadism.

44.8 Iatrogenic

In certain cases, hypogonadism may be secondary to medical intervention. This is typically an unwanted side effect of chemotherapy, radiation treatment, long-term glucocorticoid therapy, high-dose corticosteroid treatment or subsequent to narcotics use for chronic pain management. In contrast, T deficiency is the goal of androgen deprivation therapy (ADT) and is an alternative to surgical castration for the treatment of prostate cancer.

44.8.1 Post Chemotherapy or Radiation Therapy

Several different medical treatments may cause hypogonadism as an unwanted secondary effect including chemotherapy/radiation therapy, long-term glucocorticoid treatment and chronic opioid use for pain management (Ross and Bhasin 2016). The late effects of childhood cancer are reviewed extensively in an accompanying chapter yet it is worthwhile to note that hypogonadism and infertility are potential sequelae in adolescence and young adults (Dwyer et al. 2015). The late effects depend on multiple factors including sex, age and degree of pubertal development at the time of treatment, as well as the type of cancer and the specific therapeutic regimens employed (Rose et al. 2016). In particular, alkylating agents (e.g. mechlorethamine, cyclophosphamide, ifosfamide, procarbazine, busulfan, melphalan and cisplatin) and platinum compounds used in chemotherapeutic regimens can be particularly damaging to the gonads (Kenney et al. 2012). The hypothalamus is more sensitive to irradiation than the pituitary. Head

and/or brain radiotherapy (≥30 Gy) can result in secondary hypogonadism and pelvic irradiation (≥2 Gy) often causes primary gonadal failure and patients are invariably infertile following doses exceeding 4–6 Gy (Rose et al. 2016; Kenney et al. 2012). Broadly speaking, testes are more sensitive to damage from adjuvant treatment compared to ovaries (Kenney et al. 2012). Given the impact that T deficiency can have on bone health, sexual function, psychological well-being and quality of life of these patients warrant ongoing surveillance and a planned purposeful transition to adult endocrine care (Dwyer et al. 2015) (Box 44.1).

44.8.2 Medications

Chronic glucocorticoid treatment or high-dose corticosteroids may lead to hypogonadism (Ross and Bhasin 2016; Rose et al. 2016). The absence of a compensatory increase in LH among patients on long-term glucocorticoid therapy suggests that this acts via a central mechanism. Chronic opiate use for pain management (or methadone treatment for narcotic addiction) causes T deficiency (De Maddalena et al. 2012). Like the functional medication-induced hypogonadism caused by antipsychotics and SSRIs (see Sect. 43.1.4), opioid-induced hypogonadism is reversible with cessation of treatment. However, it can be a particularly challenging form of reversible hypogonadism to treat as the narcotics are typically essential for pain management. These medication-induced causes of hypogonadism underscore the necessity of careful medical history taking and medication review.

44.8.3 Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is an approach for treating prostate cancer that medically induces hypogonadism to reduce androgen action on the prostate. Long-acting GnRH analogues are used to block GnRH secretion resulting in biochemical castration. By definition, this causes T deficiency with its corresponding symptoms (Table 44.1) as well as a number of adverse effects including loss of bone density and lean muscle mass, increased risk for developing type 2 diabetes and cardiovascular disease and diminished quality of life (Ostergren et al. 2016). Men receiving ADT should be closely monitored for complications and appropriate measures including exercise can be employed to mitigate the fatigue, body composition changes, and maintain function during treatment (Ostergren et al. 2016). Nurses can play a key role in the ongoing care of these patients by assessing changing in status, discussing how therapy is impacting quality of life (including sexual function) as well as planning, implementing and encouraging physical exercise (Box 44.1).

44.9 Systemic Disease

Stress from acute illness can suppress the HPG axis causing temporary periods of reversible hypogonadism. Surgery, burn injuries, myocardial infarction, stroke and sepsis have all been noted to suppress the HPG axis (Kalyani et al. 2007). When stress becomes prolonged as in the case of chronic illness, central suppression of GnRH-induced gonadotrophin secretion can produce hypogonadotropic hypogonadism. Hypogonadism is frequently observed in patients with chronic obstructive pulmonary disease (approximately 40% of cases) and human immunodeficiency virus (HIV) infection (between 30 and 50%). Androgen deficiency is also associated with cancer, rheumatoid arthritis, sickle cell disease, chronic liver and renal disease as well as diabetes (Kalyani et al. 2007). Notably, T deficiency is observed in 50% of obese men with diabetes (Kelly and Jones 2015). While current recommendations do not call for systematic screening of men with diabetes for T deficiency (Bhasin et al. 2010), the endocrine nurse should be aware of prevalence among obese men with diabetes and can play an integral role in the ongoing assessment and monitoring for symptoms of hypogonadism (Table 44.1).

44.10 Endocrine Disrupting Chemicals

Endocrine disrupting chemicals (EDCs) are substances in foods, consumer products and the environment that interfere with hormone action and disrupt health or reproduction (Diamanti-Kandarakis et al. 2009). There is mounting concern that EDCs pose a significant public health concern. EDCs are heterogeneous and widespread in the environment, consumer goods and food. Many synthetic chemicals and solvents as well as their byproducts contain EDCs, i.e. dioxins or polychlorinated biphenyls (PCBs). Some pharmaceutical agents include harmful substances (i.e. diethylstilbestrol, DES) as do plasticizing agents (phthalates). Environmental and food exposures may result from pesticides (dichlorodiphenyltrichloroethane, DDT), fungicides (i.e. vinclozolin) or even in naturally occurring chemicals in some foods (i.e. phytoestrogens) (Diamanti-Kandarakis et al. 2009). EDCs may exert their effect through varied mechanisms including direct action on hormone receptors (i.e. diethylstilbestrol [DES] acting on oestrogen receptor α, bisphenol A [BPA] acting on oestrogen receptor β), direct/indirect interference with hormone synthesis or metabolism, altering hormone receptor expression, or by epigenetic mechanisms (Sweeney et al. 2015).

Interestingly, epigenetic modifications (i.e. DNA methylation, non-coding RNAs, histone modification, altered chromatin structure) can be passed via sperm resulting in transgenerational inheritance of diseases that include behavioural effects, obesity and reproductive disorders (Skinner 2016). There is growing evidence for early life origins of some adult diseases. The premise is that the foetal environment and environmental exposures can alter cellular, stem cell and tissue development predisposing one to obesity or reproductive disorders later in life. Lifestyle factors, notably, maternal smoking has been linked with preterm and low birth-weight infants and these children are at increased risk for developing obesity later in life (Heindel et al. 2015). Moreover, some have posited that early exposure to wide ranging environmental chemicals (i.e. bisphenol A, flame retardants, phthalates) and so-called "obesogens" predispose individuals to obesity and have helped fuel the growing obesity epidemic (reviewed in (Heindel et al. 2015)). Thus, it is tempting to speculate that such obesogen exposures could indirectly contribute to male T deficiency via obesity.

Epidemiologic data from the past 50 years demonstrate progressively earlier pubertal onset and falling fertility rates with concomitant decreasing sperm quality as well as increasing rates of cryptorchidism, hypospadias and testicular germ cell cancer (Juul et al. 2014). The Testicular Dysgenesis Syndrome (TDS) has been proposed as a potential explanation for these observations (Juul et al. 2014). This model posits that adverse environmental exposures combined with genetic defects, and the foetal environment (i.e. placental function, intrauterine growth disorders) influence testicular development and function later in life. Epidemiologic and clinical data as well as research in animal models provide support to this model. However, research clearly identifying causality between EDCs and human developmental defects and disease (i.e. cancer) is limited by a number of methodological challenges. In particular, real-world conditions are difficult to replicate using cell-based or animal models given inter-species differences and the ubiquity of EDCs (Sweeney et al. 2015). In the laboratory environment, one can study the effects of a single substance while strictly controlling the route of administration, dosage and the duration of exposure. However, this is quite different from a real-life context in which age, developmental stage, mixtures of exposures and latency from exposure likely play significant contributing roles. Certainly, more research and scientific evidence is needed to elucidate the precise mechanisms and risks associated with EDCs. In the meantime, a cautionary and preventive approach to limiting human exposure to EDCs seems warranted and is advocated (Diamanti-Kandarakis et al. 2009).

44.11 Conclusions

Congenital and acquired disorders of the hypothalamus, pituitary or testes can cause androgen deficiency eliciting signs and symptoms of hypo-

gonadism. Measuring serum gonadotrophins is a means to dissect the axis separating primary from secondary forms of hypogonadism. T deficiency can have deleterious effects on bone health, places men at higher cardio-metabolic risk and can negatively impact well-being and quality of life. Hypogonadism can be effectively managed, yet treatment should only be initiated after appropriate evaluation and unequivocal biochemical confirmation on at least two morning measurements (Bhasin et al. 2010). Endocrine nurses can play an important role for patients with hypogonadism by helping to provide comprehensive coordinated care and promoting health and well-being.

References

Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review. Psychosomatics. 2014;55(1):29–36.

Aksglaede L, Juul A. Testicular function and fertility in men with Klinefelter syndrome: a review. Eur J Endocrinol. 2013;168(4):R67–76.

Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.

Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Investig. 2015;38(12):1249–63.

Aversa A, Morgentaler A. The practical management of testosterone deficiency in men. Nat Rev Urol. 2015;12(11):641–50.

Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. J Med Genet. 2011;48(5):334–42.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.

Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547–64.

Brain CE, Creighton SM, Mushtaq I, Carmichael PA, Barnicoat A, Honour JW, et al. Holistic management of DSD. Best Pract Res Clin Endocrinol Metab. 2010;24(2):335–54.

Brioude F, Bouligand J, Trabado S, Francou B, Salenave S, Kamenicky P, et al. Non-syndromic congenital hypogonadotropic hypogonadism: clinical presentation and genotype-phenotype relationships. Eur J Endocrinol. 2010;162(5):835–51.

Castinetti F, Reynaud R, Saveanu A, Jullien N, Quentien MH, Rochette C, et al. MECHANISMS IN ENDOCRINOLOGY: an update in the genetic aetiologies of combined pituitary hormone deficiency. Eur J Endocrinol. 2016;174(6):R239–47.

Chan YM. A needle in a haystack: mutations in GNRH1 as a rare cause of isolated GnRH deficiency. Mol Cell Endocrinol. 2011;346(1-2):51–6.

Chan E, Wayne C, Nasr A, Resource FCAPSE-B. Ideal timing of orchiopexy: a systematic review. Pediatr Surg Int. 2014;30(1):87–97.

Chavan N, Dwyer A, Keefe KW, Sykiotis G, Plummer L, Seminara S, et al. Male functional hypogonadotropic hypogonadism: a distinct clinical entity? 92nd Annual Meeting of the Endocrine Society; San Diego, USA. 2010.

De Maddalena C, Bellini M, Berra M, Meriggiola MC, Aloisi AM. Opioid-induced hypogonadism: why and how to treat it. Pain Physician. 2012;15(3 Suppl):ES111–8.

Deal CL, Tony M, Hoybye C, Allen DB, Tauber M, Christiansen JS, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013;98(6):E1072–87.

Dean JD, McMahon CG, Guay AT, Morgentaler A, Althof SE, Becher EF, et al. The International Society for Sexual Medicine's process of care for the assessment and management of testosterone deficiency in adult men. J Sex Med. 2015;12(8):1660–86.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30(4):293–342.

Dwyer AA, Hayes FJ, Plummer L, Pitteloud N, Crowley WF Jr. The long-term clinical follow-up and natural history of men with adult-onset idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2010;95(9):4235–43.

Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis. 2014;9:83.

Dwyer AA, Phan-Hug F, Hauschild M, Elowe-Gruau E, Pitteloud N. TRANSITION IN ENDOCRINOLOGY:

hypogonadism in adolescence. Eur J Endocrinol. 2015;173(1):R15–24.
Dwyer AA, Raivio T, Pitteloud N. Management of endocrine disease: reversible hypogonadotropic hypogonadism. Eur J Endocrinol. 2016;174(6): R267–74.
Fourman LT, Fazeli PK. Neuroendocrine causes of amenorrhea--an update. J Clin Endocrinol Metab. 2015;100(3):812–24.
Groth KA, Skakkebaek A, Host C, Gravholt CH, review BAC. Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30.
Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. Nat Rev Endocrinol. 2015;11(11): 653–61.
Hiort O, Birnbaum W, Marshall L, Wunsch L, Werner R, Schroder T, et al. Management of disorders of sex development. Nat Rev Endocrinol. 2014;10(9): 520–9.
Hughes IA, Houk C, Ahmed SF, Lee PA, Group LC, Group EC. Consensus statement on management of intersex disorders. Arch Dis Child. 2006;91(7): 554–63.
Jadhav U, Harris RM, Jameson JL. Hypogonadotropic hypogonadism in subjects with DAX1 mutations. Mol Cell Endocrinol. 2011;346(1-2):65–73.
Juul A, Almstrup K, Andersson AM, Jensen TK, Jorgensen N, Main KM, et al. Possible fetal determinants of male infertility. Nat Rev Endocrinol. 2014;10(9): 553–62.
Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. Endocrinol Metab Clin N Am. 2007;36(2):333–48.
Kelly DM, Jones TH. Testosterone and obesity. Obesity Rev. 2015;16(7):581–606.
Kenney LB, Cohen LE, Shnorhavorian M, Metzger ML, Lockart B, Hijiya N, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(27):3408–16.
Khan SA, Muhammad N, Khan MA, Kamal A, Rehman ZU, Khan S. Genetics of human Bardet-Biedl syndrome, an updates. Clin Genet. 2016;90(1): 3–15.
Khera M, Broderick GA, Carson CC 3rd, Dobs AS, Faraday MM, Goldstein I, et al. Adult-onset hypogonadism. Mayo Clin Proc. 2016;91(7): 908–26.
Lee PA, Houk CP. Cryptorchidism. Curr Opin Endocrinol Diabetes Obes. 2013;20(3):210–6.
Mao J, Xu H, Wang X, Huang B, Liu Z, Zhen J, et al. Congenital combined pituitary hormone deficiency patients have better responses to gonadotrophin-induced spermatogenesis than idiopathic hypogonadotropic hypogonadism patients. Hum Reprod. 2015;30(9):2031–7.
Millar AC, Lau AN, Tomlinson G, Kraguljac A, Simel DL, Detsky AS, et al. Predicting low testosterone in aging men: a systematic review. CMAJ. 2016;188(13):E321–30.
Morgentaler A, Zitzmann M, Traish AM, Fox AW, Jones TH, Maggi M, et al. Fundamental concepts regarding testosterone deficiency and treatment: international expert consensus resolutions. Mayo Clin Proc. 2016;91(7):881–96.
Nachtigall LB, Boepple PA, Pralong FP, Crowley WF Jr. Adult-onset idiopathic hypogonadotropic hypogonadism--a treatable form of male infertility. N Engl J Med. 1997;336(6):410–5.
Nieschlag E, Vorona E. MECHANISMS IN ENDOCRINOLOGY: Medical consequences of doping with anabolic androgenic steroids: effects on reproductive functions. Eur J Endocrinol. 2015;173(2):R47–58.
Ostergren PB, Kistorp C, Bennedbaek FN, Faber J, Sonksen J, Fode M. The use of exercise interventions to overcome adverse effects of androgen deprivation therapy. Nat Rev Urol. 2016;13(6):353–64.
Raivio T, Avbelj M, McCabe MJ, Romero CJ, Dwyer AA, Tommiska J, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab. 2012;97(4):E694–9.
Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology. 2014;2(6):794–808.
Ritzen EM, Bergh A, Bjerknes R, Christiansen P, Cortes D, Haugen SE, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr. 2007;96(5):638–43.
Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE, et al. Late endocrine effects of childhood cancer. Nat Rev Endocrinol. 2016;12(6): 319–36.
Ross A, Bhasin S. Hypogonadism: its prevalence and diagnosis. Urol Clin North Am. 2016;43(2): 163–76.
Ryabets-Lienhard A, Stewart C, Borchert M, Geffner ME. The optic nerve hypoplasia spectrum: review of the literature and clinical guidelines. Adv Pediatr Infect Dis. 2016;63(1):127–46.
Salvi R, Pralong FP. Molecular characterization and phenotypic expression of mutations in genes for gonadotropins and their receptors in humans. Front Horm Res. 2010;39:1–12.
Skakkebaek A, Wallentin M, Gravholt CH. Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments. Curr Opin Endocrinol Diabetes Obes. 2015;22(3): 209–16.
Skinner MK. Endocrine disruptors in 2015: epigenetic transgenerational inheritance. Nat Rev Endocrinol. 2016;12(2):68–70.
Stamou MI, Cox KH, Crowley WF Jr. Discovering genes essential to the hypothalamic regulation of human reproduction using a human disease model: adjusting to life in the "-Omics" era. Endocr Rev. 2015;36(6):603–21.
Sweeney MF, Hasan N, Soto AM, Sonnenschein C. Environmental endocrine disruptors: effects on the

human male reproductive system. Rev Endocr Metab Disord. 2015;16(4):341–57.
Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab. 2010;95(4):1810–8.
Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2016;5(7):544–53.
Turriff A, Levy HP, Biesecker B. Factors associated with adaptation to Klinefelter syndrome: the experience of adolescents and adults. Patient Educ Couns. 2015;98(1):90–5.
Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008;159(5):507–14.
Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35.

Key Reading

1. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59. https://doi.org/10.1210/jc.2009-2354.
2. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, Dwyer AA, Giacobini P, Hardelin J-P, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, document YJE c. European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nat Rev. Endocrinol. 2015;11(9):547–64. https://doi.org/10.1038/nrendo.2015.112.
3. Groth KA, Skakkebæk A, Høst C, Gravholt CH, review BAC. Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30. https://doi.org/10.1210/jc.2012-2382.
4. Kelly DM, Jones TH. Testosterone and obesity. Obes Rev. 2015;16(7):581–606. https://doi.org/10.1111/obr.12282. Epub 2015 May 15
5. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30(4):293–342. https://doi.org/10.1210/er.2009-0002.

45 Evaluation of Endocrine Disorders of the Hypothalamic-Pituitary-Gonadal (HPG) Axis

Andrew A. Dwyer and Frances J. Hayes

Contents

45.1 **Introduction** 873

45.2 **Medical History** 873

45.3 **Physical Examination** 875
45.3.1 Approach to the Patient 875
45.3.2 Patients with Absent or Incomplete Puberty 876
45.3.3 Clinical Evaluation Related to Complaints of Sexual Dysfunction and/or Infertility 876
45.3.4 Examining the Penis and Testes 877

45.4 **Laboratory Investigations** 878

45.5 **Semen Analysis** 879

45.6 **Imaging Studies** 879

45.7 **Other Investigations** 880

45.8 **Conclusions** 882

References 882

Abstract

Among male adolescents, lack of spontaneous pubertal development is a common reason for presenting for endocrine evaluation. Among adult men, symptoms of androgen deficiency, sexual dysfunction and/or infertility are chief complaints that often motivate patients to seek reproductive endocrine consultation. Obtaining a comprehensive medical history, performing a clinical examination and conducting laboratory diagnostic testing are cornerstones for evaluating the hypothalamic-pituitary-gonadal (HPG) axis. Sexuality and

A. A. Dwyer (✉)
William F. Connell School of Nursing, Chesnut Hill, MA, USA

Boston College, Chesnut Hill, MA, USA
e-mail: Andrew.dwyer@bc.edu

F. J. Hayes
Endocrine Division, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA
e-mail: fhayes@mgh.harvard.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_45

reproduction can be sensitive topics and some patients may find it challenging to discuss such matters. Herein we present best nursing practices for history taking and review the clinical competencies for physical examination. The rationale and value of specific hormone assays and the role of stimulation testing will be reviewed in relation to clinical decision-making as well as the appropriate use of imaging studies. Male reproductive disorders may span several domains including endocrinology, andrology, urology and genetics. Thus, appropriate referrals and coordination of care are important factors for management. This chapter is a mini-review for endocrine nurses providing a synopsis of the approach to and evaluation of patients with hypogonadism, sexual dysfunction and infertility. Particular emphasis is placed on providing comprehensive coordinated care that includes patient education, anticipatory guidance and addressing patients' psychosocial concerns.

Keywords

Androgen deficiency · Gonadotrophins Hypogonadism · Infertility · Sexual dysfunction · Testes · Testosterone

Abbreviations

BMI	Body mass index
CBAVD	Congenital bilateral absence of the vas deferens
CDGP	Constitutional delay of growth and puberty
CFTR	Cystic fibrosis transmembrane regulator
CGH	Comparative genomic hybridization
CHH	Congenital hypogonadotrophic hypogonadism
CT	Computed tomography
DSD	Disorder of sex development
DXA	Dual X-ray absorptiometry
ED	Erectile dysfunction
EMAS	European Male Ageing Study
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin-releasing hormone
HbA1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
HPG	Hypothalamic-pituitary-gonadal
IPSS	International Prostate Symptom Score
LH	Luteinizing hormone
LOH	Late-onset hypogonadism
LUTS	Lower urinary tract symptoms
MRI	Magnetic resonance imaging
SHBG	Sex hormone binding globulin
T	Testosterone
TV	Testicular volume

Key Terms

- **Hypogonadism:** The combination of repeated, unequivocally low serum testosterone levels with clinical signs and symptoms of androgen deficiency.
- **Sexual dysfunction:** The inability to engage in normal, pleasurable sexual activity resulting from diminished desire (libido), arousal difficulties (erectile dysfunction) and/or problems with orgasm (ejaculation).
- **Infertility:** The inability to achieve pregnancy following regular unprotected intercourse for 12 months. Factors may be male, female or mixed (both) in origin.
- **Testicular volume:** A measure of testicular size. Volume predominantly reflects the development of the seminiferous tubules and is an important predictor of fertility potential. It is most frequently measured via Prader orchidometer or via calculation of ultrasound measurement in three planes.

Key Points

- The clinical presentation of androgen deficiency differs according to the underlying cause, age of onset and prior treatment(s).
- A thorough diagnostic evaluation is warranted prior to initiating testosterone replacement therapy. The decision to initiate treatment should be based on at

least two low morning serum testosterone levels and signs/symptoms of testosterone deficiency.
- Regardless of aetiology, hypogonadism, sexual dysfunction and infertility can severely impact quality of life. Nursing assessment should include evaluation of psychological and interpersonal aspects.
- Endocrine nurses can play an important role in providing clear patient communication to set appropriate expectations, effectively counsel and engage them in shared decision-making.

45.1 Introduction

The evaluation of the hypothalamic-pituitary-gonadal (HPG) axis is guided by the presenting symptoms of the patient. Therefore, a significant part of a consultation includes a careful review of systems, taking a detailed history and reviewing medications. Findings from a focused clinical examination can provide key additional information yet diagnosing endocrinologic disorders is largely based on serum hormone measurement that may be complemented by dynamic endocrine testing and imaging studies. This chapter provides the endocrine nurse with an overview of the approach to evaluating male patients presenting with complaints of hypogonadism, sexual dysfunction and/or infertility. This will include a synthesis of best practices for history taking and eliciting symptoms, a summary of skills needed to identify clinical signs on examination, a discussion of clinical judgement and decision-making related to diagnostic testing, and a review of elements contributing to comprehensive coordinated nursing care of these patients.

45.2 Medical History

The medical history is a key clinical tool that serves two important functions. First, it is typically the initial patient interaction and the first step in developing a therapeutic relationship, thus setting the tone for subsequent interactions. Second, it provides essential information on the chief complaint and guides subsequent aspects of the evaluation. History taking is a structured process following a certain logical progression beginning with open-ended questions to elicit the chief complaint and the chronology of the present problem and their reason for seeking care. While it seems completely obvious, it is worthwhile to underscore that common courtesy (i.e. introducing yourself), having good eye contact and active listening are important for developing trust (Ball et al. 2014; Keller and Carroll 1994; Brega et al. 2015) (Box 45.1).

Box 45.1 Approach to Fostering Effective Communication with Patients

- Be courteous, introduce yourself to the patient and any others accompanying them
- Ensure physical comfort for the patient in a quiet, private setting
- Take the history with the patient fully clothed
- Ask the patient about their reason for the consultation—don't simply assume that you know
- Make eye contact, don't let your face be obscured by a computer monitor or paper chart.
- Begin the encounter with open-ended questions and progress towards more directed questioning
- Try to avoid leading questions
- Use simple language
- Show empathy
- Use active listening techniques (i.e. eye contact, nodding, re-framing statements)
- Keep a neutral tone, avoid being judgemental
- Respect silent pauses, try not to interrupt unless necessary
- Do not trivialize any concerns or complaints

Box 45.1 (continued)

- For sensitive topics,
  - don't apologize
  - be direct
  - use clear language (i.e. no slang)
  - encourage them to be open and honest
  - affirm confidentiality
- Inquire how the present condition is making them feel, if it is causing them stress or impacting their quality of life
- Provide a brief summary at the end and give the patient the opportunity to elaborate or correct any points

These practices can help put patients at ease and facilitate discussion of sexuality and reproduction.

Frequent reasons for presenting for reproductive endocrine consultation include absent or incomplete puberty in adolescents (Sedlmeyer and Palmert 2002), sub-fertility in adult men (Anawalt 2013) and symptoms of androgen deficiency in older adults (Khera et al. 2016). Hypogonadism can contribute to all of these situations yet the clinical presentation depends largely on the age of onset, the severity of androgen deficiency, rapidity of onset, as well as genetic factors. A number of questionnaires have been developed to assess symptoms of hypogonadism. However, the currently available instruments lack specificity and thus are not recommended for use as a screening tool (Bhasin et al. 2010; Dean et al. 2015). Rather, a detailed medical and family history as well as a careful review of symptoms is required. Medical history should include attention to any congenital defects, growth and development, pubertal history as well as any medical problems, diagnoses and chronic health problems, surgeries and medications (including vitamins and nutritional supplements). Findings will help direct subsequent clinical and laboratory inquiry. For instance, midline defects, cryptorchidism and micropenis can be associated with congenital hypogonadotrophic hypogonadism (CHH) (Boehm et al. 2015) and learning disabilities and scholastic problems may be manifestations of Klinefelter syndrome (Skakkebaek et al. 2015). A detailed medication review is essential as a variety of medications and illicit drugs can contribute to developing hypogonadism and erectile dysfunction (ED). Additionally, probing social history may provide clues for potential contributing lifestyle factors such as illicit drug use, high alcohol consumption, tobacco use, stress or excessive exercise that can disrupt the reproductive endocrine axis function (Table 45.1) (Bhasin

Table 45.1 Conditions and medications implicated in men's reproductive health (Bhasin et al. 2010; Dean et al. 2015; Foote et al. 2015; Young 2012)

Androgen deficiency	Erectile dysfunction	Decreased semen quality
Associated factors		
Obesity Metabolic syndrome Diabetes HIV infection Sickle cell disease Eating disorders	Obesity Metabolic syndrome Diabetes Hypertension/CV disease Hyperlipidemia Androgen deficiency Lower urinary tract symptoms Depression Tobacco use	Obesity Tobacco use Heavy alcohol use
Medications and drugs		
Opioids Glucocorticoids 5-aplha reductase inhibitors, Sulfasalazine GnRH agonists (androgen deprivation therapy) Spironolactone Ketoconazole Anabolic androgen abuse Marijuana	Antidepressants Beta blockers Aldosterone receptor antagonists Thiazide diuretics	antidepressants anabolic androgen abuse marijuana

et al. 2010; Dean et al. 2015; McCabe et al. 2016; Tournaye et al. 2016a).

Family history is an important contributing factor and construction of a genogram can be particularly useful for visualizing patterns within families (Au et al. 2011). Questions about infertility in the family, difficulty conceiving, miscarriages, midline defects, chronic diseases, delayed puberty or so-called "late-bloomers" and abnormal or lack of sense of smell (anosmia) are important points to elicit. Consanguinity (when members of the family are related by blood) is not taboo in all cultures and this should be assessed using straightforward direct questioning. Notably, pubertal timing has a strong hereditary component as 50–75% of patients with delayed puberty have a family history (Wehkalampi et al. 2008). Interestingly, family pedigrees of patients with CHH are enriched for delayed puberty and recent genetic studies have begun to unravel the genetic contribution to pubertal timing (Boehm et al. 2015). However, it still remains clinically challenging to differentiate common causes of delayed puberty (i.e. constitutional delay of growth and puberty, CDGP) from much less common forms of permanent hypogonadism such as CHH (discussed in detail later in this chapter).

Lastly, an age-appropriate review of systems is effective for evaluating general health and identifying potential underlying problems. In reviewing the genito-urinary system, it is important to assess for lower urinary tract symptoms (LUTS) as these symptoms are closely associated with erectile dysfunction (Seftel et al. 2013). Using a validated instrument such as the International Prostate Symptom Score (IPSS) can be useful in quantifying the degree and severity of symptoms experienced by the patient. Sexual dysfunction warrants specific inquiry including assessing for changes in sexual desire (libido), difficulties achieving or maintaining an erection (erectile dysfunction [ED]) and problems with ejaculation, as well as for eliciting other signs and symptoms suggestive of androgen deficiency that warrant hormonal screening (Bhasin et al. 2010).

The Endocrine Society Clinical Practice Guideline (Bhasin et al. 2010) identifies a range of patient symptoms associated with androgen deficiency, some of which are considered to be more specific (See Chap. 44, Table 44.1). Importantly, the correlation between signs, symptoms and serum testosterone (T) levels is relatively weak (Millar et al. 2016). However, some general principles exist for middle-aged and older men as symptoms typically become increasingly prevalent with lower serum T levels such as decreased libido and vigour (T < 15 nmol/L), depressive symptoms and type 2 diabetes (<10 nmol/L) and ED (<8 nmol/L) (Zitzmann et al. 2006). The European Male Ageing Study (EMAS) used a systematic investigation of a large random sampling of ageing men from the general population to define "late-onset hypogonadism" (LOH) as at least three sexual symptoms in the setting of low serum total and free T (<11 nmol/L [317 ng/dL], <220 pmol/L respectively). This study provides quite good evidence that three symptoms in particular (decreased sexual interest, decreased morning erections, ED) are quite reliable for identifying testosterone deficiency among middle-aged and older men (Wu et al. 2010).

45.3 Physical Examination

45.3.1 Approach to the Patient

Depending on role and scope of practice, nurses in endocrinology may perform a physical assessment. The proper clinical assessment of pubertal disorders, signs/symptoms of androgen deficiency and/or sub-fertility requires the clinician to be knowledgeable and competent in specific skills and techniques (Box 45.2).

Box 45.2 Clinical Skills Related to Men's Reproductive Health

Taking a comprehensive medical history
Conducting a detailed review of systems
Recording current and past medications

Box 45.2 (continued)

Accurately assessing:

- height and weight
- body mass index (BMI)
- waist to hip ratio (WHR)
- eunuchoidal proportions

Differentiating lipomastia from gynaecomastia
Performing a genital examination:

- Tanner staging
- testicular exam
- testicular volume (Prader orchidometer)
- stretched penis length

Prostate examination

Before going into specific aspects of the clinical examination, a few points on approach merit comment. One of the central aspects of the focused examination is the genital exam. This may be anxiety provoking for many patients. Adolescents in particular are likely to feel nervous and uncomfortable about this part of the consultation. Providing patient-centred care demands that one is sensitive to these patient concerns. It is important for the clinician to explain briefly, yet clearly what will be done during the exam and explain any materials (i.e. orchidometer) that will be involved. Additionally, washing your hands in warm water is helpful as performing the exam with cold hands may be uncomfortable for patients. Occasionally patients may develop an erection during a genital exam. This can be an involuntary response to touch in the genital area and does not necessarily indicate sexual arousal. However it may be embarrassing for the patient and may make some clinicians uncomfortable. Should this situation arise, one should maintain a professional attitude and complete the exam without specific comment. Being direct, using clear professional language, maintaining a neutral expression and avoiding jokes will help patients maintain their dignity.

45.3.2 Patients with Absent or Incomplete Puberty

The specific components of a focused examination will be based on findings revealed during the history and review of systems. Examining adolescents and young adults typically focuses on identifying the cause of failure to initiate or complete puberty. Any obvious clinical signs suggestive of a syndromic presentation should be noted as this may warrant further molecular investigation (i.e. genetic or cytogenetic screening) (Boehm et al. 2015). Accurately measuring height (using a stadiometer) and weight to calculate body mass index (BMI) is essential and provides insight in relation to predicted mid-parental height (Foote et al. 2015). Additionally, a skeletal survey is useful for identifying scoliosis (abnormal curvature of the spine) as well as the presence of any anomalies. The body habitus should be assessed for eunuchoidal proportions as evidenced by an armspan exceeding height by >7 cm or an upper: lower segment ratio <0.9 (upper segment: symphysis pubis to crown, lower segment: symphysis pubis to floor) (Boehm et al. 2015). Visual inspection is used to identify virilization and other signs of puberty. Breast tissue may need to be palpated to differentiate lipomastia from true gynaecomastia (i.e. disc-like shaped glandular tissue under the areola) resulting from imbalanced T and oestradiol levels. Both eunuchoidal proportions and gynaecomastia are common clinical findings among patients with Klinefelter syndrome (Groth et al. 2013). Synkinesia, mirror movements of the contralateral hand/foot, is a neurologic finding observed in some patients with CHH as is anosmia (absent sense of smell) that may be elicited in the history and confirmed via cranial nerve exam or formal smell testing. Anosmia is a "red flag" sign suggesting permanent hypogonadism (i.e. Kallmann syndrome = CHH + anosmia) (Boehm et al. 2015).

45.3.3 Clinical Evaluation Related to Complaints of Sexual Dysfunction and/or Infertility

Erectile dysfunction is associated with a number of factors including psychological (stress, anxiety, depression) as well as obesity, the metabolic syndrome, hypertension and cardiovascular disease

(Table 45.1) (McCabe et al. 2016). Accordingly, physical examination should include assessment of central adiposity (assessed by waist circumference), survey for signs of insulin resistance (i.e. acanthosis nigricans), blood pressure, peripheral pulses and reflexes to assess for possible neurologic aetiology that could underlie ejaculatory dysfunction.

45.3.4 Examining the Penis and Testes

Arguably, the most important part of the physical assessment for a reproductive endocrine consultation is the genital (testicular) exam (Anawalt 2013; Tournaye et al. 2016a; Young 2012). First, visual inspection of the character and distribution of pubic hair should be done to determine Tanner staging (P1–P5). Many young men with CHH will exhibit Tanner II to III pubic hair as a result of adrenarche and the resulting production of weak adrenal androgens. However, gonadal sex steroids are needed for full pubic hair development (i.e. Tanner V) (Palmert and Dunkel 2012). Evidence of scars may indicate prior surgery (i.e. orchiopexy). The penis should be examined for placement of the meatus and assess for hypospadias—a condition when the urethra opens on the ventral side of the penis rather than at the tip. Hypospadias may be glanular, mid-shaft, or penoscrotal and falls within the spectrum of disorder of sex development (DSD). In obese patients, the suprapubic fat pad may obscure the penis and may need to be manipulated to perform a proper examination. Any lesions or ulcerations should be noted and if the penis appears atypically small, a stretched penis length should be measured and compared to age-based norms (reviewed in (Hatipoglu and Kurtoglu 2013)).

Men presenting for evaluation of infertility should have the presence of the *vasa deferentia* (spermatic cord) confirmed by palpation as congenital bilateral absence of the vas deferens (CBAVD) is a cause of azoospermia associated with cystic fibrosis (Fig. 45.1) (Tournaye et al. 2016a).

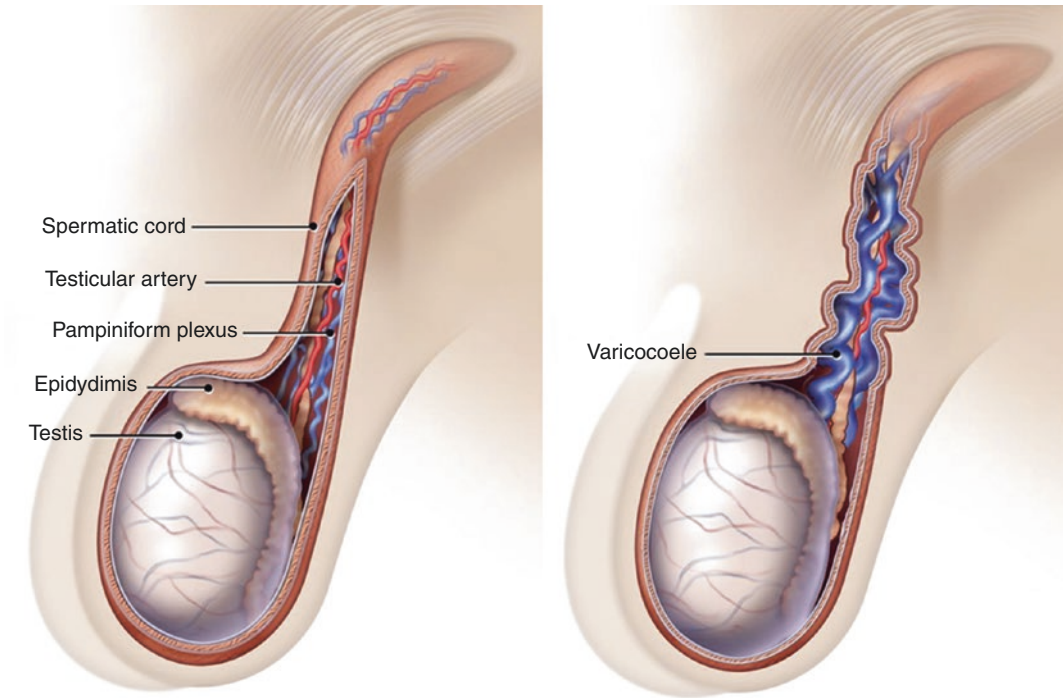


Fig. 45.1 Examination for the vasa deferentia and large varicoceles. The vasa extend from the base of the epididymi that lie posterior to each testis and run cephalad in the spermatic cord. The vas feels like a pull cord inside of the pliable tubular spermatic cord. Varicoceles feel like a "bag of worms" and enlarge when the patient stands. Published in: Bradley D. Anawalt; *The Journal of Clinical Endocrinology & Metabolism* **2013,** 98, 3532–3542. DOI: https://doi.org/10.1210/jc.2012-2400. Copyright © 2013

The spermatic vein should be palpated with the patient standing to assess for dilatation of the pampiniform venous plexus (indicated by a texture comparable to a bag of worms) indicating varicocele. Compared to the overall population, varicocele is more frequently observed in men presenting for infertility compared to the general population (40% vs. 12%) (Tournaye et al. 2016b). The epididymis and testes should be palpated with particular attention to any masses, swelling, asymmetry and testicular volume measured using a Prader orchidometer (Boehm et al. 2015). Small, firm testes (<6 mL) is a hallmark sign of Klinefelter syndrome (Groth et al. 2013). In situations of inguinal testes, hydrocele, epididymitis or thick scrotal skin, an ultrasound is useful for assessing the testes (Lotti and Maggi 2015). Testicular examination can be challenging in men with a highly reactive cremasteric reflex—a response causing the testes to retract (this response is typically absent in cases of testicular torsion). To facilitate examination, examination can be enabled by having the patient support himself on his elbows and bend his knees (i.e. mimicking frog legs) during the exam. Testicular volume (TV) of 4 mL or larger indicates onset of puberty (Palmert and Dunkel 2012) and the 50th percentile TV for an 18 year-old male is approximately 25 mL (Goede et al. 2011). Using the puberty normogram (Joustra et al. 2015) can be a valuable tool for gauging if an adolescent has a significant delay (i.e. 3+ SDs form normal) in testicular development consistent with CHH (see Chap. 44).

45.4 Laboratory Investigations

The Endocrine Society recommends against broad screening of the general population for androgen deficiency and has identified groups of patients warranting evaluation (Bhasin et al. 2010). In particular, men with sexual dysfunction, infertility, gynaecomastia, sellar mass (or prior sellar irradiation), human immunodeficiency virus (HIV) positive men with weight loss, osteoporosis (or low-trauma fracture) as well as men on certain medications are at increased risk of being androgen deficient (Bhasin et al. 2010). Further, in the setting of signs and symptoms of testosterone deficiency (See Chap. X, Table 1 in Sect. X) serum T measurement is warranted. While liquid chromatography-tandem mass spectroscopy is the gold standard for measurement, most clinical settings utilize commercially available immunoassay platforms (Taylor et al. 2015). As the initial screen, total T should be measured in a morning sample (i.e. 08:00–11:00) using a reliable assay (Bhasin et al. 2010). As men with obesity and/or diabetes may exhibit decreased levels of sex hormone binding globulin (SHBG), measurement of SHBG may be useful to aid in interpreting results (Bhasin et al. 2010). While different societies have suggested varying laboratory T cut-offs, patients exhibiting an unequivocally low serum T level based on local reference ranges (i.e. lower limit for healthy young men—approximately 9.8–10.4 nmol/L) should have a repeat confirmatory measurement. This is important as T levels can vary throughout the day and up to 15% of healthy men can have a low serum T level during the course of 24 h (yet without symptoms) and values can vary depending on whether patients are fasting or fed (Caronia et al. 2013).

If androgen deficiency is confirmed, then the next step is to differentiate primary from secondary forms of hypogonadism according to serum gonadotrophin levels (See Chap. X, Sect. X). Elevated levels are indicative of a gonadal cause such as Klinefelter syndrome. If Klinefelter syndrome is suspected (i.e. TV < 6 mL), a karyotype or comparative genomic hybridization (CGH) array is helpful in making (or ruling out) the diagnosis (Groth et al. 2013). In contrast, low levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) point to a neuroendocrine (hypothalamic-pituitary) aetiology and suggest the need for additional workup such as measurement of iron saturation, serum prolactin, pituitary function and imaging (Bhasin et al. 2010; Boehm et al. 2015) (Table 45.2).

For men with CHH, a serum inhibin B measurement can be useful as a predictor of outcome to treatment as well as a baseline measure for

Table 45.2 Biochemical evaluation of hypogonadotrophic hypogonadism (Bhasin et al. 2010; Dean et al. 2015; Boehm et al. 2015)

Test	Rationale for investigation
Prolactin	Elevated prolactin/ prolactinoma
TSH, free T4	Thyroid disorder
Cortisol	Adrenal insufficiency
IGF-1, IGFBP3	Growth hormone deficiency
LFTs, BUN, electrolytes, CBC	Overall health, systemic disease
CRP, ESR and faecal calprotectin	Inflammatory disease
Coeliac screen	Malabsorption
Ferritin, TIBC% saturation	Iron overload/ haemochromatosis
Inhibin B	Assess Sertoli Cell population

Initial screening may be complemented by dynamic endocrine testing. *TSH* thyroid stimulating hormone, *IGF-1* insulin-like growth factor-1, *IGFBP3* insulin-like growth factor binding protein 3, *LFTs* liver function tests (liver transaminases), *BUN* blood urea nitrogen, *CBC* complete blood count, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *TIBC* total iron binding capacity

evaluating response to FSH monotherapy as part of sequential treatment to induce fertility (see Chap. X, Sect. X) (Dwyer et al. 2015).

45.5 Semen Analysis

Approximately 15% of couples experience difficulty conceiving and roughly half of these cases result from either male factor or mixed (male and female) aetiology of sub-fertility (Anawalt 2013). In combination with hormone profiling, seminal fluid analysis (spermiogram) is useful to help categorize sub-fertility as either pre-testicular, testicular or post-testicular. Spermatogenesis takes between 69 and 80 days (see Chap. 42), so a single seminal fluid analysis is not always informative (Tournaye et al. 2016b). The Endocrine Society recommends that men undergoing evaluation for infertility have at least two seminal fluid analyses (Bhasin et al. 2010). Important patient teaching elements include that semen samples should be provided via masturbation following a period of abstinence (2–7 days), *coitus interruptus* is not an acceptable means to collect a sample for analysis and that the lab should be informed if there were difficulties such as incomplete collection or if there was any spillage (World Health Organization 2010). If semen collection is done at home, temperature extremes should be avoided (i.e. remaining between 20 and 37 °C) and the sample should be transported within an hour for analysis to facilitate accurate interpretation.

Perhaps the two most important components of semen analysis are the ejaculate volume and sperm concentration. The most recent reference values from the World Health Organization indicate that ejaculate be >1.5 mL in volume and contain ≥39 million sperm (World Health Organization 2010). Approximately 50–80% of the ejaculate volume is comprised of the alkaline secretions from the seminal vesicles. Therefore, low ejaculate volume and low pH (<7.4) suggest an obstructive (post-testicular) cause (Anawalt 2013; Tournaye et al. 2016b). A normal sperm concentration is considered $\geq 15 \times 10^6$/mL, while adequate motility is set at 40% of total sperm and morphology ≥4% is considered normal (World Health Organization 2010). A low sperm concentration (i.e. $<10 \times 10^6$/mL), also termed oligospermia, in the setting of elevated serum FSH levels points to a primary (testicular) failure as the cause of sub-fertility. Pre-testicular causes of male sub-fertility, such as hypogonadotrophic hypogonadism, are indicated by azoospermia (no sperm) and low to normal serum gonadotrophins (Anawalt 2013; Tournaye et al. 2016b).

45.6 Imaging Studies

Several radiologic investigations may be employed as part of a reproductive endocrine consultation. Scrotal ultrasound is informative in situations when the testes are difficult to assess clinically and such imaging may also help identify obstructive causes of sub-fertility such as agenesis of the vasa or varicocele in obese patients (Tournaye et al. 2016a). Importantly, for patients with CHH or Kallmann syndrome, a renal ultrasound is warranted to identify potential unilateral renal agenesis which can occur in a

portion of these patients (Boehm et al. 2015). In young adults being evaluated for incomplete or absent puberty a wrist X-ray reveals if the epiphyses have fused and is used to determine bone age for comparison to chronologic age (Palmert and Dunkel 2012). Young adults with CHH who have yet to receive exogenous T treatment will exhibit marked differences between chronologic age and bone age (e.g. bone age of 13 years for chronologic age of 18). Androgens play an important role in bone health so men with severe androgen deficiency (i.e. CHH or Klinefelter syndrome) and men with a history of low-trauma fracture warrant measurement and monitoring of bone density using dual X-ray absorptiometry (DXA) (Bhasin et al. 2010). While most adult men presenting for evaluation of androgen deficiency will not require cranial imaging, part of a workup for severe hypogonadotrophic hypogonadism (i.e. T $\leq$ 5.2 nmol/L) includes imaging to rule out potential tumours/space occupying lesions (Bhasin et al. 2010). Magnetic resonance imaging (MRI) of the sella turcica (hypothalamopituitary) region is necessary in such instances. MRI or computed tomography (CT) can be informative for evaluating hypoplasia or agenesis of the olfactory structures (olfactory bulbs, tracts, grooves) in the setting of anosmia (a red flag for Kallmann syndrome). Similarly, when signs suggestive of CHARGE syndrome are apparent (coloboma, heart defects, atresia of choanae, retarded growth/development, genital anomalies and ear abnormalities/deafness) imaging should be performed to visualize the semicircular canals (a diagnostic criteria of CHARGE syndrome) (Boehm et al. 2015).

45.7 Other Investigations

Based on the history, clinical presentation and serum hormone measurements, other tests may be relevant. Certainly for patients who are overweight/obese and who may exhibit characteristics of the metabolic syndrome, a standard 75 g oral glucose tolerance test and/or measurement of glycated haemoglobin (HbA1C)/fasting glucose/fasting insulin levels can be used to identify glucose intolerance and diabetes (American Diabetes Association 2016). Based on patient history, exam and initial hormone profiling, additional stimulation testing may be ordered to evaluate pituitary function (i.e. cortrosyn stimulation or insulin tolerance test) (see Chap. X Dynamic Endocrine Testing). In evaluating incomplete or absent puberty in adolescents and young adults (i.e. isolated GnRH deficiency), it would presumably follow that GnRH stimulation testing would be useful. However, results are only informative in cases of a flat response (indicating severe GnRH deficiency) as there is a broad overlap between CHH and delayed puberty (Harrington and Palmert 2012). At present there is no single gold-standard test to clearly differentiate CHH from constitutional delay of growth and puberty.

Diagnosing CHH in adolescence remains challenging (Boehm et al. 2015). One potential avenue for facilitating this is via genetic screening. However, more than 25 genes have been identified to date, thus making it challenging to select a single gene for screening—which is why next-generation sequencing is becoming increasingly prevalent for such investigations (Boehm et al. 2015). Moreover, the identified CHH loci only account for about half of cases and the condition is characterized by incomplete penetrance and variable expressivity posing further challenges interpreting test results. However, when mutated CHH genes are identified, this can be informative for guiding genetic counselling should the patient desire fertility-inducing treatment (Au et al. 2011) (see Chapters X and X, Sect. X).

Elevated serum gonadotrophins indicating hypergonadotrophic hypogonadism should raise the suspicion of Klinefelter syndrome, the most common chromosomal abnormality in men (1:660 men) (Groth et al. 2013). Cytogenetic testing such as a karyotype or CGH array (which provides much higher resolution) should be performed to confirm or alternatively rule out a diagnosis. Similarly, cytogenetic screening and testing for Y chromosome microdeletions should be conducted in azoospermic men with a presumed non-obstructive cause (i.e. normal ejaculate volume, normal pH, normal serum FSH)

(Tournaye et al. 2016a). Men with no palpable vasa should have screening for the cystic fibrosis transmembrane regulator (*CFTR*) gene as this is associated with congenital absence of the vas deferens (CBAVD) (Tournaye et al. 2016a).

Genetics and genomics are becoming increasingly part of endocrine practice. Testing not only has implications for making a diagnosis, but also for setting expectations for treatment and results can impact fertility decisions for patients and couples. Importantly, limited patient literacy and numeracy can hinder patients' understanding of genetics and genomics (National Academies of Sciences Engineering, and Medicine 2016). Therefore, it is important for health professionals to be familiar with and utilize best practices in communicating with patients (Box 45.1, 45.3) (Brega et al. 2015).

Box 45.3 Reflection on Patient-Centred Care: Patient Quotes

Healthcare professionals are expected to understand the pathophysiology, evaluation and treatment of disorders of the HPG axis. However, we may not fully appreciate how patients feel about living with their condition day-to-day. Important elements of providing patient-centred care include understanding these viewpoints, providing effective lay language education and engaging patients in shared decision-making.

These quotes are drawn from focus group discussions with men diagnosed with congenital hypogonadotrophic hypogonadism (CHH):

"It's like you are the only one going through it. How can anyone else understand? I mean, if you don't understand it completely yourself, how can anyone else?"

- Patients may not fully understand their condition contributing to feelings of isolation. What types of nursing interventions could be employed to lift the veil of isolation and empower these patients?

"After you get into treatment, you get treated like an idiot. You know? 'We'll give you this… this is what you have to do…' They tell you nothing, I knew nothing".

- Patients at all ages are capable of understanding their condition. Effective communication and coaching includes being developmentally appropriate and culturally sensitive while using lay language (i.e. avoiding medical jargon) and employing the "teach back" method. How might your approach differ between a 16 year-old adolescent presenting for evaluation of absent puberty versus a 40 year-old man with the metabolic syndrome presenting with complaints of erectile dysfunction?

"when you see the doctor, the endocrinologist, you don't get anything that comes your way that has anything remotely to do with them wanting to understand. Or asking if you have anything that you need to say or need to ask or actually how you feel".

"I think we have to find more people who are willing to take the time to understand and to explain to new people… because it's scary no matter what you get diagnosed with".

- As a healthcare professional, seeing the same chief complaints week after week it is understandable that some become "the norm". However, while the patient's condition may be routine to you, the patient likely has a vastly different perspective. Indeed, their health status may be causing them significant stress and worry. What are some simple ways you can foster a caring, therapeutic relationship during a brief consultation or medical encounter?

Remember that the consultation is not solely about identifying a problem and offering a solution. For chronic conditions, patients provide most of their own care so the 4 Es: engaging the patient, showing empathy, educating them and enlisting them in self-care are key elements of the clinical encounter that can foster effective communication and support self-management (Keller and Carroll 1994). Endocrine nurses should also be proactive and identify colleagues specializing in genetic counselling so that appropriate timely referrals can be made to adequately support patient decision-making.

45.8 Conclusions

Androgen deficiency, sexual dysfunction and subfertility are common reasons why men seek reproductive endocrine consultation. Endocrine nurses should be aware of the aetiology of these problems and practise in line with available guidelines (Bhasin et al. 2010; Dean et al. 2015; Boehm et al. 2015). Depending on the nurse's scope of practice, there are specific clinical competencies needed to effectively care for men with reproductive endocrine disorders. Because reproductive endocrine disorders can impact patient health, well-being and quality of life approach to nursing care should include aspects beyond pathophysiology and evidence based guidelines. Nursing's role also includes employing transversal skills such as giving attention to patient concerns, delivering education and anticipatory guidance in clear plain language, and providing psychosocial support. Patients with infertility may require care by multiple specialists including urologists, experts in assisted reproductive technologies, genetic counsellors and others. Navigating these specialty silos can be challenging for patients and nurses can play an important role in coordinating care and providing timely patient advocacy.

References

American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016;39 Suppl 1:S13–22.

Anawalt BD. Approach to male infertility and induction of spermatogenesis. J Clin Endocrinol Metab. 2013;98(9):3532–42.

Au MG, Crowley WF Jr, Buck CL. Genetic counseling for isolated GnRH deficiency. Mol Cell Endocrinol. 2011;346(1–2):102–9.

Ball JW, Dains JE, Flynn JA, Solomon BS, Stewart RW. Seidel's guide to physical examination. St Louis: Elsevier Health Sciences; 2014.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.

Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547–64.

Brega AG, Barnard J, Mabachi NM, Weiss BD, DeWalt DA, Brach C, Cifuentes M, Albright K, West DR. AHRQ Health Literacy Universal Precautions Toolkit, Second Edition. (Prepared by Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus under Contract No. HHSA290200710008, TO#10.) AHRQ Publication No. 15-0023-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2015.

Caronia LM, Dwyer AA, Hayden D, Amati F, Pitteloud N, Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucose load in men: implications for screening for hypogonadism. Clin Endocrinol. 2013;78(2):291–6.

Dean JD, McMahon CG, Guay AT, Morgentaler A, Althof SE, Becher EF, et al. The International Society for Sexual Medicine's process of care for the assessment and management of testosterone deficiency in adult men. J Sex Med. 2015;12(8):1660–86.

Dwyer AA, Raivio T, Pitteloud N. Gonadotrophin replacement for induction of fertility in hypogonadal men. Best Pract Res Clin Endocrinol Metab. 2015;29(1):91–103.

Foote JM, Kirouac N, Lipman TH. PENS position statement on linear growth measurement of children. J Pediatr Nurs. 2015;30(2):425–6.

Goede J, Hack WW, Sijstermans K, van der Voort-Doedens LM, Van der Ploeg T, Meij-de Vries A, et al. Normative values for testicular volume measured by ultrasonography in a normal population from infancy to adolescence. Horm Res Paediatr. 2011;76(1):56–64.

Groth KA, Skakkebaek A, Host C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30.

Harrington J, Palmert MR. Clinical review: Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. J Clin Endocrinol Metab. 2012;97(9):3056–67.

Hatipoglu N, Kurtoglu S. Micropenis: etiology, diagnosis and treatment approaches. J Clin Res Pediatr Endocrinol. 2013;5(4):217–23.

Joustra SD, van der Plas EM, Goede J, Oostdijk W, Delemarre-van de Waal HA, Hack WW, et al. New

reference charts for testicular volume in Dutch children and adolescents allow the calculation of standard deviation scores. Acta Paediatr. 2015;104(6):e271–8.
Keller VF, Carroll JG. A new model for physician-patient communication. Patient Educ Couns. 1994;23(2):131–40.
Khera M, Broderick GA, Carson CC 3rd, Dobs AS, Faraday MM, Goldstein I, et al. Adult-onset hypogonadism. Mayo Clin Proc. 2016;91(7):908–26.
Lotti F, Maggi M. Ultrasound of the male genital tract in relation to male reproductive health. Hum Reprod Update. 2015;21(1):56–83.
McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Risk factors for sexual dysfunction among women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. J Sex Med. 2016;13(2):153–67.
Millar AC, Lau AN, Tomlinson G, Kraguljac A, Simel DL, Detsky AS, et al. Predicting low testosterone in aging men: a systematic review. CMAJ. 2016;188(13):E321–30.
National Academies of Sciences Engineering, and Medicine. Relevance of health literacy to precision medicine: Proceedings of a work-shop. Washington, DC: The National Academies Press; 2016.
Palmert MR, Dunkel L. Clinical practice. Delayed puberty. N Engl J Med. 2012;366(5):443–53.
Sedlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab. 2002;87(4):1613–20.
Seftel AD, de la Rosette J, Birt J, Porter V, Zarotsky V, Viktrup L. Coexisting lower urinary tract symptoms and erectile dysfunction: a systematic review of epidemiological data. Int J Clin Pract. 2013;67(1):32–45.
Skakkebaek A, Wallentin M, Gravholt CH. Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments. Curr Opin Endocrinol Diabetes Obes. 2015;22(3):209–16.
Taylor AE, Keevil B, Huhtaniemi IT. Mass spectrometry and immunoassay: how to measure steroid hormones today and tomorrow. Eur J Endocrinol. 2015;173(2):D1–12.
Tournaye H, Krausz C, Oates RD. Concepts in diagnosis and therapy for male reproductive impairment. Lancet Diabetes Endocrinol. 2016a;5(7):554–64.
Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2016b;
Wehkalampi K, Widen E, Laine T, Palotie A, Dunkel L. Patterns of inheritance of constitutional delay of growth and puberty in families of adolescent girls and boys referred to specialist pediatric care. J Clin Endocrinol Metab. 2008;93(3):723–8.
World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO; 2010.
Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35.
Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2012;97(3):707–18.
Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006;91(11):4335–43.

Key Reading

1. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59. https://doi.org/10.1210/jc.2009-2354.
2. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, Dwyer AA, Giacobini P, Hardelin J-P, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, document YJE c. European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nat Rev. Endocrinol. 2015;11(9):547–64. https://doi.org/10.1038/nrendo.2015.112.
3. Tournaye H, Krausz C, Oates RD. Male reproductive impairment 1: novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2016). [Epub ahead of print] 1-10; https://doi.org/10.1016/S2213-8587(16)30040-7.
4. Tournaye H, Krausz C, Oates RD. Male reproductive impairment 2: concepts in diagnosis and therapy for male reproductive impairment. Lancet Diabetes Endocrinol. 2016). [Epub ahead of print] 1-11; https://doi.org/10.1016/S2213-8587(16)30043-2.
5. Brega AG, Barnard J, Mabachi NM, Weiss BD, DeWalt DA, Brach C, Cifuentes M, Albright K, West DR. AHRQ Health Literacy Universal Precautions Toolkit, 2nd ed. (Prepared by Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus under Contract No. HHSA290200710008, TO#10). AHRQ Publication No. 15–0023-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2015.

Testosterone Therapy in Adult Men with Hypogonadism

46

Sofia Llahana

Contents

46.1 **Introduction** 887

46.2 **Testosterone Function** 887
46.2.1 Testosterone Production and Metabolism 887
46.2.2 Diagnosing Testosterone Deficiency 888
46.2.3 Functions of Testosterone and Symptoms of Testosterone Deficiency 888

46.3 **Testosterone Therapy and Importance of Patient Education and Adherence to Treatment** 889
46.3.1 Testosterone Replacement Therapy Options 890

46.4 **Benefits of Testosterone Therapy** 895

46.5 **Contraindications and Adverse Effects of Testosterone Therapy** 896

46.6 **Testosterone Therapy in Men with Age-Related Testosterone Deficiency** 898

46.7 **Monitoring of Testosterone Therapy** 898

46.8 **Patient Education and Role of Patient Advocacy Groups** 899
46.8.1 The Klinefelter's Syndrome Association (KSA) 900

46.9 **Conclusions** 900

References 901

Abstract

This chapter discusses the management of male hypogonadism and focuses on the diagnosis and treatment of testosterone replacement therapy (TRT). Available TRT formulations will also be discussed by providing a rationale on their benefits and disadvantages to support the endocrine nurse in developing a tailored treatment plan in consultation with their patients.

S. Llahana (✉)
Division of Nursing, School of Health Sciences, City, University of London, London, UK
e-mail: sofia.llahana@city.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_46

Clinical guidelines and empirical evidence for diagnosis, long-term monitoring and management of adverse events are also discussed. Emphasis is given on patient education and shared decision making to support patients' self-management. Education and continuation of care for patients should be the mainstay of the role of the endocrine nurse. This aspect of the role distinguishes nursing from other health professionals within a multidisciplinary team and it is hoped that this chapter will provide an insight on the endocrine nurse practising at an advanced level and areas of involvement in caring for patients with hypogonadism treated with testosterone replacement therapy.

Keywords
Hypogonadism · Testosterone deficiency · Testosterone replacement therapy · Polycythaemia · Erythrocytosis

Abbreviations

FSH	Follicle stimulating hormone
FT	Free testosterone
GnRH	Gonadotrophin releasing hormone
LH	Luteinising hormone
LOH	Late-onset hypogonadism
PSA	Prostate specific antigen
SHBG	Sex-hormone binding globulin
T	Testosterone
TRT	Testosterone replacement therapy

Key Terms

- **Androgen** is responsible for sexual development in males and is produced by the testes and partly the adrenal glands.
- **Testosterone** is the most important androgen produced by the Leydig cells under the influence of LH. Testosterone plays a vital role in the differentiation of the male sexual organs and development of secondary sex characteristics. In the adult male, in addition to regulation of spermatogenesis, testosterone has androgenic, anabolic and psychological/psychotropic effect.
- **Gonadotrophin Releasing Hormone (GnRH)** is produced and secreted by the hypothalamus to the anterior pituitary, where it stimulates the production of follicle stimulating hormone (FSH) and luteinising hormone (LH).
- **Follicle Stimulating Hormone (FSH)** is released by the anterior pituitary for pubertal development. In males, FSH acts on the Sertoli cells of the testes to stimulate sperm production (spermatogenesis).
- **Luteinising Hormone (LH)** is a gonadotropic hormone produced in the anterior pituitary. In males, LH stimulates Leydig cells in the testes to produce testosterone.
- **Hypergonadotrophic Hypogonadism** refers to testosterone deficiency in the presence of raised concentrations of LH and FSH.
- **Hypogonadism** is the combination of repeated, unequivocally low serum testosterone levels combined with clinical signs and symptoms of androgen deficiency, typically within the framework of a recognised clinical syndrome.
- **Infertility**: The inability to achieve pregnancy following regular unprotected intercourse for 12 months. Factors may be male, female or mixed (both) in origin.
- **Sexual dysfunction**: the inability to engage in normal, pleasurable sexual activity resulting from diminished desire (libido), arousal difficulties (erectile dysfunction) and/or problems with orgasm (ejaculation).

Key Points

- Hypogonadism is a common condition in men causing adverse health effects.
- Treatment in hypogonadism involves testosterone replacement therapy.
- Replacement of testosterone normalises serum levels which can improve physical performance, sexual function, well-being and quality of life.
- Regular and appropriate monitoring is required to avoid adverse events.

46.1 Introduction

Testosterone deficiency due to male hypogonadism is a common disorder in men and requires testosterone replacement therapy. Hypogonadism is the medical term used to describe any conditions developed from the inadequate function of the testes in a man. This is normally associated with decreased or total deficiency in androgens, mainly testosterone, and sperm production. It is caused either by hypothalamic, pituitary, testicular or target organ disorders and this can be congenital (born with the disorder) or acquired later in life. Male hypogonadism is categorised into two groups according to the cause of abnormality; if the abnormality lies in the testes, this is referred to as *primary hypogonadism* (or hypergonadotrophic hypogonadism). If the cause of the testicular abnormality originates from the hypothalamus and/or the pituitary, this is referred to as *secondary hypogonadism* (or hypogonadotrophic hypogonadism).

Hypogonadism is a very common condition estimated to affect 5 in 1000 men. Hypogonadism is also common in elderly men as the function of the organs affecting testosterone production declines with age. When hypogonadism occurs in older age, it is called late-onset hypogonadism (LOH). The clinical presentation of hypogonadism in the adult male can vary and is often misdiagnosed. The most common complaints that adult patients present with are decreased sexual potency, loss of libido and impaired fertility (Allan and McLachlan 2016; Bhasin and Jameson 2017; Bhasin 2007). A detailed and careful case history and physical examination is very important in determining differential diagnosis and requesting the appropriate laboratory investigations. Please read Chaps. 44 and 45 for details on classification and diagnostic evaluation of male hypogonadism.

46.2 Testosterone Function

46.2.1 Testosterone Production and Metabolism

Testosterone is produced by the testes which lie within the scrotum and have dual action as endocrine (hormone-producing) and exocrine (sperm-producing) glands. The adult testes have a volume of 15–35 mL each and are divided in two morphologically and functionally distinct compartments: the tubular compartment where spermatogenesis occurs (seminiferous tubules and Sertoli cells) and the interstitial compartment consisting of the Leydig cells which produce testosterone. The function of the testes is controlled by the hypothalamic and the anterior pituitary hormones. In the hypothalamus, the gonadotrophin releasing hormone (GnRH) is produced under the stimulating and inhibiting influence of neurotransmitters and promotes the production of the two pituitary gonadotrophins, the luteinising hormone (LH) and the follicle stimulating hormone (FSH). GnRH is secreted in regular pulses every 90–120 min and continuous administration of GnRH causes gonadotrophin production to cease completely. This is important to remember in specific conditions requiring treatment with GnRH (Allan and McLachlan 2016).

Testosterone is the most important androgen produced by the Leydig cells under the influence of LH; 3–10 mg of testosterone is produced each day from healthy adult testes, accounting for 95% of the total circulating amount of testosterone (Neto et al. 2016). Each testis contains 500 million Leydig cells constituting about 5% of the mature testis volume (Bhasin and Jameson 2017; Traish 2018). The negative feedback of testosterone has an inhibitory effect on the neurons producing GnRH and a suppressant effect on the LH production, maintaining this way the balance of testosterone production. FSH binds to receptors on the Sertoli cells and stimulates the production of seminiferous tubule fluid and other substances important for spermatogenesis (sperm production). The hormones inhibin and activin are formed in the Sertoli cells under the influence of FSH and form an important component in the feedback system controlling FSH secretion. The enzyme aromatase which converts testosterone to oestradiol (oestrogen) is also present in the Sertoli cells (please refer to Chap. 43 for more details).

Testosterone is synthesised through a total of five enzymatic stages from cholesterol in the Leydig cells. It enters the blood circulation by diffusion and is transported to the target cell

receptor where it exerts its action. In certain target cells, testosterone is metabolised to 5α-dihydrotestosterone (DHT) by the enzyme 5α-reductase (prostate gland, hair follicles) and to oestradiol by the enzyme aromatase (adipose tissue, bone cells, prostate). Only 2% of total testosterone is free and 98% is bound to transport proteins. Of the latter, 44% is bound with high affinity to the β-globulin sex-hormone binding globulin (SHBG) and 54% is loosely bound and transported by albumin. The binding affinity of testosterone to SHBG is about 100-fold compared to albumin. However, since albumin concentration is far higher than that of SHBG, the binding capacity of both proteins for testosterone is approximately the same (Luetjens and Weinbauer 2012). Owing to the increased nightly production of LH, testosterone production follows a circadian rhythm (24 h cycle) with the highest concentration in the early morning hours (Allan and McLachlan 2016; Jockenhovel 2004).

46.2.2 Diagnosing Testosterone Deficiency

In the presence of clinical features and symptoms suggestive of possible hypogonadism, the measurement of serum total testosterone, in an early morning specimen when testosterone is at its highest, and using a reliable assay, is crucial to the diagnosis of testosterone deficiency. Total testosterone concentrations, including bound and unbound testosterone, are affected by the pulsatile, circadian and circannual rhythms of testosterone secretion, assay variability and levels of SHBG (Bhasin 2007). The timing of blood samples is more important in younger than older men as the circadian rhythm becomes less significant with increasing age (Jockenhovel 2004). Sampling for testosterone should be done when the patient is fasting as testosterone may also be suppressed by food intake or glucose. Acute illness or short-term use of medications such as opioids also suppresses testosterone. The lower limit of the normal total testosterone (TT) harmonised to the CDC standard in healthy non-obese young men is 264 ng/dL (9.2 nmol/L) (Bhasin et al. 2018a). Two separate morning fasting samples should be taken to confirm low serum testosterone concentrations, because 30% of men with an initial diagnostic low testosterone have a normal testosterone concentration on repeat measurement (Brambilla et al. 2007). This, however, can vary depending on the assay used in each laboratory and it is, therefore, important to interpret each result based on the local reference range. If there is a clinical indication or suggestive features of hypopituitarism, evaluation of LH, FSH and other pituitary hormones should be performed. Similarly, evaluation of LH and FSH can distinguish between primary and secondary hypogonadism.

Testosterone has a high affinity for sex-hormone binding globulin (SHBG) which means that less free testosterone is available in raised SHBG levels. Only 2% of total testosterone is free (unbound) and SHGB and albumin should be measured in order to calculate free testosterone (the *free androgen index* calculator can be accessed at http://www.issam.ch/freetesto.htm). The testosterone that binds loosely to albumin can be biologically readily available (bio-available or non-SHBG testosterone). Free testosterone (FT) is costly to measure and, as it correlates well with total testosterone, the latter is used as the method of choice in clinical practice, except for specific disorders such as extreme obesity and hyperthyroidism. FT should be used for diagnostic purposes in men who have conditions that alter the SHBG or whose initial testosterone concentrations are near the lower limit of the normal range (Bhasin et al. 2018a). Table 46.1 lists the conditions associated with low or high SHBG (Bhasin et al. 2018b).

46.2.3 Functions of Testosterone and Symptoms of Testosterone Deficiency

Testosterone plays a vital role in the differentiation of the male sexual organs and development of secondary sex characteristics. Its effect on the body development before the end of puberty has been discussed in Chap. 4 and will not be referred to in detail here. In the adult male, apart from regulation of spermatogenesis, testosterone plays

Table 46.1 Conditions in which FT should be used to confirm testosterone deficiency

Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
Conditions associated with increased SHBG concentrations
Ageing
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of oestrogens
Polymorphisms in the SHBG gene
Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.* 200–400 ng/dL)

Used with permission from BHASIN, S., TRAVISON, T. G., O'BRIEN, L., MACKRELL, J., KRISHNAN, V., OUYANG, H., PENCINA, K. & BASARIA, S. 2018b. Contributors to the substantial variation in on-treatment testosterone levels in men receiving transdermal testosterone gels in randomized trials. *Andrology,* 6**,** 151–157

a key role in a large number of other bodily functions. Its effects on the adult male body, detailed in Table 46.2, can be defined as androgenic, anabolic and psychological/psychotropic. Symptoms and clinical presentation of testosterone deficiency are also presented in Table 46.2 (Bhasin et al. 2018a; Jockenhovel 2004; Traish 2018).

46.3 Testosterone Therapy and Importance of Patient Education and Adherence to Treatment

The objective of TRT is to reverse or prevent the symptoms and long-term effects of male hypogonadism and to maintain general well-being (Bhasin et al. 2018a). More specifically, if administered properly, testosterone can:

- Improve libido and sexual function.
- Improve mood and emotional well-being.
- Improve muscle mass and strength as well as physical stamina.
- Prevent osteoporosis and treat low bone density mass.

Table 46.2 Effects of testosterone on the adult male body

Action	Physiological action	Effect of testosterone deficiency
Androgenic	Testicular maintenance	Decrease in the volume and consistency of testes
	Prostate gland and ejaculate	Atrophy of prostate, reduced ejaculate volume
	Pubic, axillary and body hair	Reduced density in pubic, axillary and body hair
	Beard growth	Reduced beard growth and frequency of shaving
	Regulation of spermatogenesis	Reduced sperm count or infertility
	Erectile potency	Reduced frequency of morning erections
		Difficulty in getting and maintaining an erection
		Erectile dysfunction
	Male pattern baldness	No development or progression of male pattern balding once testosterone deficiency occurs
Anabolic	Bone mineral density mass	Decrease in bone mass, osteopaenia or osteoporosis
		Increased risk of fractures
	Muscular mass and strength	Muscular weakness and reduced muscle bulk
	Distribution of adipose tissue	Increase in fat mass, pronounced hips (female-like)
	Lipid metabolism	Increase in HDL and decrease in LDL
	Promotion of erythropoiesis	Low haematocrit, anaemia
	Thickening of skin and function of sebaceous glands	Decreased sebum production, hot flashes
		Skin appears dry, thin, pale and wrinkly
Psychological/ psychotropic	Libido and sex drive	Loss of libido and lack of sexual desire
	Aggression and motivation	Loss of motivation, irritability
	Emotional well-being	Mood swings, depression
	Energy levels, physical stamina	Tiredness and fatigue
	Mental and cognitive ability	Lack of concentration, reduced spatial cognition

Patient education is imperative to optimising treatment outcome from TRT. The endocrine nurse plays a key role in supporting patients and their families to develop an individualised treatment plan, to understand their treatment and condition and to adhere to their medication. There is evidence to suggest that non-adherence to TRT can compromise the patient's quality of life, physical and cognitive performance and bone density (Dwyer et al. 2014; Zitzmann 2008; Beauchet 2006).

Low persistence with treatment gaps of more than a year and high discontinuation rates at 6 months were reported for testosterone replacement by 37% (Dwyer et al. 2014) and 65% (Schoenfeld et al. 2013) of patients, respectively. Similar high discontinuation rates for TRT were reported by Donatucci et al. (2014). This was higher for patients on daily topical TRT with 52% of patients discontinuing treatment after 3 months compared to 31% of patients on short-acting TRT injections. The latter group, however, did not include long-acting testosterone undecanoate injections. The gap between stopping and restarting TRT tended to decrease over time, suggesting that patients who experienced a benefit from TRT remained on treatment (Donatucci et al. 2014). The endocrine nurse should reinforce for the patient and their family that the treatment benefit from TRT may not be immediate and should support them to recognise and manage potential side effects. Dissatisfaction with the information received about treatment and perceived impaired communication with clinicians was reported by patients as a significant barrier to treatment non-adherence (Dwyer et al. 2014). Another survey of 99 men on TRT found that almost half of respondents had inadequate knowledge and were not satisfied with their testosterone treatment. Respondents' level of knowledge was highly correlated with their satisfaction with treatment ($r = 0.646$; $p < 0.001$), suggesting that patients who were well informed of their treatment and condition were able to select a suitable TRT option for their needs (Llahana and Conway 2006).

Individual patients' needs will often guide the treatment option for TRT; factors that influence this are ease of use, ability to raise testosterone levels, improvement in symptoms, convenience and cost (Kovac et al. 2014). Determining which TRT product is preferred by patients may be challenging, given the number of options for route of administration, i.e. injection, implant, topical and oral. Optimal patient experience and satisfaction with the treatment selected is most likely to occur when patient preferences are factored in the treatment planning and choice of TRT (Szeinbach et al. 2012). The endocrine nurse should take into account the patient's needs and individual preferences when discussing TRT treatment initiation.

46.3.1 Testosterone Replacement Therapy Options

A number of treatment options are available (Table 46.3) (Behre and Nieschlag, 2012; Bhasin and Jameson, 2017; Bhasin et al, 2018a) and, despite their disadvantages, with appropriate education and shared-decision making, the endocrine nurse should be able to develop a person-tailored TRT treatment regime to suit patients' individual needs.

46.3.1.1 Testosterone Pellet Implants

Implants are the oldest form of testosterone treatment available since 1940. These are small half-inch cylindrical pellets which are inserted in the fat tissue of the body (usually in the abdomen, thigh or buttock) following a surgical procedure under local anaesthetic. Their dose is 100 or 200 mg and 3–6 pellets are inserted every 4–6 months. The low frequency of dosing and maintenance of normal testosterone levels for up to 6 months are positive features of this method. However, as this is a minor surgery, it is related with a higher risk of infections and implant rejection from the body. It is also a painful procedure and may leave scars following each implantation. The levels of testosterone fluctuate between each implantation with higher levels, which can be associated with relevant clinical symptoms. During the first months (peaks) and low levels towards the end of the dose interval (troughs).

Table 46.3 Testosterone therapy formulations and their characteristics

Formulation and dose	Administration method	Advantages	Disadvantages
Subcutaneous implants *Testosterone pellets 100 or 200 mg to a total of 600–1200 mg T per dose*	3–6 pellets every 4–6 months. Pellets implanted in the subcutaneous adipose tissue with surgical incision under local anaesthetic.	Serum T peaks at 1 month and is sustained in normal range for up to 6 months; Convenience—twice or thrice a year application.	Painful procedure with high risk of infection at the insertion point and scar tissue; Risk of spontaneous extrusion after implantation.
Oral testosterone undecanoate capsules 40 mg *1–3 capsules (40–120 mg) twice or thrice daily with meals*	Taken orally; absorption is improved when taken with fatty meal. Swallow without chewing.	Easy and convenient administration; Suitable for patients who cannot tolerate other forms of treatment and those who require low levels of T, not a preferred treatment option.	Low bioavailability and inter- and intra-individual variability in absorption resulting in insufficient serum T levels. Normal serum T level attained for only up to 3–5 h.
Intramuscular testosterone: 1. *Combination of testosterone esters 250 mg/mL IM every 3–4 weeks (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, decanoate 100 mg);* 2. *Testosterone enanthate or cypionate 150–200 mg IM every 2 weeks of 75–100 mg/week*	Administration every 1–4 weeks depending on dose and patient needs; Oily preparation (1 mL) injected slowly deep into the gluteal muscle or upper thigh; warm ampoule to body temperature before injection.	Dose flexibility and convenient administration—relatively inexpensive. Can be self-injected. Improves symptoms of androgen deficiency; mostly noticeable in the first days after the injection Maintenance of normal level serum T for 2–4 weeks following administration.	Initially supraphysiological T levels which decline to hypogonadal range by the next injection may result in unpleasant "peak & trough" symptoms between doses; Risk of polycythaemia due to high abnormal T levels Pain, discomfort at injection site; Lifestyle restrictions for patients not self-injecting; risk of reaction to excipients (such as peanut oil).
Transdermal non-genital testosterone patches of 5 mg or 10 mg	1–2 patches once daily; patches may be removed for up to 2 h a day. Stick-on patches contain T in an alcohol gel reservoir; apply on clean, dry, healthy skin (abdomen, back, buttock, upper arms and thighs).	Convenient and easy application; Effective, provides T levels within physiological range; Steady levels of serum T with no "peak & troughs" between applications.	Skin irritation at the application site; Unsightly, discomfort at removal; "sticky" marks on skin, easily detachable; More than one patch may be required.
Transdermal topical testosterone gels and axillary solution *50–100 mg of 1%, 40–70 mg of 2% or 20.25–81 mg of 1.62% transdermal gel applied once daily* *60 mg of T solution applied in the axillae once daily*	Available in sachets, tubes and pumps; refer to each formulation for application site and package instructions. Clear alcohol gel containing T; apply on dry, clean skin on shoulders, abdomen upper arms or thighs (avoid genital area), preferably after shower; allow to dry for 5 min before dressing; wash hands with soap after applications. Have to be reapplied if swimming or showering within 3–5 h of application.	Convenient, flexible and easy application; good skin tolerability. Effective, provides T levels within normal range for 24 h; Steady physiological levels of serum T with no "peak & troughs" between applications; Dose easily adjustable to individual needs; No pain of injections.	May cause skin dryness and irritation for some patients; Takes time to apply; can be "messy"; Potential of transfer to a female partner or child by direct skin-to-skin contact. Fear of transfer may inhibit intimacy—patient education minimises potential of transfer; Increased DHT levels due to presence of 5α-reductase in the skin. Considerable inter- and intra-individual T levels require close dose titration.

(continued)

Table 46.3 (continued)

Formulation and dose	Administration method	Advantages	Disadvantages
Bioadhesive, Buccal oral T tablet *30 mg controlled-release tablets applied to the upper gum twice daily*	T is absorbed gradually from the buccal mucosa over 12 h; Place rounded side of tablet on the gum and below the lip; apply on healthy, clean gum; the solid tablet softens and moulds to the shape of the gum; replace tablet if it detaches within the 12 h dosing interval or with next dose if due.	Easy and fast to apply; Effective; serum T levels remain within physiological range with twice daily application without significant peaks and troughs; "easy to remember" administration with teeth brushing daily routine.	Risk of gum-related adverse events reported by 16% of treated men. May detach when eating shortly after application; Takes time to get used to; Instructions should be followed carefully for application; patient education is vital in increasing the success of treatment.
Long-acting T undecanoate injections *1000 mg in 4 mL ampoule of oily preparation*	1000 mg every 10–14 weeks following the initial injection at 6 weeks interval (loading dose); Weekly monitoring of serum T levels starting at 10 weeks after the third injection helps determine the frequency of injections based on trough T level; Injected very slowly deep into the gluteal muscle; warm ampoule to body temperature before injecting.	Effective, maintains physiological serum T levels for up to 3 months or longer for some men. Does not have the supraphysiological profile of serum T level seen in other intramuscular T injections and "peak and trough" symptoms are less noticeable. Convenient, 3-monthly application without the side effects seen with T implants.	Pain, discomfort and adverse reaction at injection site; Requires large muscle bulk for injection; lifestyle restrictions as it cannot be self-administered; Not recommended as first-line treatment option due to inability of withdrawal in case of adverse events (AE). Rare AE of pulmonary microembolism presenting with severe coughing episode during injection. Risk of reaction to preservative (castor oil).

Note: TRT options in this table may not be available in every country

46.3.1.2 Oral Testosterone Undecanoate (Capsules)

These capsules are taken by mouth. While oral route of delivery is very popular, these capsules have a short half-life (they maintain normal testosterone levels only for a few hours) and need to be taken three to four times a day with a fatty meal. Only a small part of the medication is absorbed and, therefore, large doses of up to eight capsules a day are required to restore testosterone levels within normal range. Oral therapy is more suitable for patients who cannot tolerate other forms of treatment or do not require large doses of testosterone. Some oral preparations (e.g. 17a-methyltestosterone and fluoxymesterone) may cause liver toxicity; these preparations, however, have been discontinued from most European countries.

46.3.1.3 Testosterone Injections

These injections are given deep into the gluteal muscles or upper thigh (intramuscular injections). They are oily preparations (such as peanut or castor oil) which allow slow release over a long period after being injected. Most patients have their injection given by their GP or practice nurse; however, this may cause restrictions in lifestyle, i.e. regular appointments, difficulty in planning holidays, etc. This form of treatment provides high levels of testosterone (peaks) immediately after the injection, which tend to drop below normal range (troughs) towards the end of the injection interval. As a result of these, some patients have symptoms of high and low testosterone levels between the injections, such as mood swings, difference in energy levels and sexual drive.

There are two options of testosterone injections:

1. Short acting
   Short-acting testosterone injections are administered IM every 1–4 weeks depending on formulation and patient's response. Education is important to support and consult patients and their families on how to monitor improvement in well-being and response to treatment and any potential side effects as well as peak and trough levels between injections. This treatment has been around since the 1950s and has been the most widely used option until other preparations became available.
2. Long-acting testosterone undecanoate 1000 mg /4 mL IM injections every 10–14 weeks. This has similar texture to short-acting injections (thick oil) but is four times larger in volume (4 mL) and should be injected very slowly into the gluteal muscle. The second injection should be given at 6 weeks (loading dose) and thereafter every 12 weeks. After the third injection, a testosterone level measured at 4, 8, 10 and 12 weeks can be helpful to monitor the TRT profile and determine the frequency of future injection intervals.

46.3.1.4 Testosterone Patches

The patch contains testosterone in an alcohol gel reservoir which is absorbed gradually through the skin. This form of treatment is quite effective as it avoids metabolism through the liver and raises testosterone to normal range within a few hours after application. Patches are applied once a day, ideally, at bed-time so that the pattern of testosterone release is closest to the normal body rhythm. They can be removed for up to 2 h a day before applying a new one. Some patients require two or more patches to get sufficient dose of testosterone. For best absorption, patches should be placed on body areas with minimal body hair, back, abdomen, upper arm, thigh or upper buttock. Skin reaction or rash is quite frequent with this form of treatment; rotation of application sites (use of different site every day) can help to minimise any skin reactions. The body patches are quite large and some patients find them unsightly and socially embarrassing.

46.3.1.5 Testosterone Gel

This is a clear alcohol gel applied once a day, preferably in the morning, to dry, clean and healthy skin, excluding the genital area, with no open sores. The gel is absorbed rapidly through the skin within 5–10 min and testosterone level rises into normal range within 2–4 h after application. Testosterone is released slowly into the blood circulation for about 24 h. Full absorption of the gel may take up to 6 h and, therefore, showering or swimming within that time should be avoided or the gel reapplied. It is important to advise patients on the potential risk of direct skin-to-skin transfer of testosterone and how to avoid this. Transfer of testosterone gel to pregnant women may cause abnormalities or harm to the unborn baby. To minimise risk of transfer advise patients to:

- Wash hands thoroughly immediately after applying the gel.
- Cover the application site (shoulders, upper arms, abdomen) with clothing once the gel has dried.
- Shower before any situation involving close skin-to-skin contact with someone else, especially if that happens within 6 h after applying the gel.

46.3.1.6 Testosterone Buccal Tablets

This, when taken twice daily, provides testosterone levels within normal range for up to 24 h. The buccal tablet is placed on the gum of the incisor tooth on either side and below the lip (just to the left and right of the two front central teeth). They should not be chewed or swallowed. Men, naturally, have an inwards curved area on their gum; the tablet has such a form to fit perfectly into that area without risk of dislodgment. The solid tablet absorbs moisture from the mouth and

begins to soften and mould to the shape of the gum about an hour after application and remains in place until next application. Testosterone is absorbed slowly through the gum into the blood circulation for up to 12 h; tablets should be replaced approximately every 12 h. The application surface must be clean; ideally after brushing the teeth. If the tablet fails to adhere properly to the gum or falls off during the 12-h dosing interval, the old tablet should be removed and a new one applied. If the tablet is swallowed, it is harmless and will be rendered ineffective as the stomach enzymes will not allow its absorption. Similarly, there is no risk of transferability to other people. The buccal tablet may occasionally cause gum irritation especially at the start of the treatment.

Box 46.1 Patient Case Study: Importance of Self-Management and Peer-Support in Testosterone Therapy

My diagnosis of Klinefelter's Syndrome (KS), at the age of 35, was as a result of fertility investigations and while it came as a shock, it was a great relief as it explained many of my limitations from childhood through to adulthood. Upon starting testosterone replacement therapy (TRT) I decided to have an outlook of "*use TRT as a catalyst to improve my life and work with it for my betterment!*". However, I learnt that TRT alone was not an answer, while it can improve life, one must work *with* it and be willing to adapt and embrace a change in life-long habits. My life pre-treatment and post-treatment are very different. I lacked confidence, had social anxiety, low self-confidence, had difficulty concentrating at times and staying fit was challenging. All these have improved significantly since starting on TRT.

Successful self-management of TRT involves patients working with their clinicians and being aware and well informed about their condition, their treatment and how to monitor their progress and well-being. Observations such as the effects of TRT on moods, energy levels and appetite can assist in the management of patient-specific care. My current TRT is long-acting testosterone undecanoate injections. I recommend using a patient diary to note when the dose begins, when the next is due, side effects experienced and how one feels in-between doses at different weeks. I found after a point, lethargy would begin, and it impacted my day-to-day life.

Development of the Peer Support Group

In 2014, I organised my first KS Support group and meet-up. This was borne out of a need for support and to gain accurate and up-to-date information regarding KS. It gave attendees the opportunity to learn more about their condition in an informal, friendly, understanding and safe environment. Support groups help bring people together to ask questions, offer advice or simply to listen to one another and make friends. To date I have organised ten events, some of which have included workshops facilitated by clinicians to educate patients about their condition and how to better manage it. Attendees can ask questions in an informal environment without the time restrictions and medical environment of a clinical appointment. For clinicians, it gives an opportunity to meet a large group of patients in a single session and to gain an understanding of the issues frequently experienced by patients from which common themes can arise and may highlight overlooked personal experiences.

I regularly liaise with patients to discuss their concerns or key questions and feed this back to healthcare professionals to increase awareness of concerns and enable presentations to be tailored accordingly to give attendees "take home advice". Clinicians can also assist patients with KS to form a support group by organising open patient education events in their Centre and, thereafter, further facilitation can be undertaken by a group member. For further information on educational resources, please refer to my website "*The Klinefelter's Network*" www.klinefelters.net.

46.4 Benefits of Testosterone Therapy

The objective of testosterone replacement therapy is to reverse and/or prevent the effects of low testosterone described above. In particular, testosterone therapy aims to:

- Improve sex drive, libido and sexual function.
- Improve mood and well-being.
- Improve muscle mass and strength.
- Restore or maintain masculine characteristics such as facial and body hair.
- Maintain bone strength and prevent osteoporosis.

Testosterone replacement therapy does not restore fertility. Effects of testosterone therapy are not immediate and can often take up to 18 months (Bhasin and Jameson 2017; Saad et al. 2011). It is important for the endocrine nurse to consult the patient on what to expect from TRT and the estimated time periods when he will experience the benefits of TRT. Effects on sexual interest appear after 3 weeks plateauing at 6 weeks, with no further increments expected beyond. Changes in erections/ejaculations may require up to 6 months (Saad et al. 2011) (Fig. 46.1). Effects on quality of life manifest within 3–4 weeks, but maximum benefits take longer. Effects on depressive mood become detectable after 3–6 weeks with a maximum after 18–30 weeks. Effects on erythropoiesis are evident at 3 months, peaking at 9–12 months. Prostate specific antigen and volume rise, marginally, plateauing at 12 months; further increase should be related to ageing rather than therapy. Effects on lipids appear after 4 weeks, maximal after 6–12 months. Insulin sensitivity may

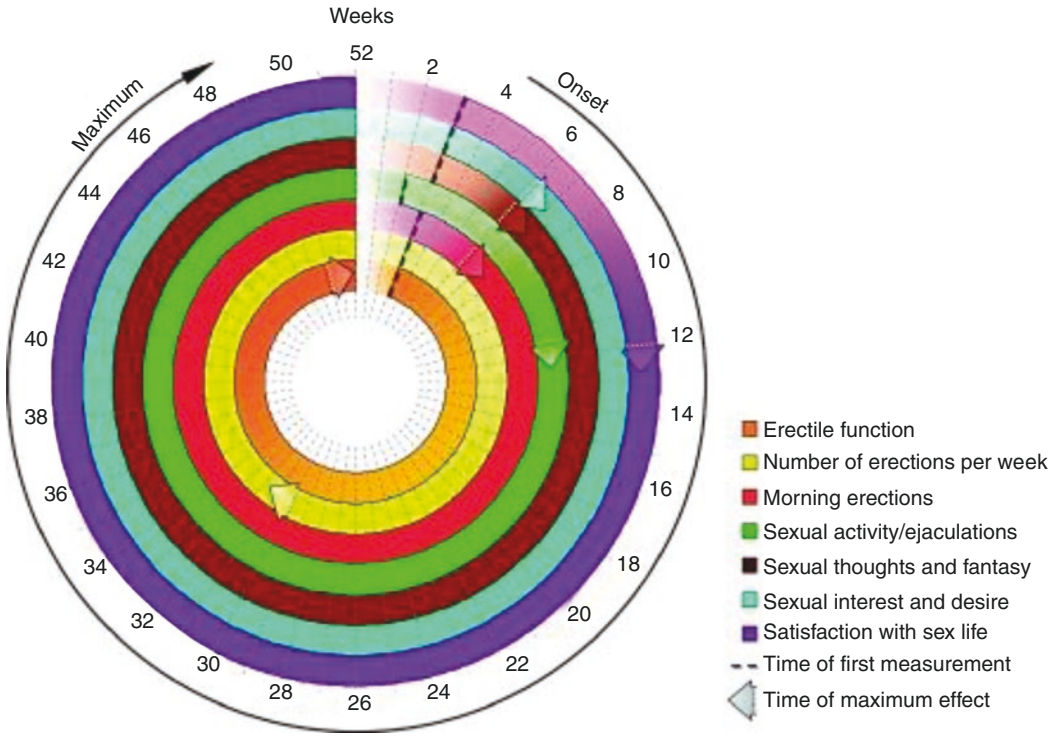


Fig. 46.1 Effects of testosterone therapy over time on sexual function and parameters. **FROM:** SAAD, F., AVERSA, A., ISIDORI, A. M., ZAFALON, L., ZITZMANN, M. & GOOREN, L. 2011. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol,* 165**,** 675–85. This is an Open Access article distributed under the terms of the European Journal of Endocrinology's Re-use License which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited

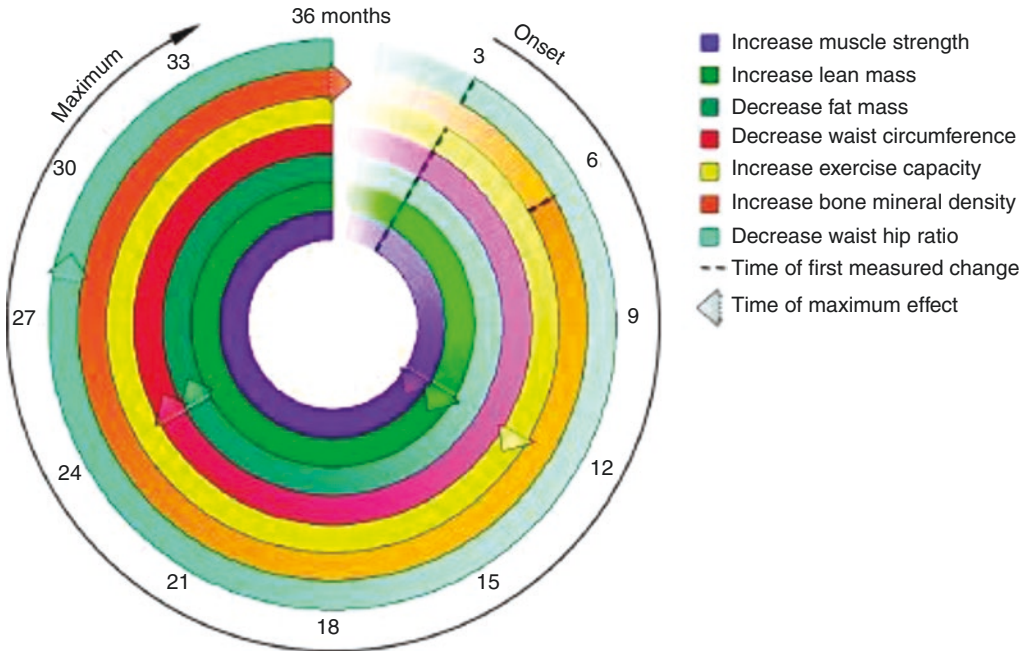


Fig. 46.2 Effects of testosterone therapy over time on body composition and strength**. FROM:** SAAD, F., AVERSA, A., ISIDORI, A. M., ZAFALON, L., ZITZMANN, M. & GOOREN, L. 2011. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol,* 165**,** 675–85. This is an Open Access article distributed under the terms of the European Journal of Endocrinology's Re-use License which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited

improve within few days, but effects on glycemic control become evident only after 3–12 months. Changes in fat mass, lean body mass and muscle strength occur within 12–16 weeks, stabilise at 6–12 months, but can marginally continue over years (Fig. 46.2). Effects on bone are detectable already after 6 months while continuing at least for 3 years (Saad et al. 2011).

46.5 Contraindications and Adverse Effects of Testosterone Therapy

The recent clinical practice guidelines issued by the Endocrine Society (Bhasin et al. 2018a) recommend that TRT should not be used in patients with:

- Prostate or breast cancer.
- Prostate benign hyperplasia and unexplained elevated prostate specific antigen (PSA) without further urological investigation.
- Polycythaemia (elevated haematocrit and haemoglobin).
- Untreated obstructive sleep apnoea.
- Uncontrolled severe heart failure.

The suitability of each treatment option and any formulations-specific side effect (listed in Table 46.4) should be assessed and addressed in each consultation. The most frequent side effects seen with TRT are acne, gynaecomastia, fluid retention, mood swings and male pattern baldness (Bhasin et al. 2018a).

The following side effects may occur from the testosterone replacement therapy. The patient should be advised to discuss any of these symptoms with their endocrine team to review the treatment regimen:

- Irritability, nervousness, aggressiveness
- Mood swings, depression (more noticeable with testosterone injections)
- Weight gain, water retention

Table 46.4 Potential adverse effects of testosterone therapy

Adverse events for which there is evidence of association with T administration
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with T administration
Gynaecomastia
Male pattern balding (familial)
Growth of breast cancer
Induction or worsening of obstructive sleep apnea
Formulation-specific adverse effects
Intramuscular injections of T enanthate, cypionate or undecanoate
Fluctuation in mood or libido
Pain at injection site
Coughing episodes immediately after the intramuscular injection[a]
Transdermal patches
Frequent skin reactions at application site
Transdermal gels and solutions
Potential risk for T transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person)
Skin irritation and odour at application site
Stickiness, slow drying, dripping
Buccal T tablets
Alterations in taste
Irritation of gums
Pellet implants
Infection, expulsion of pellet
T nasal gel
Rhinorrhea, epistaxis, nasal discomfort, nasal congestion, parosmia
Oral tablets (methylT)—not recommended
Effects on liver and cholesterol[b]

Used with permission from BHASIN, S., BRITO, J. P., CUNNINGHAM, G. R., HAYES, F. J., HODIS, H. N., MATSUMOTO, A. M., SNYDER, P. J., SWERDLOFF, R. S., WU, F. C. & YIALAMAS, M. A. 2018a. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab,* 103, 1715–1744

[a]The mechanism of cough, which has been reported rarely after intramuscular injections of T undecanoate and even more rarely after T enanthate and cypionate, is unknown, but it has been attributed to pulmonary oil microembolisation

[b]Liver toxicity has been reported mostly with oral 17α-alkylated androgens

- Prolonged painful or frequent erections
- Headache
- Acne
- Elevated haematocrit and haemoglobin on blood test—raised red blood cell count
- Increase of prostate gland (prostatic hyperplasia) and elevated PSA on a blood test
- Male pattern baldness
- Breast enlargement

Testosterone stimulates erythropoiesis (red cell production) and can lead to polycythaemia or erythrocytosis characterised by increased haematocrit and haemoglobin and long-term risk of thrombosis. The effects of erythrocytosis, defined by a haematocrit >54%, are related to T doses and circulating concentrations and is more prevalent in older men than in younger men (Bhasin et al. 2018a; Haddad et al. 2007). For men on TRT, the risk of developing erythrocytosis is well established, with short-acting testosterone IM injections having the highest risk (Ohlander et al. 2018). Pastuszak et al. (2015) reported a raised haematocrit >50% in 67% of men treated with short-acting IM T injections and in 35% treated with subcutaneous T pellets but only in 13% of men treated with T transdermal gels ($P < 0.0001$). Erythrocytosis was also found in men with higher trough serum testosterone levels treated with T pellets (Ip et al. 2010).

A study of men treated with long-acting T undecanoate IM injections ($N = 347$) showed a low prevalence of erythrocytosis with 7% of men having haematocrit >0.50 and 1% >0.54 (Middleton et al. 2015), although there is no evidence from this group of patients in relation to trough T levels and risk of erythrocytosis. It is therefore important to monitor trough serum T after the third injection of T undecanoate and yearly thereafter to adjust the frequency of injections appropriately in order to minimise the risk of erythrocytosis. The impact of testosterone on erythropoiesis is delineated in Fig. 46.3.

Androgens (testosterone and DTH) stimulate prostatic growth and therefore the long-term effects of their elevated levels on the prostate is often a cause for concern. Circulating levels of

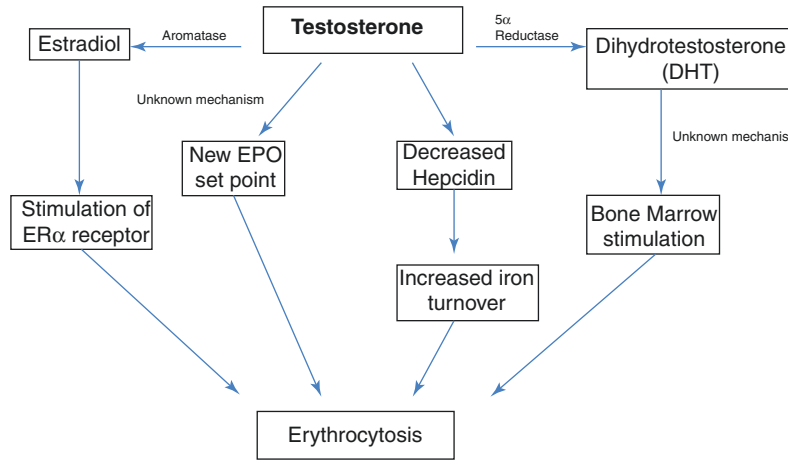


Fig. 46.3 Impact of testosterone on erythropoiesis. Key: *EPO* erythropoietin, *ERa* estrogen receptor-a. **Used with permission from** OHLANDER, S. J., VARGHESE, B. & PASTUSZAK, A. W. 2018. Erythrocytosis Following Testosterone Therapy. *Sexual Medicine Reviews,* 6**,** 77–85

androgens have not been found to be strongly related to prostate cancer, but it is suggested that high levels of testosterone may promote the growth of an existing cancer (Gould et al. 2006; Walsh et al. 2018; Kang and Li 2015; Osterberg et al. 2014). The side effects can be minimised with strict treatment surveillance. The endocrine nurse has a vital role in developing and applying treatment monitoring protocols as well as educating patients on recognising and reporting the side effects from this treatment.

46.6 Testosterone Therapy in Men with Age-Related Testosterone Deficiency

A decline in the testicular and pituitary function is associated with ageing in men resulting in reduced testosterone levels and hypogonadism. Clinical symptoms along with low testosterone level confirm diagnosis of LOH. However, it is difficult to diagnose LOH based on clinical presentation as symptoms are often similar to those found in other conditions prevalent in older men and a careful and detailed clinical history taking is vital. The use of validated questionnaires (Heinemann 2005; Morley et al. 2000) can assist the endocrine nurse in screening for testosterone deficiency in older age. It has also been suggested that low levels of serum T in healthy older men are associated with reduced cognitive performance, particularly spatial ability and memory (Beauchet 2006). Therefore, hypogonadism and testosterone deficiency should be included in the differential diagnosis of older men reporting cognitive dysfunction. Testosterone replacement therapy can reverse hypogonadal symptoms and is commenced once prostate cancer has been excluded (Bhasin et al. 2018a; Wang et al. 2008). Initiation of treatment with half of the standard dose and frequent monitoring is recommended (Bhasin et al. 2018a; Wang et al. 2008; Osterberg et al. 2014).

46.7 Monitoring of Testosterone Therapy

Long-term monitoring involves assessment of hypogonadal symptoms and measurement of testosterone, LH and FSH (in primary hypogonadism), prostate specific antigen (PSA) and rectal examination of the prostate, haematocrit and haemoglobin, and serum lipids at 3 months after initiating TRT and then 6–12 monthly (Traish 2018; Bhasin et al. 2018a). Bone mineral density examination should be undertaken at the start of treatment and then repeated at intervals indicated by the bone density and the risk fracture score (Bhasin et al. 2018a). Table 46.5 presents an overview of the long-term monitoring for patients on testosterone replacement therapy (TRT).

Table 46.5 Monitoring of patients on testosterone therapy

Explain the potential benefits and risks of monitoring for prostate cancer and engage the patient in shared decision making regarding the prostate monitoring plan.
Evaluate the patient at 3–12 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
Monitor T concentrations 3–6 months after initiation of T therapy:
Therapy should aim to raise serum T concentrations into the mid-normal range.
Injectable T enanthate or cypionate: measure serum T concentrations midway between injections. If mid-interval T is >600 ng/dL (24.5 nmol/L) or <350 ng/dL (14.1 nmol/L), adjust dose or frequency.
Transdermal gels: assess T concentrations 2–8 h following the gel application, after the patient has been on treatment for at least 1 week; adjust dose to achieve serum T concentrations in the mid-normal range.
Transdermal patches: assess T concentrations 3–12 h after application; adjust dose to achieve T concentration in the mid-normal range.
Buccal T bioadhesive tablet: assess concentrations immediately before or after application of fresh system.
T pellets: measure T concentrations at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to maintain serum T concentrations in the mid-normal range.
Oral T undecanoate[a]: monitor serum T concentrations 3–5 h after ingestion with a fat-containing meal.
Injectable T undecanoate: measure serum T levels at the end of the dosing interval just prior to the next injection and aim to achieve nadir levels in low-mid range.
Check haematocrit at baseline, 3–6 months after starting treatment, and then annually. If haematocrit is >54%, stop therapy until haematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
Measure BMD of lumbar spine and/or femoral neck after 1–2 years of T therapy in hypogonadal men with osteoporosis, consistent with regional standard of care.
For men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer who choose prostate monitoring, perform digital rectal examination and check PSA level before initiating treatment; check PSA and perform digital rectal examination 3–12 months after initiating T treatment, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
Obtain urological consultation if there is:
An increase in serum PSA concentration >1.4 ng/mL within 12 months of initiating T treatment
A confirmed PSA >4 ng/mL at any time
Detection of a prostatic abnormality on DRE
Substantial worsening of LUTS
Evaluate formulation-specific adverse effects at each visit as per Table 46.3.

Used with permission from BHASIN, S., BRITO, J. P., CUNNINGHAM, G. R., HAYES, F. J., HODIS, H. N., MATSUMOTO, A. M., SNYDER, P. J., SWERDLOFF, R. S., WU, F. C. & YIALAMAS, M. A. 2018a. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab,* 103, 1715–1744

[a]Not available in the United States

46.8 Patient Education and Role of Patient Advocacy Groups

Most of the endocrine reproduction disorders are chronic in nature and continuation of care for these patients is the most important aspect of maintaining and enhancing their well-being. From discussions in this chapter it is apparent that the use of certain medication can be quite complex and lifestyle changes may be required depending on the patient's age at diagnosis and the severity of each case. Patients are not always familiar with the purpose of and how to use these medications. Barber et al. found that a significant percentage of patients newly started on a chronic medication quickly became non-compliant, mainly due to lack of knowledge of their treatment (Barber et al. 2004). A survey which involved 99 men on testosterone replacement therapy found that patients taught by the endocrine nurse reported a high level of knowledge and satisfaction with the control of their condition and their treatment (Llahana and Conway 2006), emphasising once again the important role of nursing in patient education (Llahana 2005).

Patient advocacy groups (PAGs) play an essential role in raising awareness of conditions that can lead to male hypogonadism and providing patients with reassurance that they are not alone. PAGs work closely with health-

care professionals to develop evidence-based information leaflets and educational resources. The Klinefelter's Syndrome Association (KSA) in the UK, as described below, is a great example of a PAG with a vital contribution in the support and self-management of patients with hypogonadism.

46.8.1 The Klinefelter's Syndrome Association (KSA)

After her infant son was diagnosed with Klinefelter's Syndrome (KS/XXY) (please refer to Chap. 44 for more details on KS), Sue Cook found it very difficult to find good information out about the condition. She was given no support. Determined that others wouldn't have to struggle as she had, in the late 1980s, with the support of Contact a Family, Sue, her husband David, and an XXY adult, Steve Hammett, started The Klinefelter Syndrome Association (KSA) to provide reliable information and support for others affected.

The KSA has a worldwide membership. It organises an annual conference, produces a quarterly newsletter for members and hosts an excellent website. It runs several hidden Facebook groups and is building a network of social events across the country to allow those affected to have contact with others. It organises Activity Weekends twice a year which have prompted several members to say that they now feel part of a "second family" of people who understand how they feel, the challenges they face and amongst whom they can relax and truly be themselves. The KSA also produces various booklets and a Members' Handbook most of which can be downloaded from the website. It runs a Helpline and offers free membership to medical professionals—available from the website.

The KSA is presently working with medical professionals to identify the many areas—such as gender identity issues, the effects of testosterone replacement on muscle and bone development, the causes of excessive abdominal weight distribution—where information is lacking, with a view to commissioning further research.

The KSA is encouraging the production of guidelines for the treatment of KS/XXY to ensure that all affected receive appropriate treatment.

Below are two case studies which highlight the importance of the work carried out by the KSA.

- A. contacted the helpline when her husband was told that he would have to stop testosterone treatment as his blood count was too high. She was concerned that he was in a physically demanding job and couldn't remain alert without his medication. After A. sent over her husband's blood test results, the call handler realised that he needed urgent venesection. The KSA contacted an experienced endocrinologist who gave A's husband an emergency appointment.
- KSA was contacted by a male in his 30s who had recently discovered, when going through his deceased mother's papers, that he had been diagnosed with karyotype XXY in childhood. He had never been told and was very confused and upset. The KSA volunteer talked with him for an hour, answering many of his questions and allaying some of his fears, and advised him to talk to his general practitioner to arrange a referral to an Endocrinology Clinic for specialist diagnosis and follow-up. Peer support was also offered and he was advised that when he was ready, he could ask to join one of the Facebook groups which the KSA supports.

Please pass our details to all KS/XXY patients:
Website: www.ksa-uk.net.
Contact for information: Email: Chair@ksa-uk.net

46.9 Conclusions

Male hypogonadism is a frequent, but also underdiagnosed, endocrine condition. Testosterone replacement therapy, treatment option, long-term monitoring and adverse effects were discussed in this chapter with a focus on the aspects relevant to endocrinology nursing. It is widely recognised

that when patients have adequate understanding of their condition, they are more empowered and able to choose an individualised treatment tailored to their needs. The endocrine nurse is the most important member of the team, in providing patients and their families with education, continuous support and consultation on new treatments and coping strategies necessary following diagnosis.

Acknowledgments With special thanks to Alison Bridges, Chair of Trustees, Klinefelter's Syndrome Association (KSA) (www.ksa-uk.net) and Zahir Barmania from The Klinefelter's Network, Greater London (www.klinefelters.net) for their contribution to this chapter with case studies, patient resources and information on the Patient Advocacy Group.

References

Allan CA, McLachlan RI. Chapter 139: androgen deficiency disorders. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, et al., editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: W.B. Saunders; 2016. p. 2394–420. e13.

Barber N, Parsons J, Clifford S, Darracott R, Horne R. Patients' problems with new medication for chronic conditions. Qual Saf Health Care. 2004;13(3):172–5.

Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. Eur J Endocrinol. 2006;155(6):773–81.

Behre HM, Nieschlag E. Testosterone preparations for clinical use in males. In: Nieschlag E, Behre HM, Nieschlag S, editors. Testosterone: action, deficiency, substitution. 4th ed. Cambridge: Cambridge University Press; 2012. p. 309–35.

Bhasin S. Testicular disorders. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th ed. Philadelphia: Saunders Press; 2007. p. 645–700.

Bhasin S, Jameson JL. Disorders of the testes and male reproductive system. In: Jameson JL, editor. Harrison's endocrinology. 4th ed. New York: McGraw Hill Education; 2017. p. 159–85.

Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018a;103(5):1715–44.

Bhasin S, Travison TG, O'Brien L, MacKrell J, Krishnan V, Ouyang H, et al. Contributors to the substantial variation in on-treatment testosterone levels in men receiving transdermal testosterone gels in randomized trials. Andrology. 2018b;6(1):151–7.

Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf). 2007;67(6):853–62.

Donatucci C, Cui Z, Fang Y, Muram D. Long-term treatment patterns of testosterone replacement medications. J Sex Med. 2014;11(8):2092.

Dwyer A, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis. 2014;9:83.

Gould DC, Feneley MR, Kirby RS. Prostate-specific antigen testing in hypogonadism: implications for the safety of testosterone-replacement therapy. BJU Int. 2006;98(1):1–4.

Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Boloña ER, Sideras K, Uraga MV, Erwin PJ, Montori VM. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82(1):29–39.

Heinemann LA. Aging males' symptoms scale: a standardized instrument for the practice. J Endocrinol Investig. 2005;28(11 Suppl Proceedings):34–8.

Ip FF, di Pierro I, Brown R, Cunningham I, Handelsman DJ, Liu PY. Trough serum testosterone predicts the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. Eur J Endocrinol. 2010;162(2):385–90.

Jockenhovel F. Male hypogonadism. Bremen: UNI-MED Verlag AG; 2004.

Kang D-Y, Li H-J. The effect of testosterone replacement therapy on prostate-specific antigen (PSA) levels in men being treated for hypogonadism: a systematic review and meta-analysis. Medicine. 2015;94(3):e410.

Kovac JR, Rajanahally S, Smith RP, Coward RM, Lamb DJ, Lipshultz LI. Patient satisfaction with testosterone replacement therapies: the reasons behind the choices. J Sex Med. 2014;11(2):553–62.

Llahana SV. A theoretical framework for clinical specialist nursing: an example from diabetes. Wiltshire: APS Publishing; 2005.

Llahana S, Conway G. Knowledge of testosterone replacement therapy is significantly correlated with patient satisfaction suggesting greater need for education; 2006.

Luetjens CM, Weinbauer GF. Testosterone: biosynthesis, transport, metabolism and (non-genomic) actions. In: Nieschlag E, Behre HM, Nieschlag S, editors. Testosterone: action, deficiency, substitution. 4th ed. Cambridge: Cambridge University Press; 2012. p. 15–32.

Middleton T, Turner L, Fennell C, Savkovic S, Jayadev V, Conway AJ, Handelsman DJ. Complications of injectable testosterone undecanoate in routine clinical practice. Eur J Endocrinol. 2015;172(5):511–7.

Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, et al. Validation of a screening ques-

tionnaire for androgen deficiency in aging males. Metabolism. 2000;49(9):1239–42.
Neto FT, Bach PV, Najari BB, Li PS, Goldstein M. Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol. 2016;59:10–26.
Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis following testosterone therapy. Sex Med Rev. 2018;6(1):77–85.
Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. Indian J Urol. 2014;30(1):2–7.
Pastuszak AW, Gomez LP, Scovell JM, Khera M, Lamb DJ, Lipshultz LI. Comparison of the effects of testosterone gels, injections, and pellets on serum hormones, erythrocytosis, lipids, and prostate-specific antigen. Sex Med. 2015;3(3):165–73.
Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol. 2011;165(5):675–85.
Schoenfeld MJ, Shortridge E, Cui Z, Muram D. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims analysis. J Sex Med. 2013;10(5):1401.
Szeinbach SL, Seoane-Vazquez E, Summers KH. Development of a men's Preference for Testosterone Replacement Therapy (P-TRT) instrument. Patient Prefer Adherence. 2012;6:631–41.
Traish AM. Benefits and health implications of testosterone therapy in men with testosterone deficiency. Sex Med Rev. 2018;6(1):86–105.
Walsh TJ, Shores MM, Krakauer CA, Forsberg CW, Fox AE, Moore KP, et al. Testosterone treatment and the risk of aggressive prostate cancer in men with low testosterone levels. PLoS One. 2018;13(6):e0199194.
Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008;159(5):507–14.
Zitzmann M. Effects of testosterone replacement and its pharmacogenetics on physical performance and metabolism. Asian J Androl. 2008;10(3):364–72.

Key Reading

1. Allan CA, McLachlan RI. Chapter 139: androgen deficiency disorders. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, Grossman AB, Melmed S, et al., editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: W.B. Saunders; 2016. p. 2394–420. e13.
2. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715–44.
3. Bhasin S, Jameson JL. Disorders of the testes and male reproductive system. In: Jameson JL, editor. Harrison's endocrinology. 4th ed. New York: McGraw Hill Education; 2017. p. 159–85.
4. Hohl A. Testosterone: from basic to clinical aspects. Cham: Springer; 2017.
5. Nieschlag E, Behre HM, Nieschlag S, editors. Testosterone: action, deficiency, substitution. 4th ed. Cambridge: Cambridge University Press; 2012.
6. Zitzmann M. Effects of testosterone replacement and its pharmacogenetics on physical performance and metabolism. Asian J Androl. 2008;10(3):364–72.

Spermatogenesis and Assisted Fertility Treatment

47

Andrew A. Dwyer, Elizabeth Williamson, Margaret G. Au, and Channa Jayasena

Contents

47.1 **Introduction** 905

47.2 **Approach to Fertility Treatment** 907

47.3 **Predictors of Outcome** 908
47.3.1 Testicular Volume 908
47.3.2 Cryptorchidism 910
47.3.3 Inhibin B (IB) 910

47.4 **Spermatogenesis Induction** 910
47.4.1 Pulsatile GnRH Therapy 910
47.4.2 Human Chorionic Gonadotrophin (hCG) Mono-therapy 911
47.4.3 Combined Gonadotrophin Treatment 911
47.4.4 Sequential Treatment 912
47.4.5 Patient Education and Monitoring During Treatment 913

47.5 **Assisted Fertility** 914
47.5.1 Surgical Sperm Retrieval 914
47.5.2 Intracytoplasmic Sperm Injection (ICSI) 915
47.5.3 Sperm Cryopreservation 915

47.6 **Ethics of Assisted Fertility** 916
47.6.1 Ethical Issues Related to Future Children 917
47.6.2 Ethical Issues Related to Patients 917
47.6.3 Ethical Issues Related to Gamete Donors 918

A. A. Dwyer (✉)
William F. Connell School of Nursing, Boston College, Chestnut Hill, MA, USA

Boston College, Chestnut Hill, MA, USA
e-mail: Andrew.dwyer@bc.edu

E. Williamson
Reproductive Medicine Unit, University College London Hospitals, London, UK
e-mail: elizabeth.williamson@uclh.nhs.uk

M. G. Au
Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA, USA

C. Jayasena
Reproductive Endocrinology and Andrology, Imperial College and Hammersmith Hospital, London, UK

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_47

47.6.4 Access to Assisted Reproduction..... 918
47.6.5 Assisted Reproduction and Pre-implantation Genetic Testing..... 918
47.7 **Conclusions**..... 919
References..... 920

Abstract

Approximately 15% of couples are affected by infertility and it is estimated that male factors contribute to roughly half of cases. Careful history and clinical assessment is warranted in men presenting with infertility. Genetic defects such as Klinefelter syndrome and iatrogenic causes such as exogenous testosterone treatment are not uncommonly identified causes of infertility in men presenting for endocrine consultation. Importantly, neuroendocrine aetiologies of male infertility such as congenital hypogonadotrophic hypogonadism (CHH) are more amenable to treatment compared to gonadal defects causing hypergonadotrophic hypogonadism. Assessing predictors of outcomes is an important aspect of setting appropriate patient expectations prior to beginning fertility-inducing treatment. Tailored hormonal therapies can effectively develop sperm in approximately 75% of men with CHH. Additionally, assisted reproductive technologies can be a helpful complement in challenging cases. This chapter is intended to give the endocrine nurse context for the approach to male infertility and provides an overview of hormonal treatments and relevant assisted reproductive technologies. Emphasis is given to setting realistic patient expectations, delivering coordinated care including appropriate referral to fertility specialists and elements related to therapeutic education and psychosocial support relevant for this patient population.

Keywords

Ethics · Fertility agents, male · Follicle stimulating hormone · GnRH · Gonadotrophins · Infertility, male · Spermatogenesis

Abbreviations

ART	Assisted reproductive technologies
ASRM	American Society of Reproductive Medicine
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CBAVD	Congenital bilateral absence of the *vas deferens*
CFTR	Cystic fibrosis transmembrane regulator
CGH	Comparative genomic hybridization
CHH	Congenital hypogonadotrophic hypogonadism
CPHD	Combined pituitary hormone deficiency
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin-releasing hormone
hCG	Human chorionic gonadotrophin
HIV	Human immunodeficiency virus
HPG	Hypothalamic-pituitary-gonadal
IB	Inhibin B
ICSI	Intracytoplasmic sperm injection
IUI	Intra-uterine insemination
IVF	In vitro fertilization
LH	Luteinizing hormone
MESA	Microsurgical epididymal sperm aspiration
micro-TESE	Microsurgical testicular sperm extraction
PCAs	Permeable cryoprotective agents
PESA	Percutaneous epididymal sperm aspiration
PGD/PGS	Pre-implantation genetic diagnosis/screening

SHBG	Sex hormone binding globulin
T	Testosterone
TARTs	Testicular adrenal rest tumours
TV	Testicular volume

Key Terms

- **Assisted reproductive technologies (ART):** Procedures employed to achieve pregnancy such as hormonal stimulation followed by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).
- **Autonomy:** Respect for persons, allowing for fully informed decision-making free of coercion.
- **Azoospermia:** The absence of sperm in the ejaculate.
- **Beneficence:** Doing good, providing the maximum benefit for a patient.
- **Infertility:** The inability to achieve pregnancy following regular unprotected intercourse for 12 months. Aetiologies may be male, female or mixed (both).
- **Justice:** Insuring equal distribution of resources, risks and benefits,
- **Nonmaleficence:** Doing no harm, or preventing/minimizing harm whenever possible.
- **Oligospermia:** Decreased number of sperm in the ejaculate. The World Health Organization considers oligospermia as the fifth percentile for fertile men (15 million/mL). Severe oligospermia is considered as <5 million/mL.
- **Spermatogenesis:** The process of producing spermatozoa. Both mitosis and meiosis are involved in the complex development from spermatogonia to spermatozoa in the ejaculate. The entire process takes between 69 and 80 days.
- **Testicular volume:** A measure of testicular size. Volume reflects predominantly the development of the seminiferous tubules and is an important predictor of fertility potential. It is most frequently measured via Prader orchidometer or via calculation of ultrasound measurement in three planes.

Key Points

- Hypogonadotrophic hypogonadism is a treatable form of male infertility.
- Testosterone treatment suppresses spermatogenesis and is contraindicated in men seeking fertility.
- Predictors of outcome should be thoroughly evaluated to appropriately gauge patient expectations for response to treatment.
- Hormonal treatment should be tailored and supervised by clinicians experienced with these specialized treatment regimens.
- Assisted reproductive technology can be used to complement hormonal treatments and enhance fertility outcomes.

47.1 Introduction

Infertility is common and is estimated to affect 15% of couples. Estimating the prevalence of male infertility is challenging since a female partner with normal fertility may still conceive if their male partner has mild infertility; however, male factor infertility is reported as contributing to 20–70% of infertility (Tournaye et al. 2016).

Broadly, male fertility problems fall into several categories: abnormal spermatogenesis (quantitative/qualitative), problems with sperm transport (i.e. ductal obstruction), gonadal disorders (e.g. hypergonadotrophic hypogonadism) or neuroendocrine dysfunction (e.g. hypogonadotrophic hypogonadism). Quantitative and qualitative spermatogenic problems are identified via seminal fluid analysis (see Chap. 45) (World Health Organization 2010) (Fig. 47.1 and Box 47.1).

Aetiologies may be genetic (e.g. Y chromosome microdeletions, Klinefelter syndrome), mumps

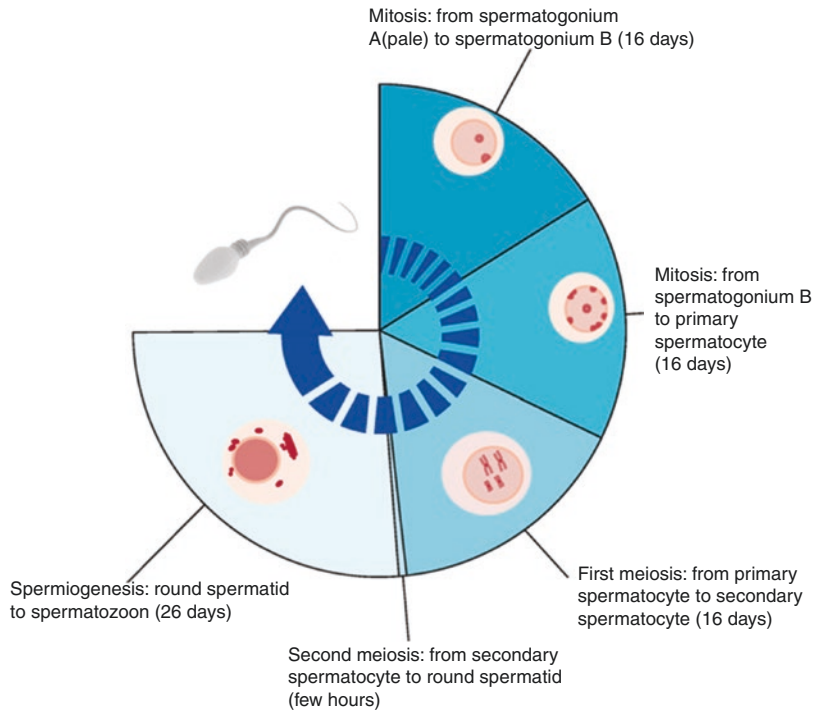


Fig. 47.1 Process of spermatogenesis Tournaye et al. 2016 (used with permission from Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2016 Jul 6. pii: S2213-8587(16)30040-7. doi: 10.1016/S2213-8587(16)30040-7)

Box 47.1 World Health Organization (WHO) Seminal Fluid Analysis Reference Values*

WHO 2010 reference values for normal fertility

Semen volume 1.5 mL

Sperm concentration 15 × 106/mL

Total sperm concentration 39 × 106 spermatozoa per ejaculate

Total motility 40%

Progressive motility 32%*

Normal morphology 4%

WHO Laboratory manual for the examination and processing of human semen (5th edn.), World Health Organization, Geneva (2010)

infection, cancer related (chemotherapy or localized radiotherapy), or secondary to maldescended testes (cryptorchidism) or varicocele (Tournaye et al. 2016). Sperm transport problems may result from sexually transmitted infections (STI, e.g. chlamydia, tuberculosis), pelvic trauma or neurologic problems (e.g. diabetes mellitus) as well as retrograde ejaculation and erectile dysfunction (see Chap. 46). Men harbouring mutations in the cystic fibrosis gene (cystic fibrosis transmembrane regulator, *CFTR*) may have congenital bilateral absence of the *vas deferens* (CBAVD) despite having no other clinical features of cystic fibrosis. This problem can be identified by clinical examination of the testes and scrotum and may be manifested in a low volume, low pH, azoospermic seminal fluid analysis (Tournaye et al. 2017).

Primary gonadal failure (i.e. Klinefelter syndrome) results in hypergonadotrophic hypogonadism and infertility. The most common chromosomal anomaly in males, 47, XXY occurs in approximately 1:660 and adults are infertile in 90–99% of cases (Groth et al. 2013). There is evidence that testicular failure and progressive hyalinization of seminiferous tubules occur in mid-puberty (Rohayem et al. 2016). Hormonal treatments are not effective for such cases yet advances in assisted reproductive technologies (ART) provide new possibilities for potential fertility in these men as sperm can be retrieved surgically in about half of cases (Corona et al. 2017).

For men with infertility arising from a hypothalamic or pituitary origin (e.g. congenital hypogonadotrophic hypogonadism, CHH) treatment options are quite effective in developing fertility. This chapter will focus primarily on the hormonal treatment regimens for such patients as well as providing an overview of relevant ART and discussion of appropriate urologic consultation and referral to an infertility specialist.

47.2 Approach to Fertility Treatment

As reviewed in Chap. 45 (evaluation of HPG axis), careful evaluation is needed to identify the underlying aetiology of infertility so treatment can be appropriately targeted. Importantly, iatrogenic causes must be ruled out. Exogenous testosterone (T) treatment suppresses the hypothalamic-pituitary-gonadal (HPG) axis and spermatogenesis. The Endocrine Society and the American Society and the International Society for Sexual Medicine both consider testosterone therapy as contraindicated in men seeking fertility (Bhasin et al. 2010; Dean et al. 2015); unfortunately this clinical guidance is not always adhered to. A 2012 survey of nearly 400 practising urologists revealed that 1 in 4 (25%) would prescribe T treatment to infertile men actively trying to conceive (Ko et al. 2012).

Recovery of spermatogenesis following cessation of testosterone therapy can be protracted. Indeed, an integrated analysis of male contraception studies by Liu and colleagues found that roughly two-thirds of men recover normal sperm counts (20 million/mL) within 6 months (95% CI: 61–72%) and all men recovered within 2 years (95–93% at 12 months, 92–98% at 16 months) (Liu et al. 2006). However, recent clinical data suggest that age and sperm count prior to starting testosterone treatment are predictive of spermatogenic recovery (Kohn et al. 2017). Notably, men who use performance enhancing drugs such as anabolic androgenic steroids can suppress their HPG axis for extended periods of time and may remain infertile long after cessation of use (Christou et al. 2017).

It is worthwhile to note that among the most common causes of male factor infertility is idiopathic (Anawalt 2013). These men typically exhibit sperm counts of 10 million/mL (or less) and often abnormal sperm morphology and/or motility. Such cases should be referred for consultation with a fertility specialist to discuss ART options. Of men presenting with very low sperm counts or azoospermia, approximately 15% have chromosomal anomalies (Hofherr et al. 2011) (Table 47.1). Among the most frequent is Klinefelter syndrome—which can be identified by karyotype or comparative genomic hybridization (CGH). Advances in surgical techniques, specifically microsurgical testicular sperm extraction (micro-TESE), provide the possibility for these men to have fertility. A recent meta-analysis found that sperm extraction was possible in approximately half of cases (44%, 95% CI: 39–48%) (Corona et al. 2017), although the live birth rate following micro-TESE for Klinefelter syndrome remains under-reported. Notably, as the gonadal failure is progressive, some have proposed to perform extraction during adolescence for long-term cryopreservation and potential fertility in adulthood using ART. However, there is considerable controversy regarding this and it

Table 47.1 Aetiological factors in male infertility

Abnormal spermatogenesis	Sperm transport problems	Hypogonadotrophic hypogonadism (HH)
Varicocele Mumps infection Maldescended testes (cryptorchidism) Cancer therapy Genetic Y chromosome microdeletions Klinefelter syndrome	Congenital bilateral absence of the *vas deferens* (2° to *CFTR* mutations) Sexually transmitted infections (e.g. chlamydia) Pelvic trauma Neurologic problems e.g. diabetes mellitus Retrograde ejaculation Erectile dysfunction	Congenital GnRH deficiency Normosmic HH Kallmann syndrome Combined pituitary hormone deficiency

should be considered on a case-by-case basis given ethical concerns related to non-essential invasive procedures in minors as well as potential confounding issues related to the young adult's comprehension and ability to weigh risk-benefit (Ramstein et al. 2017; Franik et al. 2016). It is advisable that discussions occur with adolescents 16+ years to review the option as part of shared decision-making and management (Dwyer et al. 2015a). In the event that patients are interested in pursuing this option, a referral to a urologic surgeon with expertise in micro-TESE should be made in a timely manner.

A number of endocrine disorders can disrupt spermatogenesis. Hyper- and hypothyroidism can disrupt sperm morphology and motility—yet thyroid disorders are rarely the sole cause of male factor infertility (Krassas et al. 2010). While a relatively rare endocrine cause of male infertility, hyperprolactinaemia can underlie some cases (see also Chap. 45). Accordingly, sub-fertile males should have a thorough medication history taken to identify possible contribution of antipsychotic drugs or dopamine agonists to elevated serum prolactin levels (Patel et al. 2016). Severe cases of congenital adrenal hyperplasia (CAH) are usually diagnosed in infancy yet milder forms of 21 hydroxylase deficiency may not be identified until adolescence to early adulthood. Males with congenital adrenal hyperplasia (CAH) have impaired fertility related to hypogonadotrophic hypogonadism and gonadal failure related to testicular adrenal rest tumours (TARTs) (King et al. 2016).

Rising obesity rates are contributing to a growing number of consultations evaluating subfertility in overweight men. A meta-analysis of 21 observational studies including over 13,000 men demonstrates that obese men have a doubled risk of sperm abnormalities when compared with men of normal weight (Du Plessis et al. 2010). The precise mechanism of how obesity impairs fertility remains unclear and it may result from several interacting factors. Contributors include thermal effects of increased scrotal temperature (secondary to a scrotal adiposity or a panniculus—overhanging belly), the pro-inflammatory state of obesity and oxidative stress that can impair sperm quality, as well as altered adipokines (e.g. adiponectin, leptin) and hormonal disturbances (Cabler et al. 2010). Obesity-induced hormonal alterations including decreased sex hormone binding globulin (SHBG) increased aromatization of T to oestradiol with a resulting decrease in serum gonadotrophins via oestradiol-induced negative feedback at the hypothalamus/pituitary (Pitteloud et al. 2008). Thus, first-line interventions include lifestyle interventions for weight loss—yet this can be challenging to maintain in the long term. Bariatric surgery has a potent impact on sex steroids and a recent meta-analysis indicates that serum T levels increase by 8.1 nmol/L (95% CI: 6–11 nmol, 173–317 ng/dL) and this normalizes serum levels in 87% of men (95% CI: 76–95%) (Escobar-Morreale et al. 2017). Such increases likely impact fertility yet well-designed studies examining the ultimate effect on conception and pregnancy outcomes are lacking (Abiad et al. 2017). A pharmacologic approach to improve sub-fertility in obese men has been to use either aromatase inhibitors (AIs) or selective oestrogen receptor modulators (SERMs) to reduce the negative hypothalamic-pituitary feedback of oestradiol (Rambhatla et al. 2016). However, caution is warranted as these applications are unapproved (so-called "off-label" treatments), increase the risk of thrombosis, and recent meta-analyses reveal limited supporting data that are often from single-centre, methodologically weak studies (Chua et al. 2013; Ribeiro et al. 2016).

For men with a hypothalamic aetiology such as isolated gonadotrophin-releasing hormone (GnRH) deficiency (i.e. CHH) or a pituitary gonadotrophin deficiency (combined pituitary hormone deficiency, CPHD), infertility can be effectively treated with hormonal regimens to induce spermatogenesis (Dwyer et al. 2015b). In cases when limited sperm production (or poor quality sperm) hinders conception, ART may be employed to enhance chances for achieving a biologic pregnancy.

47.3 Predictors of Outcome

47.3.1 Testicular Volume

To date, several predictors of fertility outcomes have been identified (Table 47.2). Testicular

Table 47.2 Predictors of outcome for fertility induction in men with hypogonadotrophic hypogonadism

Report	Sample size	Treatment (duration)	Sperm positive	Time to sperm	Negative predictor	Comments
Burris et al. (1988) J Clin Endocrinol Metab	22	hCG: 2′000 U 3×/wkly (24 mos)	15/22 (68%)	n/a	TV <4 mL	Larger initial TV → better outcomes for hCG mono-therapy
Pitteloud et al. (2002a, b) J Clin Endocrinol Metab	76	Pulsatile GnRH 25–600 ng/kg Q 2 h (12–24 mos)	57/76 (75%)	2–24 mos	TV <4 mL Cryptorchidism IB <60 pg/mL	Cryptorchidism more common with absent puberty (TV <4 mL) 50% of bilateral cryptorchidism remained azoospermic Sperm by 12 mos: 24/31 (77%), by 24 mos: 42/51 (82%)
Miyagawa et al. (2005) J Urol	18	hCG: 3′000 U 2× weekly FSH: 75 IU 2× weekly (12–24 mos)	9/18 (50%)	n/a	TV <4 mL	Cryptorchidism more common with absent puberty (TV <4 mL) Initial TV was positively correlated with sperm count
Liu et al. (2009) J Clin Endocrinol Metab	75	hCG: 1′500–2′000 U 2×/wk FSH (post 6 mos hCG): 75–150 IU 3×/wk (23 ± 2 mos)	85–90%	7 mos 95% CI: 6–10	TV <4 mL Prior TRT	Time to response effected by initial TV Positive effect of prior cycles
Warne et al. (2009) Fertil Steril	81	hCG: 1′000 U 3×/wk or 2′000 U 2×/wk FSH (post 3–6 mos hCG): 150–300 3×/wk (18 mos)	68/81 (84%)	6 mos 95%CI: 3–18	TV <4 mL BM I > 30	Time to response effected by initial TV No effect of prior gonadotrophin treatment All non-responders had absent puberty (TV <4 mL)
Liu et al. (2016) Medicine (Baltimore)	223	hCG: 2′000–5′000 U 2×/wk FSH (post 6 mos hCG): 75–150 U 2×/wk (23 ± 13 mos)	143/223 (64%)	14 ± 8 mos	TV <4 mL Cryptorchidism	Higher LH levels on GnRHa stimulation → positive predictor No effect of prior TRT or BMI
Rohayem et al. (2016) Andrology	51	hCG: 1′500 U 2×/wk FSH (post 3 mos hCG): 150 U 3×/wk (27 ± 18 mos)	50/51 (98%)	11 ± 8 mos	TV <4 mL Cryptorchidism	Cryptorchidism more common with absent puberty (TV <4 mL) Initial TV and IB positively correlated with final TV No effect of BMI

hCG human chorionic gonadotrophin, *FSH* follicle stimulating hormone (purified urinary formulation or recombinant), *GnRH* gonadotrophin-releasing hormone, *mos* months, *TV* testicular volume, *IB* inhibin B, *BMI* body mass index, *TRT* testosterone replacement therapy

volume (TV) is an important predictor of spermatogenesis (Dwyer et al. 2015b) and pregnancy (Liu et al. 2002). Men with CHH/CPHD may have either partial pubertal development or no spontaneous development at all. Those with a complete absence of puberty (TV <4 mL) lack the important proliferative window of mini-puberty (Dwyer et al. 2016) (see Chap. 43) and consistently have poorer fertility outcomes. As such careful assessment of TV via Prader

orchidometer is a key aspect of evaluation. Importantly, one must take into consideration any prior gonadotrophin exposure may confound interpretation of current TV.

47.3.2 Cryptorchidism

Maldescended testes, either unilateral or bilateral, is another prognostic factor for men with CHH/CPHD (Table 47.2) (Dwyer et al. 2015b). Cryptorchidism is evident in 2–5% of full-term neonates (Chan et al. 2014) yet testes subsequently descend spontaneously by 6 months in three quarters of cases. If this does not resolve, and surgical correction is not done in the first year of life, the long-term impact on fertility can be significant (Chan et al. 2014). Indeed, men with bilateral cryptorchidism are six times more likely to be infertile compared to men with a history of either unilateral cryptorchidism or normally descended testes (Lee et al. 1996). A study suggested that orchiopexy at 9 months (current recommendation) (Chan et al. 2014; Ritzen et al. 2007) was associated with significant higher TV and numbers of germ and Sertoli cells when compared with later correction at 3 years—thus making a compelling case for early surgical intervention to correct maldescended testes (Kollin et al. 2012).

47.3.3 Inhibin B (IB)

Sometimes used as a surrogate measure of Sertoli cell number, IB is correlated with a number of fertility measures such as TV and sperm count (Pitteloud et al. 2002a). Indeed, lack of spontaneous puberty is biochemically manifested as low serum inhibin B (IB) levels (i.e. <60 pg/mL) (Pitteloud et al. 2002b). While IB is indirectly related to the other two predictors, it can be a useful biomarker to examine response to treatment during fertility-inducing treatment (Dwyer et al. 2013). There are some remaining questions related to how modifiable the predictors of outcome are. For instance, small pilot studies administering gonadotrophins to neonates lacking mini-puberty offer some promise for improving potential fertility in the future (Bouvattier et al. 2012). While long-term follow-up and definitive data are pending, these initial studies raise important questions regarding the optimal timing for hormonal intervention. There has been some suggestion that prior T treatment may have detrimental effects on later fertility induction (Liu et al. 2009). A recent meta-analysis by Rastrelli and colleagues did not find evidence of this (Rastrelli et al. 2014). However, caution is warranted in interpreting their findings as a number of studies examined in the meta-analysis excluded men with prior T treatment—thus raising a potential source of bias in these data. More data are needed to address this unanswered question.

In summary, a careful history and clinical examination can provide important information for tailoring hormonal treatment and maximizing potential fertility outcomes. This information should be contextualized for the patient and partner. Clear communication on this topic is a key element for helping to establish appropriate expectations for response to treatment. This should not be ignored as conception, clinical pregnancy and birth of a child is not achieved in all cases.

47.4 Spermatogenesis Induction

47.4.1 Pulsatile GnRH Therapy

For patients with hypothalamic defects and isolated GnRH deficiency (CHH), pulsatile GnRH therapy is an effective treatment for both normalizing serum T levels and for inducing spermatogenesis (Hoffman and Crowley 1982; Delemarre-Van de Waal 1993). This treatment involves a subcutaneous bolus of GnRH every 2 h via microinfusion pump and the dose is titrated to achieve normal serum T levels. Three quarters of men are able to develop sperm in their ejaculate on long-term treatment (Rastrelli et al. 2014). Typically, men with some spontaneous puberty (TV ≥4 mL) develop sperm more rapidly than men with absent puberty (6–12 months compared to 18–24 months) (Pitteloud et al. 2002a).

Pulsatile GnRH is a physiologic approach but it is limited by two main factors. First, there are limited options for the microinfusion pump. The device must deliver programmed boluses without a basal rate—this is a feature that is not a design feature in insulin pumps where delivering a basal rate is a central aspect of treatment. Second, managing men on pulsatile GnRH therapy requires particular expertise and thus is typically only available at specialized centres (Dwyer et al. 2015b; Boehm et al. 2015). Thus, it may not be a feasible treatment option for many patients.

47.4.2 Human Chorionic Gonadotrophin (hCG) Mono-therapy

Unlike pulsatile GnRH, exogenous gonadotrophin treatment is a treatment approach that is effective for men with hypothalamic and pituitary aetiologies alike (Finkel et al. 1985). However, mono-therapy with hCG is best reserved for men with a larger TV (Dwyer et al. 2015b). It is a viable option for men with suppressed spermatogenesis following T treatment and for men on the milder end of the CHH phenotypic spectrum (e.g. "fertile eunuch" variant, see Chap. 44). Mono-therapy is much less successful in men who lack testicular development (Rastrelli et al. 2014), as only approximately half of men with no testicular development are able to develop sperm in the ejaculate in long-term hCG mono-therapy (Dwyer et al. 2015b). Treatment regimens vary according to the available formulation yet typically involve subcutaneous injections every other day or three times per week of 1000–1500 units (titrated to achieve mid-normal serum T) (Boehm et al. 2015) (Table 47.3).

47.4.3 Combined Gonadotrophin Treatment

Spermatogenesis outcomes are improved for men with TV <4 mL with the use of combined gonadotrophin therapy, i.e. hCG + follicle

Table 47.3 Treatment regimens for fertility induction in men with hypogonadotrophic hypogonadism

Treatment	Type(s) of patients	Regimen	Titration targets	Notes
Pulsatile GnRH therapy	• Isolated GnRH deficiency	GnRH (25–600 ng/kg) via SC bolus every 2 h	GnRH adjusted to reach low-mid normal serum T	• Sperm in 75% of cases • Can be used as part of sequential treatment
hCG mono-therapy	• Partial puberty (TV >4) or full pubertal development	SC injection 1′000–2′000 U 2 or 3×/week	Trough T adjusted to low-mid normal range	• Monitor haematocrit and gynaecomastia • hCG dose can often be decreased once T is normalized
Combined gonadotrophins (hCG + FSH[a])	• Isolated GnRH deficiency • Pituitary LH/FSH deficiency	hCG via SC injection 1′000–2′000 U, 2 or 3×/week FSH* via SC injection 75–150 IU, 2 or 3×/week	hCG: Trough T adjusted to low-mid normal range FSH: Trough serum level of 4–6 IU/L	• FSH can be started immediately or following 3 or 6 mos hCG alone • Serum FSH level of 9 IU/L or higher should be avoided
Sequential treatment (FSH priming)	• Absent puberty (TV <4 mL)	FSH* via SC injection 75–150 IU, daily or 3×/week (for 2–4 months) → then GnRH or hCG + FSH	FSH: Trough serum level of 4–6 IU/L GnRH/hCG as above	• Ultrasound is helpful for monitoring TV • Growth during FSH priming • Post-priming both pulsatile GnRH and combined gonadotrophins are effective

GnRH gonadotrophin-releasing hormone, *hCG* human chorionic gonadotrophin, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *T* testosterone, *TV* testicular volume, *SC* subcutaneous

[a]Refers to either purified urinary forms or recombinant FSH

stimulating hormone (FSH) (Rastrelli et al. 2014). Combined treatment outcomes are comparable to pulsatile GnRH therapy (75%, 95% CI: 69–81% vs. 75%, 95%CI: 60–85% with sperm, respectively). Formulations come as either a highly purified urine FSH preparation or recombinant form. FSH is delivered via subcutaneous injection and the choice of FSH preparation does not appear to influence outcome (Rastrelli et al. 2014). Notably, the development of long-acting FSH preparations (Nieschlag et al. 2017) may be highly relevant for treating men as the frequency of FSH injections could be reduced and this could conceivably have beneficial impact on adherence to treatment. Approaches vary in the literature yet most often hCG and FSH are initiated simultaneously or FSH is added following 3–6 months of hCG mono-therapy (Table 47.3).

A large study of 75 men with CHH/CPHD identified that the median time to develop sperm in the ejaculate was 7 months (Liu et al. 2009). Notably, in a separate analysis the authors identified that half of the treatment cycles result in pregnancy with a median time to conception of 28 months (Liu et al. 2002). However, caution is warranted in interpreting findings regarding pregnancy and live births as not all study participants are not always actively seeking to conceive. Mean sperm concentration on long-term combined therapy is 5.9 million/mL (95% CI: 4.7–7.1 × 10^6) (Rastrelli et al. 2014). While 6–7 months of treatment may be sufficient to develop sperm in the ejaculate among men with partial pubertal development (Pitteloud et al. 2002a; Liu et al. 2009), maximal TV (and chances for having sperm in the ejaculate) is reached following 12–18 months of treatment (Dwyer et al. 2015b). However, in men with a history of bilateral cryptorchidism extended treatment of up to 24 months (or longer) may be required (Dwyer et al. 2015b). Importantly, analysis of patients receiving multiple rounds of gonadotrophin treatment reveals that regaining spermatogenesis is achieved two to threefold faster in subsequent courses compared to the initial induction (Liu et al. 2009).

47.4.4 Sequential Treatment

Men with prepubertal testes (TV <4 mL) have sub-optimal outcomes to both pulsatile GnRH and combined gonadotrophin treatment (Rastrelli et al. 2014). Some have posited this is because they lack the proliferative benefits of mini-puberty (Bouvattier et al. 2012; Boehm et al. 2015). Importantly, the androgen receptor on Sertoli cells is not active during this neonatal window so there is unopposed FSH stimulation which has proliferative effects (Grinspon et al. 2014). Similarly, in early puberty, FSH increases ahead of rising serum testicular androgen levels that mature the Sertoli cells (Boehm et al. 2015; Boyar et al. 1974). Based on these physiologic observations, sequential treatments have been developed in an effort to maximize the potential for fertility in men with severe gonadotrophin deficiency caused by CHH, CPHD or following surgical intervention of intracranial tumours in the most severe cases (Dwyer et al. 2013; Raivio et al. 1997, 2007). Essentially, FSH treatment is initiated unopposed to recapitulate the hormonal dynamics of these proliferative periods during development (Table 47.3).

A 2007 study by Raivio and colleagues reported outcomes for 14 young men who received pre-treatment with recombinant FSH using varied regimens prior to pubertal induction with the addition of hCG (Raivio et al. 1997). Notably, some patients with prepubertal testes and a history of cryptorchidism were able to develop sperm in their ejaculate suggesting that FSH priming may have a role in treating such severe cases. Subsequently, a randomized open-label study outcomes between two groups of men with CHH and prepubertal testes (without cryptorchidism or prior gonadotrophin treatment). The control group (n = 6) received 24 months of standard pulsatile GnRH therapy (i.e. LH + FSH) while the intervention group (n = 7) received 4 months of FSH pre-treatment followed by 2 years pulsatile GnRH (Dwyer et al. 2013). The 4-month FSH priming induced normal serum IB levels, a doubling of TV and proliferation of Sertoli cells/spermatogonia evident on histological examination. All the men

in the FSH pre-treatment arm developed sperm in their ejaculate and they trended toward higher maximal sperm counts. However, the pilot was underpowered to definitively determine the optimal treatment and a large, multicentre international study would be required to fully address this question (Boehm et al. 2015). Despite these small numbers, these data demonstrate that pre-treatment with FSH successfully induces testicular development and positive fertility outcomes in CHH who have a complete absence of puberty and may be beneficial for those with a history of cryptorchidism. It is important to underscore that such tailored approaches be monitored by clinicians with experience with these specialized regimens.

47.4.5 Patient Education and Monitoring During Treatment

Patient education and anticipatory guidance is extremely important for fertility induction. Following careful assessment of predictors of outcome patients should be counselled on findings in clear language to help them understand the nature of their infertility and the likelihood of fertility. It is a good practice to include the partner in such conversations as relevant. Second, genetic counselling is recommended for these patients (Boehm et al. 2015; Au et al. 2011). In some cases, genetic testing can be informative. However, when considering genetic testing for CHH it is worthwhile to note that the 25+ loci identified to date only account for approximately 50% of cases (Boehm et al. 2015; Stamou et al. 2015). So it is relevant to discuss with patients that while genetic testing may not reveal the molecular cause of their CHH, hormonal profiling of their child in the neonatal window of mini-puberty can identify if CHH has been passed to the offspring (Dwyer et al. 2016; Quinton et al. 2017). This can allay concerns as appropriate sex steroid therapy can be initiated so as to induce the development of secondary sexual characteristics in line with peers. Thus, the child can avert the psychological effects of not spontaneously starting puberty that is so common among patients with CHH (Dwyer et al. 2014, 2015c, 2017).

Infertility is stressful on couples and the endocrine nurse can be a key source of support and can suggest psychological referral as appropriate. Additionally, fertility treatments are expensive and treatment duration may be lengthy in certain cases. As such, ongoing monitoring for adherence and appropriate therapeutic education (with teach-back) should be done to ensure patients have the appropriate knowledge, know-how and confidence (self-efficacy) to reconstitute medications and deliver self-administered subcutaneous injections (intramuscular injections are not necessary). During fertility induction, regular assessment of TV is warranted (Anawalt 2013). This is typically done using a Prader orchidometer, but ultrasound measurement in three planes can provide accurate information for those severe cases when FSH pre-treatment is used (Dwyer et al. 2015b; Boehm et al. 2015). Typically a TV of 8–10 mL is consistent with active spermatogenesis yet some men are fertile with less robust development (i.e. 4–5 mL) (Dwyer et al. 2015b). While it may seem completely evident, it is good practice to educate patients on the fertile part of the menstrual cycle so that timed intercourse around the time of ovulation can enhance chances for conception.

Nurses should be aware of, and assess for untoward effects of gonadotrophin therapy. Gynaecomastia can develop in up to one-third of men on treatment (Boehm et al. 2015). It is presumed the growth of this glandular tissue results from excessive LH-induced oestrogen secretion and this can be minimized by using the lowest dose of hCG able to maintain trough serum T levels in the low-mid normal range (Dwyer et al. 2015b; Boehm et al. 2015). In terms of pharmacokinetics, the half-life of hCG is roughly 36 h so serum T should be monitored during trough levels (i.e. prior to the subsequent injection) to adjust dose and avoid overly high serum T excursions. Falling T levels can indicate problems with adherence or, in rare cases, may suggest the development of hCG antibodies

secondary to intermittent/sporadic adherence (Boehm et al. 2015). This is an important teaching point to underscore that poor adherence can undermine successful fertility treatment on several levels.

Serum IB levels can be useful from a prognostic point of view (Pitteloud et al. 2002a) as well as a means to monitor the response to treatment (Dwyer et al. 2013). In the randomized study employing FSH pre-treatment (75 IU daily), serum IB levels plateaued after 2 months—suggesting that this might be a sufficient amount of priming prior to adding hCG or pulsatile GnRH (Dwyer et al. 2013). For sequential or combined gonadotrophin treatment, target serum FSH levels are 4–6 IU/L and levels 9 IU/L or higher should be avoided (Dwyer et al. 2013). Additionally, a marker of Leydig cell function, insulin-like 3 (INSL3) may have a role in assessing response to hCG treatment—just as IB is sometimes used as a proxy for Sertoli cells (Trabado et al. 2014).

Most men will not attain sperm counts that are normal as defined by the World Health Organization (Box 47.1) (World Health Organization 2010). Median sperm counts for gonadotrophin and pulsatile GnRH therapy are similar—in the range of 4–6 million/mL (Rastrelli et al. 2014). Importantly, such low sperm counts do not preclude fertility (Burris et al. 1988). Typically serial seminal fluid analyses are initiated after a few months of treatment. As patients with negative predictors (i.e. maldescended testes) may require extended treatment, it is recommended to initiate treatment well in advance (i.e. 6–12 months) of the time which fertility is desired. Treatment is typically continued after conception and well into the second trimester in the event of miscarriage. Mono-therapy with hCG can maintain spermatogenesis yet sperm counts tend to progressively fall over time (Boehm et al. 2015). While previous gonadotrophin treatment accelerates the process of restarting spermatogenesis on subsequent cycles (Liu et al. 2009), this does not guarantee success later cycles and patients may opt to bank samples (see section below on cryopreservation).

47.5 Assisted Fertility

The past decades have witnessed remarkable advances in the field of assisted reproductive technology (ART) and it is now possible for men with even severely impaired number or quality of sperm to have conceive (Cissen et al. 2016). Typically approaches begin with less invasive approaches and progress to more invasive techniques, i.e. intra-uterine insemination (IUI), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and microsurgical testicular sperm extraction (micro-TESE). For men with low sperm counts or motility problems, IUI can be useful. The principle is to inject spermatozoa into the uterus to bring them in closer proximity to the oocyte to enhance chances for fertility (Bahadur et al. 2016; Veltman-Verhulst et al. 2016). This is less invasive and less costly than IVF and success rates are approximately 13% per cycle (Bahadur et al. 2016). In IVF, the female undergoes hormonal treatment to induce ovarian hyperstimulation (superovulation) for subsequent harvesting of oocytes (Pandian et al. 2015). The oocyte is then fertilized in a laboratory setting and grown in a culture medium for several days then one (or more) blastocyst stage embryos are implanted in the uterus. Unused embryos can be frozen and stored for possible future use.

47.5.1 Surgical Sperm Retrieval

For men with obstructive forms of azoospermia (e.g. STI, CBAVD), sperm can be effectively aspirated from the epididymis using percutaneous epididymal sperm aspiration (PESA) or the more invasive microsurgical epididymal sperm aspiration (MESA) (Verheyen et al. 2017). Outcomes are excellent following PESA/MESA for obstructive azoospermia. Men with non-obstructive azoospermia have a problem with spermatogenesis, so sperm must be harvested from the testes. Both sperm retrieval and live birth rates are lower with micro-TESE compared to PESA/MESA (Tournaye et al. 2017). Testicular sperm recovery requires conventional (open) testicular sperm extraction (TESE) or microsurgical

testicular sperm extraction (micro-TESE) (Tournaye et al. 2017). This is an invasive procedure performed under general anaesthesia and sperm recovery is possible in approximately 40–50% of cases (Verheyen et al. 2017). There is mounting evidence suggesting that micro-TESE is more effective option and a recent meta-analysis identified that sperm retrieval is 1.5 times more likely with a microsurgical approach compared to conventional TESE (Bernie et al. 2015). Sperm can then be used for immediate use in combination with oocyte retrieval ("synchronous sperm retrieval") and/or frozen for future use by their partner, usually with ICSI.

47.5.2 Intracytoplasmic Sperm Injection (ICSI)

In contrast to IVF, ICSI is a procedure wherein a single sperm is selected and used to fertilize an oocyte. For men with CHH, this approach was initially used as a means to shorten the duration of hormonal treatment (Yong et al. 1997). However, it has become increasingly clear that outcomes are improved when intervention is delayed until maximal testicular development has been reached. Overall, success rates of ICSI in men with CHH are high with fertilization rates in the range of 50–60% and pregnancy occurs in approximately 30% of cases per cycle (93–96). While the numbers of patients limit analysis, one published report on sperm quality concluded that CHH per se does not appear to impair DNA integrity nor does it elevate the risk of chromosomal aberrations (Krabchi et al. 2011).

Potential risk for birth defects has been raised as a possible result of ART. Several meta-analyses demonstrate that ART-conceived children have a 30–40% increased risk of birth defects compared to fertile counterparts who conceive spontaneously (Chen and Heilbronn 2017). However this is a complicated issue to tease apart as women undergoing IVF tend to be older, have more pre-existing health conditions and at baseline are at higher risk for complications (Luke et al. 2017). Interestingly, there is growing attention to the epigenetic aspects of ART as there is emerging evidence that ART impacts methylation and imprinting (Lazaraviciute et al. 2014). Consequently, some have raised questions regarding the potential long-term risk for certain types of cancers, cardiovascular disease, and metabolic problems such as obesity and diabetes mellitus in children conceived using ART (Chen and Heilbronn 2017). However, this area of investigation is still relatively nascent and there is no clear consensus regarding risk for birth defects or long-term health consequences for children born to ART. Indeed, while remarkable technologic advances have been made, many questions remain (Box 47.2).

Box 47.2 Unanswered Questions and Future Directions

Is there a role of neonatal treatment to optimize potential for developing future fertility?

What is the optimal treatment regimen(s) for inducing spermatogenesis?

What is the best way to optimize fertility potential in those men with a history of maldescended testes?

Does prior testosterone treatment impact the success of subsequent spermatogenesis induction?

How will the evolving understanding of genetics and genomics alter our approach to treatment and counselling of these patients?

Do assisted reproductive technologies have long-term health consequences for the children conceived via these procedures?

47.5.3 Sperm Cryopreservation

Cryopreservation is the storage of cells or tissues at ultra-low temperatures for future use and is a well-established and widely used procedure in the fertility field. It is based on the principle that biological activity ceases below −135 °C (Benson et al. 2012) and therefore, thawed cryopreserved cells will continue to function as

before, providing the damage caused by the freezing and thawing processes is minimized. Sperm cryopreservation is used for several reasons. First, it is used to ensure availability of sperm for fertility treatments. Second, it can serve as an "insurance policy" for those with testicular failure, following treatment to induce spermatogenesis, or prior to certain some surgical interventions/gonadotoxic or gonado-suppressive treatments. Importantly, cryopreserved sperm may represent a man's only opportunity for fatherhood, and laboratories employ methodologies for cryopreservation that maximize sperm cell survival and therefore, maximize fertility options for men at risk of infertility.

Current cryopreservation practices involve the storage of cells in liquid nitrogen or nitrogen vapour (−196 °C) and provide sperm survival rates of around 30–60%, with the remainder being lost to cryo-injury. Cells are considered inert during storage so the damage to cells is caused during the cooling and warming processes when ice crystal formation and high intracellular solute concentrations can rupture cell membranes (Benson et al. 2012; Gao and Critser 2000). Accordingly, successful cryopreservation and thawing depends on a careful balance of cooling and warming rate as well as intracellular solute concentration resulting from osmosis secondary to ice crystal formation. As the cell suspension cools below −5 °C, water crystallization begins in the extracellular medium. This draws water out of the cells increasing their internal concentration of solutes. If this happens too slowly, cell damage can occur as a result of osmotic shock (or extreme cell shrinkage). If cells are cooled too quickly, the water in the cells cannot leave, and instead freezes into crystals within the cell membrane rupturing the cell (Gao and Critser 2000; Woods et al. 2004). Surviving cells must then endure the repeat stressors during thawing process.

When referring a patient for sperm cryopreservation, it is important to counsel the patient that a strict consent process and viral screening must be fulfilled before a sample can be obtained. Current minimum European standards require valid consent for sperm storage as well as screening for blood-borne pathogens including human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C. Ejaculated sperm samples should be produced directly into an approved sterile container that has been tested for toxicity to sperm. Surgically retrieved sperm (e.g. during micro-TESE) should be obtained under sterile conditions, and handled by trained scientists to minimize contamination by potentially toxic agents. Samples must be transported to the laboratory in secure, sterile containers at 37 °C to maintain their viability, and should be processed within 1 h.

An analysis of sperm quality must be carried out before cryopreservation begins. This ensures the suitability of the sample for storage i.e. that there are viable sperm present; however, the pre-freeze analysis, along with post-thaw survival data, provides important information for the future of the samples, in particular for the suitability for use in certain types of fertility treatment and the number of attempts at the fertility treatments that may be afforded by the quantity stored. This is an important factor when considering "how much is enough" and how many samples should be stored, especially in cases of fertility preservation where the availability of more sperm in the future is uncertain. Accordingly, it is generally recommended that patients attend on multiple occasion to produce a sample, to ensure that adequate sperm are cryopreserved for future treatment.

Most European countries have strict regulations surrounding the storage of gametes and embryos. Although the specific rules will vary from country to country, each will have specific rules on the requirements for consent in relation to stored material. The maximum duration of storage, the permissible use of the samples and what actions should be taken in the event of death or mental incapacity of the gamete or embryo provider represent the minimum requirements for consent to storage.

47.6 Ethics of Assisted Fertility

Medical ethics is guided by four principles proposed by Tom Beauchamp and James Childress (2008): autonomy, beneficence, nonmaleficence

and justice. These principles are applied to ethical questions to better understand which principles may be in conflict. Autonomy is often described as respect for persons. Involving patients in decision-making is a common example of promoting autonomy. Doing good is the definition of beneficence, while nonmaleficence is preventing harm. The principle of justice applies to questions of fairness, equality and allocation of resources.

47.6.1 Ethical Issues Related to Future Children

Assisted reproduction presents some unique medical ethics challenges. Perhaps the most fundamental issue, however, involves beliefs about the presence or absence of personhood status held by an embryo or foetus. These beliefs are informed by cultural, religious and personal factors (and personal practices surrounding) assisted reproduction and termination of pregnancy. For example, whether a couple or family believe that personhood of an embryo begins at conception may dramatically impact assisted reproduction decisions based on their perceived beneficence or nonmaleficence, e.g. not pursuing in vitro fertilization (IVF) or creating unused embryos. Beyond personal choices, these beliefs also influence the regulatory landscape. In the United States, so-called personhood amendments to several state constitutions (Oklahoma, Virginia, Colorado, Nevada, Missouri) have sought to legally establish personhood from the moment of conception (fertilized egg) to birth. To date, many such campaigns have not been enacted as law (Suckow and Yates 2015).

Practitioners who offer assisted reproductive services may be asked to consider beneficence and nonmaleficence toward a child created through these techniques. This could potentially conflict with the autonomy of the individual seeking fertility treatment. The United Kingdom, via the Fertility and Embryology Act and European Society of Human Reproduction and Embryology (ESHRE) practitioners are required to consider the welfare of the future child and not contribute to the creation of a child at high risk for psychological and physical harm (Harper et al. 2014). Though children created with assisted reproduction are usually healthy, there may be some increased risk for epigenetic/imprinting disorders (i.e. Beckwith-Wiedemann syndrome, Angelman syndrome). These risks have been most associated with conception using intracytoplasmic sperm injection (ICSI). Risk for other genetic conditions (e.g. chromosomal abnormalities, cystic fibrosis) and birth defects may also be increased, and possibly related to the cause of one's infertility (Kurinczuk and Bhattacharya 2014). Screening patients for chromosome rearrangements, Y chromosome microdeletions, and CFTR gene mutations prior to treatment facilitates a better understanding of a family's specific risk for these conditions.

47.6.2 Ethical Issues Related to Patients

Promoting autonomy, beneficence, and nonmaleficence in assisted reproduction toward the patient alone is constantly evolving as new technologies emerge and our understanding grows regarding risks and outcomes. The American Society of Reproductive Medicine (ASRM) and the ESHRE offer some practice guidelines (Practice Committee of the American Society for Reproductive Medicine et al. 2014) for clinicians to provide the most effective, safe and ethical care. The guidelines, however, are dependent on the completeness and consistency of outcomes data derived from numerous sources and are limited by the paucity of solid evidence regarding long-term outcomes, particularly for newer treatments. An informed consent process that addresses the capabilities, limitations and risks of assisted reproduction and a clear delineation between clinical and experimental/research protocols is essential. This may be more challenging when the patient is a child. Fertility preservation has been proposed as an option for

children facing cancer treatment, as well as those with Klinefelter and Turner syndromes. For the latter conditions, extraction of gonadal tissue at young ages may be needed to obtain viable gametes (Franik et al. 2016; Londra et al. 2014).

47.6.3 Ethical Issues Related to Gamete Donors

When sperm or egg donors are added to the equation, additional considerations must be made. Donor programmes/banks have obligations to both families and gamete donors. Donors should be advised of potential associated risks, limitations to their anonymity, and their rights and even responsibilities. Families who use gamete donors should have some mechanism to report adverse outcomes (birth defects, genetic disease) to donor programmes as this information can benefit other recipients as well as the donors themselves. Donors have an obligation to provide truthful information about their health and family history and update donor programmes with changes to that information (Ethics Committee of the American Society for Reproductive Medicine 2014). Egg donors in particular face health risks associated with ovulation induction and egg retrieval. Concerns regarding coercion from excessive payment beyond compensating donors for their time and discomfort, and perhaps based on other features (education, race, physical traits) have also been raised (Londra et al. 2014). Infectious disease and genetic screening of gamete donors is not uncommon in the United States and Europe. Currently, genetic screening focuses on carrier status for recessive conditions and Fragile X Syndrome. Increasing accessibility to larger-scale genomic testing will make it possible to test donors for a wider range of genetic conditions. Importantly, such testing may reduce some, but not all, risk for recipient families. Indeed, providing adequate pre- and post-test genetic counselling for donors is needed to promote autonomy, maximize the benefits, and minimize harms (Dondorp et al. 2014).

47.6.4 Access to Assisted Reproduction

Access to assisted reproduction remains a significant ethical and social issue. Local restrictions in the form of regulatory and/or financial barriers to accessing assisted reproduction have led some families to seek these services abroad. In many European countries, families must meet specific criteria (age, medical necessity, marital status and sexual orientation) to be eligible for IVF. However, these criteria vary across countries. Similarly, the availability of public funding for IVF and regulation of gamete donors also vary widely by country (Berg Brigham et al. 2013). In the United States, infertility treatment is often not covered by health insurance and given the needed financial resources required, assisted fertility treatment is out of reach for many families. One response to this has been to seek services outside one's home country or so-called "medical tourism". Yet concerns have been noted regarding safety and quality of services, both for patients and gamete donors, as well as barriers for sharing outcome data (Harper et al. 2014).

47.6.5 Assisted Reproduction and Pre-implantation Genetic Testing

People undergoing assisted reproduction treatment may elect to have pre-implantation genetic screening/testing (PGS/PGD) of embryos for specific conditions. Benefits of PGS/PGD include a decreased risk of miscarriage in women over age 35, likely the result of aneuploidy screening (Chang et al. 2016), avoiding pregnancy termination, and avoiding a fully penetrant life-limiting genetic disease. The use of PGD to create "saviour siblings" via human leukocyte antigen typing and testing for less penetrant and/or serious genetic conditions has raised concerns about rights and welfare of the child. Such cases present a potentially slippery slope toward genetic designer babies. To date there is no clear consensus. However, in these instances, determining the

necessity of PGD and the "seriousness" of a particular condition may be best understood by evaluating each situation in its unique context (Harper et al. 2014). Examining potential principles in conflict is also helpful in these situations. For example, autonomy and beneficence/nonmaleficence as defined by the patient versus the autonomy and beneficence/nonmaleficence toward the potential child. Sex selection and the potential for gender discrimination, the destruction of embryos with genetic disorders, as well as limited knowledge of risks to children created with PGD are all potential concerns (Londra et al. 2014). While PGD provides a great service to many families, patients should be properly consented, offered genetic counselling, and informed of the known risks and benefits—including the possibility of false positive and negative results. The Society for Assisted Reproductive Technology and ASRM recommend follow-up prenatal diagnostic testing with chorionic villus sampling or amniocentesis is recommended to confirm the PGD result (Practice Committee of Society for Assisted Reproductive Technology and Practice Committee of American Society for Reproductive Medicine 2008). Given the growing availability of multi-gene panels and whole exome sequencing in the postnatal setting, it seems plausible that such approaches may be applied for PGD. However, consideration of the necessary pre-test counselling, criteria for selecting embryos, and goals for outcomes (healthy child and/or no predisposition for adult-onset disorders) is warranted and necessary for such testing approaches to be implemented (Harper et al. 2014).

Ever-changing technology in reproductive technology adds to the complexity of the ethical issues. The interests of patients, future children and gamete donors must be examined with the realization that these may sometimes conflict. The rapidly changing landscape of reproductive technologies means that recommendations and regulations may not be up to date with current practices and are not consistent across countries. Barriers to obtaining fertility treatment still exist, primarily due to cost and regulations. Ongoing evaluation of risks and long-term outcomes is needed to provide appropriately informed consent and to promote and support the tenets beneficence and nonmaleficence.

47.7 Conclusions

Male factors contribute to approximately half of all couples presenting for evaluation of infertility. Thorough history, clinical examination and biochemical profiling can help identify iatrogenic causes of male infertility (i.e. T treatment) and cases that require referral for urologic consultation with a specialist in ART. Men with obstructive azoospermia, sperm transport problems and gonadal failure require this type of consultation. Hypogonadotrophic hypogonadism with a hypothalamic or pituitary aetiology is amenable to hormonal therapy to induce spermatogenesis. Based on the presence of negative predictors of outcome (i.e. TV <4mL, history of cryptorchidism, serum IB <60 pg/mL), treatment can be tailored and appropriate expectations for treatment can be set. Fertility-inducing hormone treatments are best managed by clinicians with experience and expertise with these specialized regimens. The majority of men (75%) will be able to develop sperm in their ejaculate (Rastrelli et al. 2014), and low sperm counts do not preclude fertility in these men (Burris et al. 1988). ART can complement hormonal therapies for those men with severely compromised sperm counts and/or motility problems. A rational approach is to progress from less invasive to more invasive measures with ICSI and micro-TESE reserved for poor responders.

While remarkable technologic advances have made fertility a possibility for many, reproduction has humanistic meaning. Infertility is not simply a physiologic problem—it also has psychological, emotional and social meaning and consequences. Thus, a holistic approach is central to the care of patients with infertility. The endocrine nurse can play an important role in caring for and managing men presenting with infertility. Infertility can be a stressful situation for

couples and many find it challenging to navigate the health system given that care may involve endocrinology, urology, andrology labs, psychology and genetic counselling as well as payers (i.e. health insurers). Appropriate, timely referrals are a critical aspect of care coordination and nurses can have an important role in coordinating care and providing psychological support for patients and couples. Additionally, therapeutic education, assessing adherence, monitoring response to treatment (i.e. hormonal, TV, spermatogenesis) and effective interprofessional communication and collaboration are all part of comprehensive care for these patients.

References

Abiad F, Awwad J, Abbas HA, Zebian D, Ghazeeri G. Management of weight loss in obesity-associated male infertility: a spotlight on bariatric surgery. Hum Fertil. 2017;20(4):227–35.

Anawalt BD. Approach to male infertility and induction of spermatogenesis. J Clin Endocrinol Metab. 2013;98(9):3532–42.

Au MG, Crowley WF Jr, Buck CL. Genetic counseling for isolated GnRH deficiency. Mol Cell Endocrinol. 2011;346(1–2):102–9.

Bahadur G, Homburg R, Muneer A, Racich P, Alangaden T, Al-Habib A, et al. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016;31(6):1141–6.

Beauchamp TL, Childress JF. Principles of biomedical ethics. 6th ed. London: Oxford; 2008.

Benson JD, Woods EJ, Walters EM, Critser JK. The cryobiology of spermatozoa. Theriogenology. 2012;78(8):1682–99.

Berg Brigham K, Cadier B, Chevreul K. The diversity of regulation and public financing of IVF in Europe and its impact on utilization. Hum Reprod. 2013;28(3):666–75.

Bernie AM, Mata DA, Ramasamy R, Schlegel PN. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. Fertil Steril. 2015;104(5):1099–103 e1–3.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.

Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547–64.

Bouvattier C, Maione L, Bouligand J, Dode C, Guiochon-Mantel A, Young J. Neonatal gonadotropin therapy in male congenital hypogonadotropic hypogonadism. Nat Rev Endocrinol. 2012;8(3):172–82.

Boyar RM, Rosenfeld RS, Kapen S, Finkelstein JW, Roffwarg HP, Weitzman ED, et al. Human puberty. Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. J Clin Invest. 1974;54(3):609–18.

Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril. 1988;50(2):343–7.

Cabler S, Agarwal A, Flint M, du Plessis SS. Obesity: modern man's fertility nemesis. Asian J Androl. 2010;12(4):480–9.

Chan E, Wayne C, Nasr A, FRCSC for Canadian Association of Pediatric Surgeon Evidence-Based Resource. Ideal timing of orchiopexy: a systematic review. Pediatr Surg Int. 2014;30(1):87–97.

Chang J, Boulet SL, Jeng G, Flowers L, Kissin DM. Outcomes of in vitro fertilization with preimplantation genetic diagnosis: an analysis of the United States Assisted Reproductive Technology Surveillance Data, 2011-2012. Fertil Steril. 2016;105(2):394–400.

Chen M, Heilbronn LK. The health outcomes of human offspring conceived by assisted reproductive technologies (ART). J Dev Orig Health Dis. 2017;8(4):388–402.

Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S. Effects of anabolic androgenic steroids on the reproductive system of athletes and recreational users: a systematic review and meta-analysis. Sports Med. 2017;47:1869.

Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology. 2013;1(5):749–57.

Cissen M, Bensdorp A, Cohlen BJ, Repping S, de Bruin JP, van Wely M. Assisted reproductive technologies for male subfertility. Cochrane Database Syst Rev. 2016;2:CD000360.

Corona G, Pizzocaro A, Lanfranco F, Garolla A, Pelliccione F, Vignozzi L, et al. Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2017;23(3):265–75.

Dean JD, McMahon CG, Guay AT, Morgentaler A, Althof SE, Becher EF, et al. The International Society for Sexual Medicine's process of Care for the Assessment and Management of testosterone deficiency in adult men. J Sex Med. 2015;12(8):1660–86.

Delemarre-Van de Waal HA. Induction of testicular growth and spermatogenesis by pulsatile, intravenous administration of gonadotrophin-releasing hormone in patients with hypogonadotrophic hypogonadism. Clin Endocrinol. 1993;38(5):473–80.

Dondorp W, De Wert G, Pennings G, Shenfield F, Devroey P, Tarlatzis B, et al. ESHRE Task Force on Ethics and Law 21: genetic screening of gamete donors: ethical issues. Hum Reprod. 2014;29(7):1353–9.

Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. Nat Rev Urol. 2010;7(3):153–61.

Dwyer AA, Sykiotis GP, Hayes FJ, Boepple PA, Lee H, Loughlin KR, et al. Trial of recombinant follicle-stimulating hormone pretreatment for GnRH-induced fertility in patients with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2013;98(11):E1790–5.

Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis. 2014;9:83.

Dwyer AA, Phan-Hug F, Hauschild M, Elowe-Gruau E, Pitteloud N. TRANSITION IN ENDOCRINOLOGY: hypogonadism in adolescence. Eur J Endocrinol. 2015a;173(1):R15–24.

Dwyer AA, Raivio T, Pitteloud N. Gonadotrophin replacement for induction of fertility in hypogonadal men. Best Pract Res Clin Endocrinol Metab. 2015b;29(1):91–103.

Dwyer AA, Quinton R, Pitteloud N, Morin D. Psychosexual development in men with congenital hypogonadotropic hypogonadism on long-term treatment: a mixed methods study. Sex Med. 2015c;3(1):32–41.

Dwyer AA, Jayasena CN, Quinton R. Congenital hypogonadotropic hypogonadism: implications of absent mini-puberty. Minerva Endocrinol. 2016;41(2):188–95.

Dwyer AA, Tiemensma J, Quinton R, Pitteloud N, Morin D. Adherence to treatment in men with hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf). 2017;86(3):377–83.

Escobar-Morreale HF, Santacruz E, Luque-Ramirez M, Botella Carretero JI. Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. Hum Reprod Update. 2017;23(4):390–408.

Ethics Committee of the American Society for Reproductive Medicine. Interests, obligations, and rights in gamete donation: a committee opinion. Fertil Steril. 2014;102(3):675–81.

Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. N Engl J Med. 1985;313(11):651–5.

Franik S, Hoeijmakers Y, D'Hauwers K, Braat DD, Nelen WL, Smeets D, et al. Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. Hum Reprod. 2016;31(9):1952–9.

Gao D, Critser JK. Mechanisms of cryoinjury in living cells. ILAR J. 2000;41(4):187–96.

Grinspon RP, Loreti N, Braslavsky D, Valeri C, Schteingart H, Ballerini MG, et al. Spreading the clinical window for diagnosing fetal-onset hypogonadism in boys. Front Endocrinol. 2014;5:51.

Groth KA, Skakkebaek A, Host C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome—a clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30.

Harper J, Geraedts J, Borry P, Cornel MC, Dondorp WJ, Gianaroli L, et al. Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy. Hum Reprod. 2014;29(8):1603–9.

Hoffman AR, Crowley WF Jr. Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. N Engl J Med. 1982;307(20):1237–41.

Hofherr SE, Wiktor AE, Kipp BR, Dawson DB, Van Dyke DL. Clinical diagnostic testing for the cytogenetic and molecular causes of male infertility: the Mayo Clinic experience. J Assist Reprod Genet. 2011;28(11):1091–8.

King TF, Lee MC, Williamson EE, Conway GS. Experience in optimizing fertility outcomes in men with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. Clin Endocrinol. 2016;84(6):830–6.

Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol. 2012;187(3):973–8.

Kohn TP, Louis MR, Pickett SM, Lindgren MC, Kohn JR, Pastuszak AW, et al. Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. Fertil Steril. 2017;107(2):351–7 e1.

Kollin C, Stukenborg JB, Nurmio M, Sundqvist E, Gustafsson T, Soder O, et al. Boys with undescended testes: endocrine, volumetric and morphometric studies on testicular function before and after orchidopexy at nine months or three years of age. J Clin Endocrinol Metab. 2012;97(12):4588–95.

Krabchi K, Berthaut I, Chantot-Bastaraud S, Ravel C, Chabbert-Buffet N, de Larouziere V, et al. Quality assessment of induced spermatogenesis in hypogonadotrophic hypogonadic men treated with gonadotrophins. Reprod Biomed Online. 2011;22(3):277–83.

Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702–55.

Kurinczuk JJ, Bhattacharya S. Rare chromosomal, genetic, and epigenetic-related risks associated with infertility treatment. Semin Fetal Neonatal Med. 2014;19(4):250–3.

Lazaraviciute G, Kauser M, Bhattacharya S, Haggarty P, Bhattacharya S. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. Hum Reprod Update. 2014;20(6):840–52.

Lee PA, O'Leary LA, Songer NJ, Coughlin MT, Bellinger MF, LaPorte RE. Paternity after unilateral

cryptorchidism: a controlled study. Pediatrics. 1996;98(4 Pt 1):676–9.

Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab. 2009;94(3):801–8.

Liu PY, Gebski VJ, Turner L, Conway AJ, Wishart SM, Handelsman DJ. Predicting pregnancy and spermatogenesis by survival analysis during gonadotrophin treatment of gonadotrophin-deficient infertile men. Hum Reprod. 2002;17(3):625–33.

Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C, Hormonal Male Contraception Summit Group. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet. 2006;367(9520):1412–20.

Londra L, Wallach E, Zhao Y. Assisted reproduction: ethical and legal issues. Semin Fetal Neonatal Med. 2014;19(5):264–71.

Luke B, Gopal D, Cabral H, Stern JE, Diop H. Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology. Am J Obstet Gynecol. 2017;217(3):e1–327.e14.

Miyagawa Y, Tsujimura A, Matsumiya K, Takao T, Tohda A, Koga M, Takeyama M, Fujioka H, Takada S, Koide T, Okuyama A. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. J Urol. 2005;173(6):2072–5.

Nieschlag E, Bouloux PG, Stegmann BJ, Shankar RR, Guan Y, Tzontcheva A, et al. An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic hypogonadism. Reprod Biol Endocrinol. 2017;15(1):17.

Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2015;(11):CD003357.

Patel DP, Chandrapal JC, Hotaling JM. Hormone-based treatments in subfertile males. Curr Urol Rep. 2016;17(8):56.

Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002a;87(9):4128–36.

Pitteloud N, Hayes FJ, Boepple PA, DeCruz S, Seminara SB, MacLaughlin DT, et al. The role of prior pubertal development, biochemical markers of testicular maturation, and genetics in elucidating the phenotypic heterogeneity of idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002b;87(1):152–60.

Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, et al. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 2008;93(3):784–91.

Practice Committee of Society for Assisted Reproductive Technology, Practice Committee of American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice Committee opinion. Fertil Steril. 2008;90(5 Suppl):S136–43.

Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology, Practice Committee of the Society of Reproductive Biology and Technology. Revised minimum standards for practices offering assisted reproductive technologies: a committee opinion. Fertil Steril. 2014;102(3):682–6.

Quinton R, Mamoojee Y, Jayasena CN, Young J, Howard S, Dunkel L, et al. Society for Endocrinology UK guidance on the evaluation of suspected disorders of sexual development: emphasizing the opportunity to predict adolescent pubertal failure through a neonatal diagnosis of absent minipuberty. Clin Endocrinol. 2017;86(2):305–6.

Raivio T, Toppari J, Perheentupa A, McNeilly AS, Dunkel L. Treatment of prepubertal gonadotrophin-deficient boys with recombinant human follicle-stimulating hormone. Lancet. 1997;350(9073):263–4.

Raivio T, Wikstrom AM, Dunkel L. Treatment of gonadotropin-deficient boys with recombinant human FSH: long-term observation and outcome. Eur J Endocrino. 2007;156(1):105–11.

Rambhatla A, Mills JN, Rajfer J. The role of estrogen modulators in male hypogonadism and infertility. Rev Urol. 2016;18(2):66–72.

Ramstein JJ, Halpern J, Gadzinski AJ, Brannigan RE, Smith JF. Ethical, moral, and theological insights into advances in male pediatric and adolescent fertility preservation. Andrology. 2017;5(4):631–9.

Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology. 2014;2(6):794–808.

Ribeiro MA, Gameiro LF, Scarano WR, Briton-Jones C, Kapoor A, Rosa MB, et al. Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: a systematic review of randomized controlled trials. JBRA Assist Reprod. 2016;20(2):82–8.

Ritzen EM, Bergh A, Bjerknes R, Christiansen P, Cortes D, Haugen SE, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr. 2007;96(5):638–43.

Rohayem J, Nieschlag E, Zitzmann M, Kliesch S. Testicular function during puberty and young adulthood in patients with Klinefelter's syndrome with and without spermatozoa in seminal fluid. Andrology. 2016;4(6):1178–86.

Stamou MI, Cox KH, Crowley WF Jr. Discovering genes essential to the hypothalamic regulation of human reproduction using a human disease model: adjusting to life in the "-Omics" Era. Endocr Rev. 2015;36(6):603–21.

Suckow M, Yates B, editors. Research regulatory compliance. New York: Elsevier; 2015.

Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. Lancet Diabetes Endocrinol. 2016;5(7):544–53.

Tournaye H, Krausz C, Oates RD. Concepts in diagnosis and therapy for male reproductive impairment. Lancet Diabetes Endocrinol. 2017;5(7):554–64.

Trabado S, Maione L, Bry-Gauillard H, Affres H, Salenave S, Sarfati J, et al. Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/Kallmann syndrome and effects of different modalities of hormonal treatment: a single-center study of 281 patients. J Clin Endocrinol Metab. 2014;99(2):E268–75.

Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2016;2:CD001838.

Verheyen G, Popovic-Todorovic B, Tournaye H. Processing and selection of surgically-retrieved sperm for ICSI: a review. Basic Clin Androl. 2017;27:6.

Warne DW, Decosterd G, Okada H, Yano Y, Koide N, Howles CM. A combined analysis of data to identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin. Fertil Steril. 2009;92(2):594–604.

Woods EJ, Benson JD, Agca Y, Critser JK. Fundamental cryobiology of reproductive cells and tissues. Cryobiology. 2004;48(2):146–56.

World Health Organization. WHO laboratory manual for the examination and processing of human semen. Geneva: World Health Organization; 2010. Report No.: 978 92 4 154778 9.

Yong EL, Lee KO, Ng SC, Ratnam SS. Induction of spermatogenesis in isolated hypogonadotrophic hypogonadism with gonadotrophins and early intervention with intracytoplasmic sperm injection. Hum Reprod. 1997;12(6):1230–2.

Diagnosis and Management of Erectile Dysfunction in Men

48

Fiona Holden, Clare Akers, and Sofia Llahana

Contents

48.1 **The Physiology of Erections** 926

48.2 **Diagnosing Erectile Dysfunction** 928
48.2.1 Sexual History 930
48.2.2 Physical Examination 930
48.2.3 Blood Tests 930
48.2.4 The Cardiovascular System and Sexual Activity 930
48.2.5 Specialist Diagnostic Tests 932

48.3 **Treatment Options for ED** 932
48.3.1 First Line Treatment 932
48.3.2 Second Line Treatment 934
48.3.3 Third Line Therapy 936
48.3.4 Other Available Treatments 937

48.4 **Conclusions** 939

References 939

Abstract

Erectile Dysfunction (ED) has been defined as a persistent inability to attain or maintain erection adequate to permit satisfactory sexual function (National Institute of Health 1993). It is estimated that a third of men will be affected by ED at some point during their lives (Heidelbaugh 2010). Whilst published figures provide an indication of the prevalence of ED, they are likely to underestimate the true number as many men will not seek help either due to embarrassment or through acceptance that ED is inevitable with advancing age (Hatzimouratidis et al. 2010).

The pathophysiology of ED may be neurogenic, hormonal, vasculogenic, drug-induced, anatomical, and/or psychogenic. However, regardless of the pathological basis for ED, the condition can have a profoundly negative psychological impact on relationships, quality of life and overall affect self-esteem (Gruenwald 2012). Therefore, to establish an

F. Holden (✉) · C. Akers
Urology Department, Westmorland Street Hospital, University College London Hospitals NHS Foundation Trust, London, UK
e-mail: fiona.holden1@nhs.net; clare.akers@nhs.net

S. Llahana
School of Health Sciences, City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_48

effective ED management plan in a timely fashion is of paramount importance for the well-being of the sufferer and partner.

By the end of this chapter we hope that you will have a better understanding of the pathophysiology and management of ED.

Keywords
Erectile dysfunction · Phosphodiesterase 5 inhibitors · Alprostadil · Invicorp · Vacuum erection devices · Penile prosthesis

Abbreviations

ATP	Adenosine Triphosphate
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CVD	Cardiovascular disease
EAU	European Association of Urology
ED	Erectile dysfunction
IIEF	International Index for Erectile Function
MUSE	Medicated Urethral System for Erection
NO	Nitric oxide
NPT	Nocturnal penile tumescence
PDE5i	Phosphodiesterase 5 inhibitor
PGE1	Prostaglandin E1
PSA	Prostate-specific antigen
VED	Vacuum erection device
VIP	Vasoactive intestinal peptide

Key Terms

- An **erection** is reliant upon a complex interplay of arterial, venous, neurological, hormonal and psychological elements. The erectile tissue comprises two cylinders of smooth muscle (corpus cavernosum) which become engorged with blood when sexually aroused and during sleep (nocturnal erections). The increase in arterial inflow through the cavernosal arteries into cavernosal tissue and occlusion of venous outflow results in penile rigidity and erections.
- **Erectile dysfunction (ED)** is a common male sexual disorder which describes the inability to achieve or maintain an erection to enable satisfactory sexual function.
- **Infertility:** the inability to achieve pregnancy following regular unprotected intercourse for 12 months. Factors may be male, female or mixed (both) in origin.
- **Sexual dysfunction:** the inability to engage in normal, pleasurable sexual activity resulting from diminished desire (libido), arousal difficulties (erectile dysfunction) and/or problems with orgasm (ejaculation).

Key Points

- To describe and present evidence on the definition, prevalence and pathophysiology of erectile dysfunction (ED).
- To describe the clinical presentation, symptoms and investigations to diagnose ED.
- To present latest evidence on the management of ED with medical treatment, surgical pathway and additional therapies.

48.1 The Physiology of Erections

The erectile tissue comprises two cylinders of smooth muscle (corpus cavernosum) which become engorged with blood when sexually aroused and during sleep (nocturnal erections). The increase in arterial inflow through the cavernosal arteries into cavernosal tissue and occlusion of venous outflow results in penile rigidity. Pelvic nerves that run intermittently around the prostate and end within the penis facilitate this complex process (Fig. 48.1). Testosterone has effect on every component required for erectile function (Isadori et al. 2014).

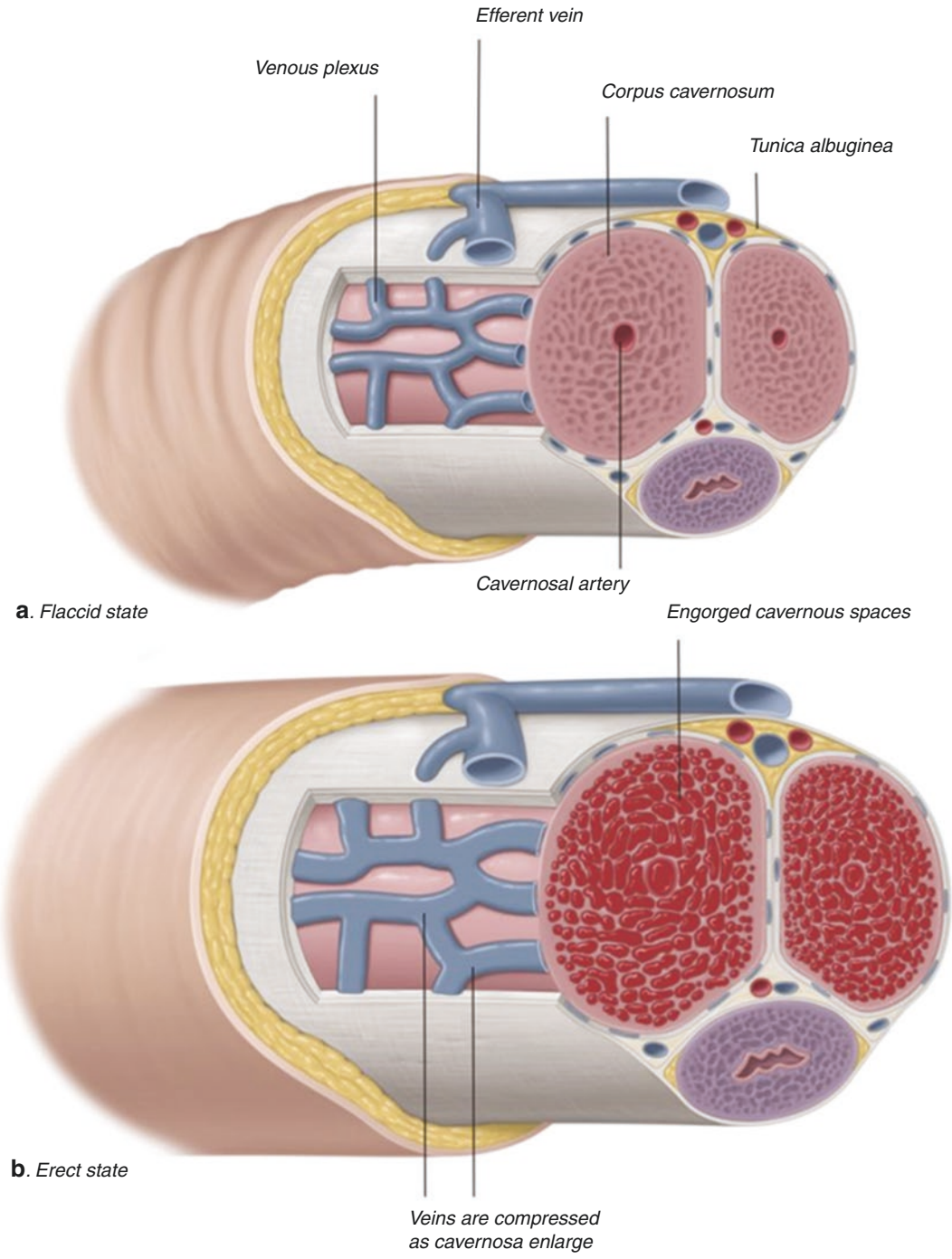


Fig. 48.1 Physiology of erectile function and erections. Used with permission from the European Association of Urology Patient Information http://patients.uroweb.org/erectile-dysfunction/

Table 48.1 Common medical conditions or medications associated with erectile dysfunction

Vascular	Neurogenic	Hormonal
• Diabetes • Congestive heart failure • Peripheral vascular disease • Hypertension • Hypercholestraemia • Kidney disease • Atherosclerosis • Pelvic trauma (fracture) • Smoking	• Radical prostatectomy • Spinal cord injury • Cerebrovascular accident (CVA) • Multiple sclerosis (MS) • Peripheral neuropathy • Diabetes • Pelvic radiotherapy • Parkinson's disease	• Increased prolactin • Low testosterone • Low luteinising hormone (LH)
Psychological	**Medications**	
• Depression • Anxiety • Schizophrenia • Bipolar disorder • Substance abuse	• Anti-androgens • Anxiolytics • Tobacco • Alcohol • Recreational drugs • Antihistamines • Antidysrhythmics • Antihypertensives • Antidepressants • Antipsychotics • Anticonvulsants	

In the normal erection process, sexual stimulation triggers the local release of nitric oxide (NO) which has long been recognised as the most important mediator for smooth muscle relaxation (Sullivan et al. 1999). NO effects intracellular activation of guanylate cyclase which regulates conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP mediates intracellular signal transduction which leads via protein activation mechanisms to a reduction in intracellular calcium, resulting in dilatation of the cavernosal arteries and relaxation of the smooth muscle (Moreland et al. 2001). This process enables an increase of blood flow into the cavernosal tissues resulting engorgement, and ultimately erection.

As described above, an erection is a complex phenomenon reliant upon a complex interplay of arterial, venous, neurological, hormonal and psychological elements and any disturbance to this process can result in erectile dysfunction (Montague et al. 2005). Erectile dysfunction (ED) is a common male sexual disorder which describes the inability to achieve or maintain an erection to enable satisfactory sexual function.

Medical risk factors for ED include diabetes, hypertension, cardiac disease, hypogonadism, dyslipidaemia, neurological disease including multiple sclerosis and Parkinson's disease, spinal injury, and depression renal failure, chronic liver disease, chronic respiratory disease (Hackett et al. 2008). It is not unusual for men to possess multiple risk factors, therefore establishing the exact cause of ED is not always possible (Dean and Lue 2005).

Lifestyle factors that can predispose men to ED include sedentary lifestyle, smoking, obesity and alcoholism (Hackett et al. 2008; Hatzimouratidis et al. 2010). Iatrogenic causes for ED include medications such as anti-androgens, antihypertensives and antidepressants (Table 48.1). Pelvic radiotherapy can also result in ED (Hackett et al. 2008). Direct trauma to the nerves of the penis either through injury or as a consequence of pelvic/genital surgery can result in ED. In men who have undergone radical prostatectomy surgery for cancer (nerve sparing and non-nerve sparing), the incidence ranges between 40 and 85% (Nandipati et al. 2006).

48.2 Diagnosing Erectile Dysfunction

The first and most important stage in diagnosing the cause of ED is to undertake a detailed medical history of patients including a history of their

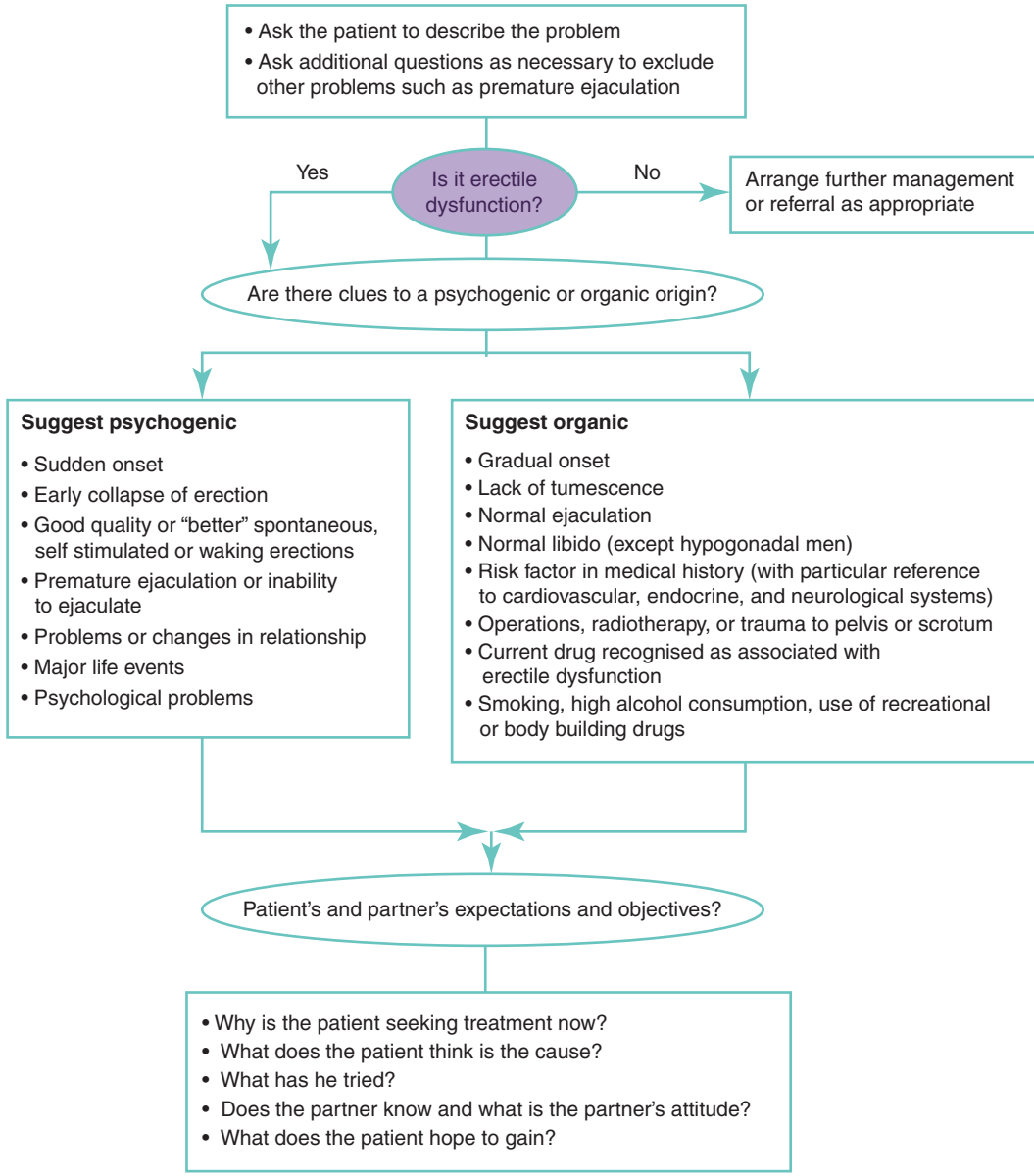


Fig. 48.2 History-taking in erectile dysfunction. Source: Ralph, D and McNicholas, T (2000) UK management guidelines for erectile dysfunction. *Bmj,* 321, 499–503. (link for copyright https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1118395/figure/F1/)

erectile function (Davis-Joseph et al. 1995; Hatzichristou et al. 2002). If the initial assessment indicates the possibility of an important psychiatric problem, this should be addressed before treatment for erectile dysfunction (Ralph and McNicholas 2000) (Fig. 48.2).

The pathophysiology of ED may be neurogenic, hormonal, vasculogenic, drug-induced, anatomical and/or psychogenic, thus obtaining a comprehensive medical history may elicit one of the conditions typically associated with ED. ED may be associated with modifiable risk factors, including lifestyle, medications or undiagnosed illness/conditions.

These issues may be addressed either before, or at the same time as specific treatments are used.

Medical conditions such as endocrine and metabolic disorders (e.g. hypogonadism, hyperprolactinaemia and diabetes) should always be treated and well controlled as the first step of ED treatment.

Treatment options for ED should be tailored according to patient (and partner) satisfaction, QoL factors and treatment-related safety and efficacy. The management algorithm for ED recommended by the European Association of Urology (EAU) (Hatzimouratidis et al. 2016) is presented in Fig. 48.3.

The physician–patient (partner) dialogue is essential throughout the management of ED. It is important to create a relaxed atmosphere during history-taking, ideally involving the patients' partner if possible. This will make it easier to ask personal questions regarding the patient's erectile function which will also include other aspects of sexual history.

48.2.1 Sexual History

This should include information regarding duration of the erectile problem and whether onset was gradual or sudden. Details relating to previous treatments trialled and information on any previous or current relationships, including current emotional status must also be documented. Additional information to be sought includes rigidity and duration of both sexually stimulated, morning or nocturnal erections, and any problems with ejaculation, arousal or orgasm.

Psychometrically validated questionnaires, such as the International Index for Erectile Function (IIEF) (Rosen et al. 1997), are useful tools to assist the clinician to measure the patient's different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, ejaculation, intercourse and overall satisfaction), as well as the effect of a specific treatment. Patients should be questioned for symptoms of possible hypogonadism, for example, decreased libido, energy, fatigue and cognitive impairment, as well as for symptomatic lower urinary tract symptoms (Hatzimouratidis et al. 2016).

48.2.2 Physical Examination

Every patient should undergo a physical examination focusing on the genitourinary, vascular, endocrine and neurological systems (Davis-Joseph et al. 1995), as this could divulge signs suggesting hypogonadism (e.g. small testes) or penile disorders such as Peyronie's disease (Hatzichristou et al. 2002). In addition, the EAU guidelines stipulate the need for rectal examination in men over 40 years to identify prostatic problems (Hatzimouratidis et al. 2016), and blood pressure and heart rate should be checked in those men who have not had this assessed within the past 6 months to elicit possible cardiovascular causes.

48.2.3 Blood Tests

Fasting blood glucose, lipid profile and early morning testosterone are essential laboratory tests that must be obtained in males presenting with ED. Additional tests that should be considered include prostate-specific antigen (PSA) for detection, or suspicion, of prostate cancer (Heidenreich et al. 2011), and hormonal tests, including prolactin and luteinising hormone, when low testosterone levels are discovered. Indeed, for these males, referral to an endocrinologist may be appropriate (Lue et al. 2004a).

48.2.4 The Cardiovascular System and Sexual Activity

Patients who pursue treatment for sexual dysfunction have a high incidence of cardiovascular disease (Montorsi et al. 2010); in addition, the cardiac risks coupled with sexual activity are well established. It is imperative that clinicians can identify those men who may require additional cardiological workup, and additionally ensure that each man's cardiovascular health is harmonious with the physical demands of sexual activity before prescribing ED treatment (Nehra et al. 2012). For men determined as 'high risk',

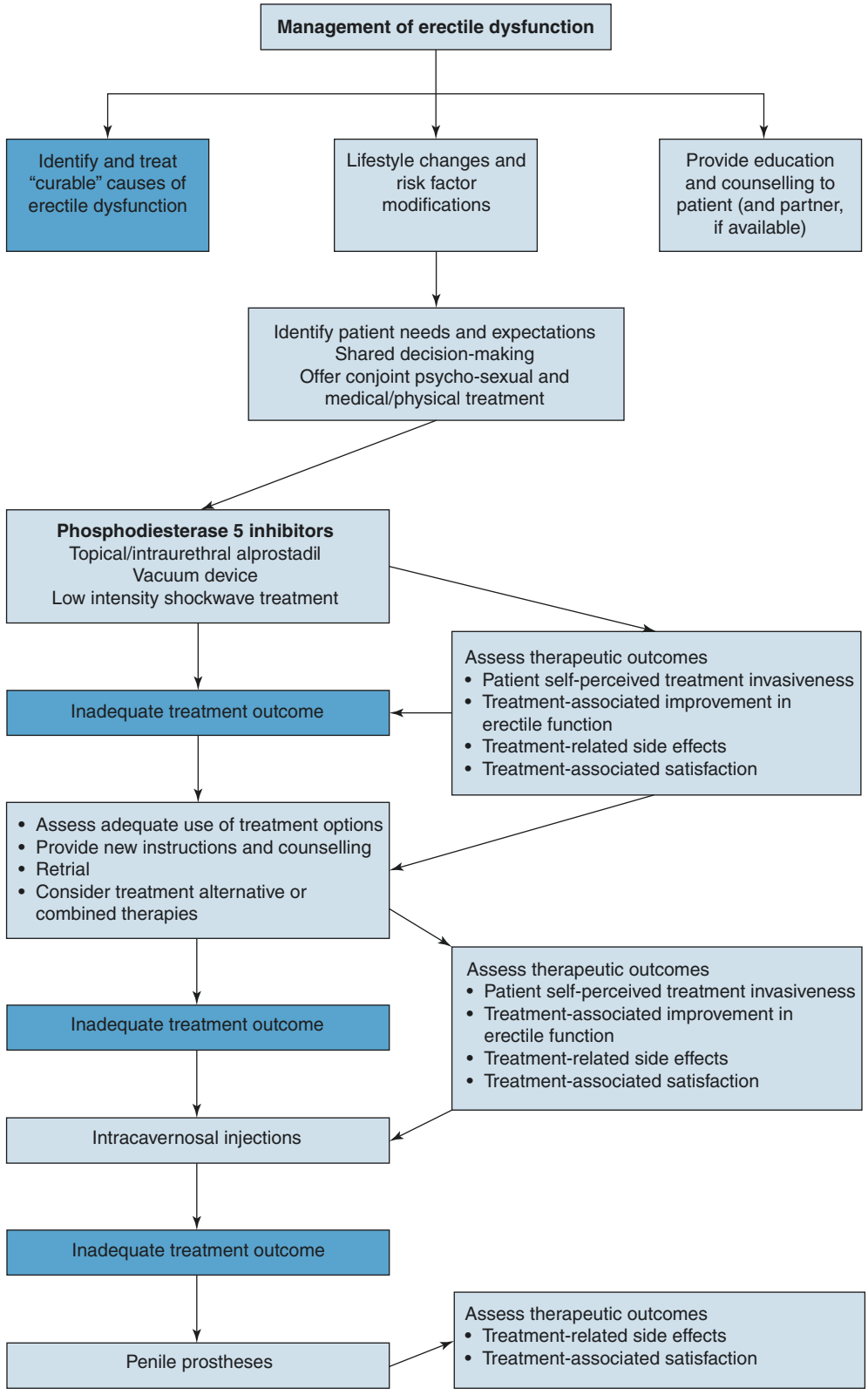


Fig. 48.3 Algorithm for the evaluation and management of patients with ED (used with permission from the European Association of Urology, accessed via http://uroweb.org/guideline/male-sexual-dysfunction/#3)

referral should be made to a cardiologist for assessment, possible treatment and an opinion that it is safe to resume sexual activity.

48.2.5 Specialist Diagnostic Tests

Although not essential, it may be pertinent to perform specialist tests on some males with erectile dysfunction.

These include:

- **Nocturnal penile tumescence (NPT) study**
  This sleep study is used to determine nocturnal penile tumescence and rigidity, with an erectile event indicated by a minimum of 60% rigidity recorded on the tip of the penis, lasting for >10 min (Hatzichristou et al. 1998). A positive NPT result (where strong erectile activity is recorded) indicates psychogenic erection dysfunction and a physical cause can be excluded.
- **Duplex ultrasound of the penis**
  The aim of Doppler ultrasound is to assess the inflow and outflow of blood through the cavernosal arteries after an intracavernosal injection of a pharmaco-stimulant (e.g. alprostadil) a peak systolic blood flow >30 cm/s, an end-diastolic velocity of <3 cm/s and a resistance index >0.8 are generally considered normal (Meuleman and Diemont 1995). In such circumstances where a normal duplex ultrasound is reported, further vascular investigation is unnecessary.
- **Cavernosography**
  The purpose of cavernosography is to identify veno-occlusive dysfunction in men with suspected organic ED (Glina and Ghanem 2013), thus it should only be performed in patients who are being considered for vascular reconstructive surgery (Wespes and Schulman 1993). This test is rarely offered today, even in specialist UK andrological centres.

48.3 Treatment Options for ED

Guidelines on the Management of Erectile Dysfunction (Hackett et al. 2008) were developed to standardise ED care. The standards describe the ED pathway as a three-stage process, commencing with first line oral phosphodiesterase 5 inhibitors (PDE5i's), followed by more invasive second line pharmacological injectables/intraurethral pellets, and lastly for refractory ED cases, penile prosthesis surgery (Fig. 48.4).

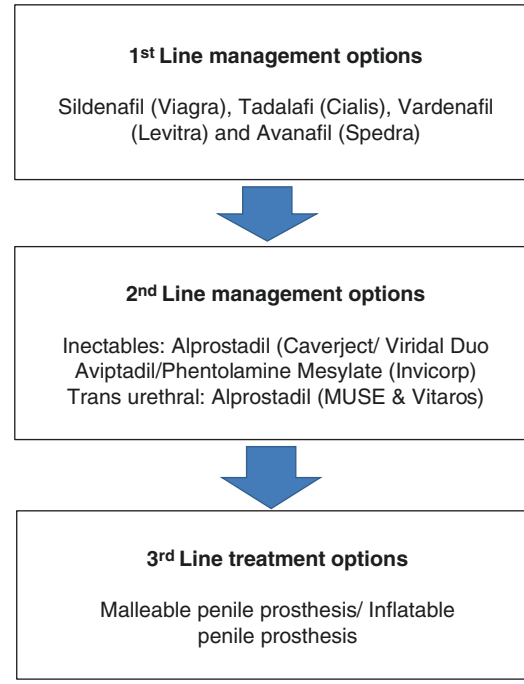


Fig. 48.4 Treatment algorithm for ED (adapted from Hackett et al. 2008)

48.3.1 First Line Treatment

48.3.1.1 PDE5 Inhibitors

Evidence suggests that phosphodiesterase 5 (PDE5) is the most important isoenzyme in the physiological control of normal penile activity (Gresser and Gleiter 2002), although tissue distribution of PDE5 also includes vascular smooth muscle, kidney, CNS, platelets and digestive smooth muscle (Lue et al. 2004b). In the penis, PDE5 is responsible for the breakdown of cGMP which leads to an increase in the tone of the cavernosal vessels resulting in contraction of the smooth muscle which induces de-tumescence usually after ejaculation or when sexual stimuli has been removed (Lue et al. 2004b).

PDE5i's selectively inhibit PDE5 to reduce breakdown of cGMP. They do not exert relaxant effect directly on the cavernosal tissue but can augment the relaxant effect of NO on the tissue which is released during sexual stimulation (Sussman 2004), therefore, in order to optimise the effect of a PDE5i, stimulation is necessary.

PDE5i oral tablets are recommended as the first line therapy for men with ED as they are well tolerated and non-invasive. These include sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) and avanafil (Spedra). Although components of each PDE5i are slightly different, all PDE5i's are considered relatively similar in efficacy and tolerability (Hackett et al. 2008). The most significant difference to the drugs relates to their pharmacokinetics in that sildenafil, vardenafil and avanafil are relatively short acting with a half-life of 4–6 h, whereas tadalafil has a considerably longer 17.5 h half-life (Electronic Medicines Compendium 2017f) (Table 48.2).

The shorter acting PDE5i's sildenafil and vardenafil are more readily absorbed with higher plasma concentration in the fasted patient, whereas tadalafil is better absorbed with food (Electronic Medicines Compendium 2017e). Avanafil can be taken with or without food. Adherence to administration advice is essential to maximise efficacy potential, and standard protocol indicates that a PDE5i should be trialled at maximum dose on at least eight separate occasions before it can be deemed a failure (Hackett et al. 2008).

As previously discussed, expression of PDE5 is present in other structures including the vascular and digestive smooth muscle and therefore side effects including headache, flushing and dyspepsia are common. Particular to sildenafil is its effect on inhibition of phosphodiesterase 6 inhibitor (PDE6) in the cones of the retina which may cause visual disturbance including 'blue vision'.

With their known effects on the NO/cGMP pathway, all PDE5i's have been shown to significantly potentiate the hypotensive effects of nitrates. As a result, PDE5i's are contraindicated in men using nitrates in any form (Electronic Medicines Compendium 2017d). Special caution must be employed to those with cardiovascular disease which could be compromised further by vaso-dilatory effects. Men with recent

Table 48.2 Characteristics of PDE-5I medications (adapted from McVary 2017)

Medication	T-max	Half-life	Duration	Dose (mg)	Adverse effects	Affected by	Contraindications
Sildenafil	30–120 min	2–5 h	4 h	25–100 mg (starting dose 50 mg)	Headaches, flushing, dyspepsia, nasal congestion, altered vision	High fat meal decreases absorption; alcohol may affect efficacy	Nitrates Hypotension Cardiovascular risk factors Change dose with some antiretrovirals Should be on stable dose for alpha blockers
Vardenafil	30–120 min	4.5 h	4–5 h	5–10 mg	Headaches, flushing, rhinitis, dyspepsia	High fat meal decreases absorption; alcohol may affect efficacy	Same as sildenafil May have minor prolongation of QT interval Concomitant use of Class I antiarrhythmic
Tadalafil	30–60 min	17.5 h	12–36 h	10, 20, 2.5, or 5 mg for daily dose	Headaches, dyspepsia, back pain, nasal congestion, myalgia	Plasma concentration NOT affected by food or alcohol	Same as sildenafil
Avanafil	30 min	3–5 h	2 h	50, 100, or 200 mg	Headache, flushing, nasal congestion, nasopharyngitis, back pain	Plasma concentration NOT affected by food	Same as sildenafil

Abbreviations: *T-max* time to maximum plasma concentration, *min* minutes, *h* hours

history of cerebrovascular accident or myocardial infarction should also refrain from using PDE5i's until deemed fit by a physician or cardiologist (Hackett et al. 2008; Hatzimouratidis et al. 2010). PDE5i's are predominantly metabolised by the enzyme CYP3A4 in the liver, therefore concomitant use of CYP3A4 inhibitors can increase exposure to PDE5i's, therefore these should be avoided (Electronic Medicines Compendium 2017a).

48.3.2 Second Line Treatment

48.3.2.1 Intracavernosal Injection

In the event PDE5i's prove ineffective, intolerable or are contraindicated, second line pharmacological options are offered (Hackett et al. 2008).

Worldwide, a number of injectable drugs for ED are available. In the UK, the first line injectable drug is alprostadil which is available as Caverject or Viridal Duo. Alprostadil is not dependent on NO or an intact nervous system, therefore making it a viable treatment option for a range of ED aetiologies including peripheral nerve injury, severe vascular disease, and diabetes associated with neuropathy, vasculopathy and myopathy (Nehra 2007).

Chemically identical to prostaglandin E1 (PGE1), alprostadil targets an enzyme called adenylate cyclase, which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP is the active second messenger that lowers intracellular calcium, resulting in smooth muscle relaxation (Lue et al. 2004b). It is associated with vasodilation which facilitates increased cavernosal arterial flow resulting in engorgement of the tissue.

Intracavernosal injections are administered by the patient; however for purpose of safety, the initial injection must be given following training and under supervision in the clinical setting (see Fig. 48.5 and Box 48.1). Different doses of alprostadil are required for each individual to achieve a satisfactory response. The starting dose is either 1.25 or 2.5 μg with dose titration up to a maximum of 60 μg (Electronic Medicines Compendium 2017b), in 2.5 or 5 μg increments until the patient achieves a satisfactory response.

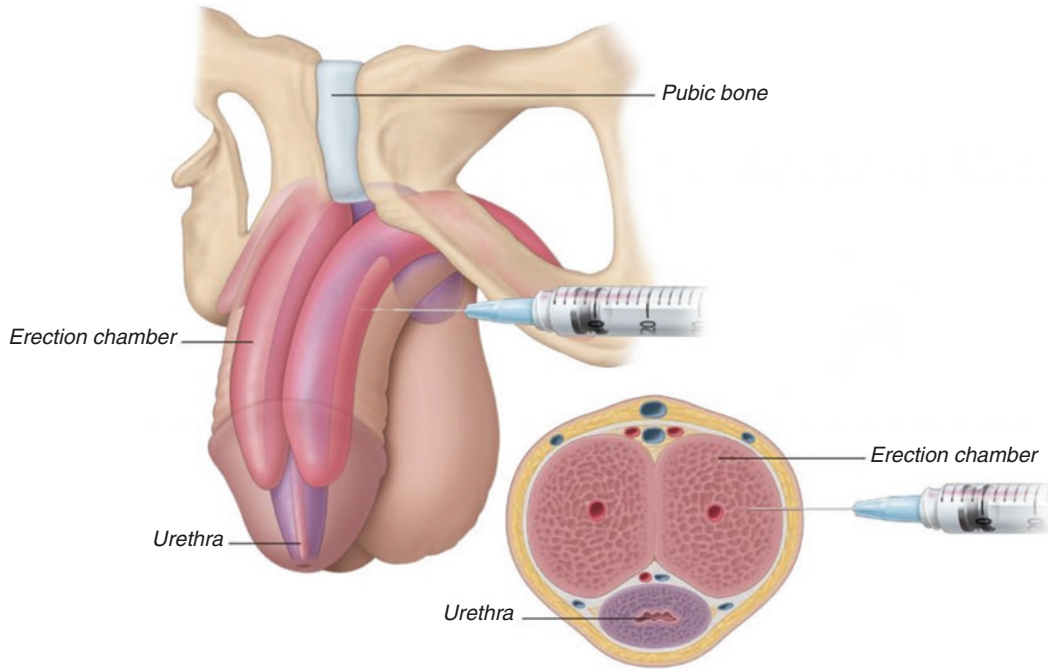


Fig. 48.5 Administration of intracavernosal alprostadil (used with permission from the European Association of Urology Patient Information, accessed via http://patients.uroweb.org/erectile-dysfunction/)

Box 48.1 Instructions on Administration of Intracavernosal Alprostadil

How to Administer Intracavernosal Alprostadil

- Patients may wish their partner to be involved in administering the medication and may need to attend the hospital in order to be taught. This may be essential in men whose body habitus does not allow direct visualisation of the penis.
- After washing hands, patients are shown how to prepare the medication for administration.
- The usual site for injection is within the proximal third of the penis along the dorsolateral aspect of the shaft (Electronic Medicines Compendium 2017b). This is to ensure the patient injects in the corpus cavernosum.
- Patients are advised to inject in both sides of the penis to prevent fibrosis and potential penile curvature development and to avoid the underside (risk of injecting into urethra) or the top (to avoid nerves).
- Visible veins are avoided to prevent bruising.
- Following administration patients are advised to massage the penis for 10 min sitting or standing in order to elicit a response.
- Erection occurs within 10–15 min of administration and should last between 30 and 60 min.
- Intracavernosal alprostadil should not be used more than once in 24 h or more than three times a week.

Common side effects include headache, dizziness and localised discomfort/pain. More serious systemic effects such as syncope and hypotension are rare due to minimal levels of alprostadil in the peripheral venous circulation. However concomitant use of antihypertensives with alprostadil can enhance hypotension, therefore caution should be employed when trialling the drug. Repeated injections into the corporeal tissue can lead to fibrosis, therefore varying the injection site is important. An important but uncommon side effect of the alprostadil injection is priapism (Electronic Medicines Compendium 2017b). Priapism is a prolonged full erection lasting in excess of 4 h without spontaneous resolution. Urgent medical attention is vital because of the potential detrimental effects on the viability and function of the corporal tissue if intervention is delayed (Bassett and Rajfer 2010).

Alprostadil use for ED is well tolerated and has a good safety profile; however, it is contraindicated in some men including those with known hypersensitivity to alprostadil or any of its excipients. It is contraindicated in men with severe penile deformity as well as those with unstable cardiovascular or cerebrovascular status. Men with sickle cell disease, multiple myeloma and leukaemia have an increased potential for priapism, therefore alprostadil should either be avoided in this group or used with extreme caution (Electronic Medicines Compendium 2017b).

Men who abandon alprostadil because of penile pain or who fail to respond at maximum dose can be offered other second line injectable agents. Although not licensed for ED, papaverine and phentolamine used in low dose combination known as ‘bi-mix’, and ‘tri-mix’ (with the addition of alprostadil) have been shown to be effective (Bechara et al. 1997; McMahon et al. 1999).

In the UK, the aforementioned drug combinations are rarely used, but another combination intracavernosal injection Invicorp is available and is licensed for ED. Invicorp comprises aviptadil (Vasoactive Intestinal Peptide—VIP), a naturally occurring amino acid neuro-transmitter, and phentolamine, an alpha blocker. When injected directly into the cavernosal tissues, the drug relaxes the smooth muscle of the penis (Dinsmore and Wyllie 2008).

Invicorp is available in only one dose, 25 μg/2 mg, therefore dose titration is not possible. The most common adverse reaction is facial flushing. Other potential side effects include dizziness, tachycardia/palpitations, and headache. As with all intracavernosal injections, the development of cavernosal fibrosis is a risk. Contraindications for Invicorp use mirror that of alprostadil.

48.3.2.2 Intraurethral Alprostadil

Intraurethral administration of alprostadil is considered less invasive than hypodermic injection (Mulhall et al. 2001; Dinsmore et al. 2014), and for the needle phobic, it is the preferred mode of delivery. There are two available intraurethral alprostadil preparations namely the medicated urethral system for erection (MUSE) and Vitaros.

MUSE comes in the form of a 3 mm pellet which is administered via the urethral meatus into the penile urethra using a small polypropylene instillation applicator (Electronic Medicines Compendium 2017c). In accordance with national guidelines (Hackett et al. 2008), the first dose of 500 μg is administered in the clinical setting. Response to this will determine subsequent prescription to trial at home. MUSE is available in 125 μg, 250 μg, 500 μg and 1 mg pellets. In order to facilitate easy introduction of the applicator and to expedite breakdown of the pellet, urination is recommended prior to insertion. The penis should be held in an upright position until the pellet has dissolved. At this point the penis can be dropped down and massaged to encourage distribution of the drug into the penile tissues and increase gravitational engorgement of blood. Erection occurs within 10–15 min of administration and should last between 30 and 60 min (MEDA 2011).

Vitaros is an intraurethral cream which is available in two strengths 200 and 3 mg/g. A preloaded syringe is used to administer the cream into the urethra via the urethral meatus (Ferring 2016). Erection is usually achieved 5–30 min following instillation and duration of effect ranges between 1 and 2 h (Electronic Medicines Compendium 2017g).

Intraurethral alprostadil in whichever form is readily absorbed through the urethral mucosa. It is metabolised both locally and within the cavernosal tissue via the lungs. Metabolites of intraurethral alprostadil are excreted primarily via the kidney (90%) within 24 h and the remainder in the faeces (Electronic Medicines Compendium 2017g).

The most common adverse effects associated with intraurethral alprostadil are transient urethral and penile burning/pain affecting around 7% of men (Electronic Medicines Compendium 2017g). Other side effects include dizziness and headache. The contraindications associated with ICI alprostadil pertain to intraurethral alprostadil. In addition, MUSE should be avoided in those with distal urethral stricture. Due to its vasodilating properties, men who have partners with possible or confirmed pregnancy should avoid intraurethral alprostadil, unless with condom protection (Electronic Medicines Compendium 2017c).

48.3.3 Third Line Therapy

48.3.3.1 Penile Prostheses

Penile prosthesis (Fig. 48.6) has become effective surgical treatment for patients who have failed or declined other available treatments, including oral pharmacotherapy, a vacuum erection device, intraurethral suppositories or intracavernosal injection (Hellstrom et al. 2010). Consequently, it is classified as a third line or 'end stage' ED treatment, as during placement the corpus cavernosa is damaged.

The two available types of penile implants include inflatable (2- and 3-piece) and malleable devices (Montague 2011; Martinez-Salamanca et al. 2011). Three-piece implants are the most preferred device due to the patient's ability to maintain a more 'natural' erection. These implants include a separate reservoir placed in the abdominal cavity, allowing the user to inflate the device by continuous squeezes of a pump located in the scrotum until erection is achieved, thus affording men the opportunity to achieve spontaneity for intercourse. Overall, three-piece devices provide the best rigidity and the best flaccidity; however, the two-piece inflatable prosthesis can be a viable option for patients who are deemed high risk of complications with reservoir placements, such as those who have undergone major pelvic surgery. Malleable prostheses are the least invasive implant but result in a firm penis and men must be coun-

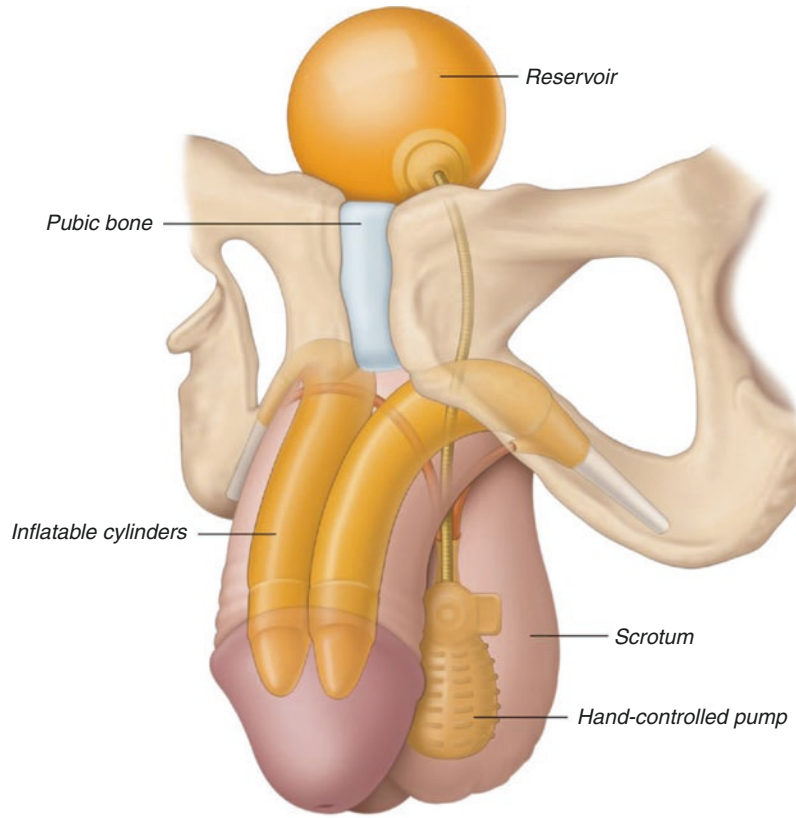


Fig. 48.6 A common type of inflatable penile implant (used with permission from the European Association of Urology Patient Information, accessed via http://patients.uroweb.org/erectile-dysfunction/)

selled of the need to conceal the device. Placement of a penile prosthesis will not increase the patient's libido, change his ability to ejaculate, or orgasm, and it does not alter penile sensations (Le and Burnett 2015).

It is proffered that satisfaction rates following prosthesis insertion are high, with researchers citing patient and partner satisfaction above 80% (Vitarelli et al. 2013). Pre-operative counselling at a specialist centre is imperative to ensure that patient expectations are not disproportionate, as this could lead to lower satisfaction rates. Patients should be afforded the opportunity to see and handle the different devices. They should also be informed that the procedure is irreversible and associated with significant procedural risks such as infection, erosion and mechanical failure (Vitarelli et al. 2013). It is essential that patients have realistic expectations in terms of erect penile length post implant insertion.

48.3.4 Other Available Treatments

48.3.4.1 Vacuum Erection Devices (VEDs)

Vacuum erection devices (VEDs) are clear plastic chambers, tightened against the lower abdomen with a mechanism to create a vacuum insider the chamber. This action provides passive engorgement of the corpora cavernosa, and the use of a constriction ring at the base of the penis will enable the user to retain blood within the corpora. Due to this action, erections with these devices are abnormal as there is no initial relaxation of the sinus smooth muscle in the corpora cavernosa. Instead all penile tissue becomes engorged with trapped blood, which is drawn into the penis by the action of negative pressure. In some men, the size of the penis is larger than that obtained with a normal erection, during use the penis may feel cooler, slightly numb or blueish in colour due to tissue cyanosis (Lewis and Witherington

1997). It is crucial for men to be appropriately consulted on this adverse effect.

The most common side events of VEDs include pain, inability to ejaculate and bruising, particularly in those patients with bleeding disorders or those on anticoagulant therapy. Users are reminded to remove the constriction ring within 30 min to avoid skin necrosis. Satisfaction for intercourse has been reported as to be as little as 27% and as high as 94% (Levine and Dimitriou 2001). Men who have an understanding and motivated partner report the highest rates and the feeling of coolness of the penis and the need to use lubrication gel have been cited as reasons for partner dissatisfaction. Long-term use decreases to 50–64% after 2 years (Cookson and Nadig 1993) and most men, who discontinue use, do so within the first 3 months.

VEDs may be the preferred treatment for older patients who practise infrequent sexual intercourse and those with comorbidities requiring non-invasive, drug-free management of ED (Levine and Dimitriou 2001). VEDs are also used by men to practise penile rehabilitation to prevent penile shrinkage such as those recovering from radical prostatectomy (Hoyland et al. 2013).

48.3.4.2 Shockwave Therapy

Recently, low intensity extracorporeal shock wave therapy has been considered a potential innovative treatment for the management of ED (Vardi et al. 2010). Since the 1980s when it was first introduced for renal lithotripsy, shock wave therapy has been adopted around the world for various conditions. The shock wave produces a wave of energy and when delivered through a medium, can be targeted non-invasively to affect a desired anatomical region. When low intensity shock wave therapy is applied to an organ, the shock waves interact with the tissues that have been targeted and stimulate a cascade of biological reactions. This results in the release of growth factors, which in turn activates neovascularisation of the tissue with successive improvement of the blood supply (Rassweiler et al. 2011). Still in its infancy for erectile dysfunction, the mechanism by which this treatment improves the symptoms of sufferers is not fully understood. Current research is limited and certainly more trials are needed to fully determine its safety and efficacy. However, initial reports suggest this has the potential to be a safe and alternative non-invasive treatment for ED sufferers.

A Patient Case Study

John a 52-year-old accountant, presents to the nurse-led ED clinic with his wife Mary. Throughout their marriage they report to having a healthy sexual relationship until 12–18 months ago where gradually his erections became weak. They are now unable to have penetrative sexual intercourse although they still desire it. John is becoming depressed that he is no longer able to 'satisfy' his wife, and has been to see his GP regarding the possibility of commencing an antidepressant.

The nurse takes a full medical history and notes John has an 8-year history of type 2 diabetes controlled with metformin, and gliclazide. The gliclazide is a recent addition as John's HbA1c has been deteriorating and he admits that his diabetes has been poorly controlled. He has gained 10 kg due to a change in his job and has a body mass index of 33 and a waist circumference of 42 in. (106 cm). In addition to diabetes, he suffers with hypercholesterolemia for which he is prescribed atorvastatin and ramipril for hypertension. Physical examination is unremarkable. His blood pressure and pulse are within normal limits.

The nurse notes that John has several organic and psychological factors (diabetes, cardiovascular disease, obesity, lack of exercise and depression) that have the potential to contribute to his decrease in erectile function.

In clinic, the nurse formulates a plan to improve John's physical and psychological well-being and he reports to feeling more positive now he has sought help. Mary is happy that a cause for his erectile dysfunction has been established and plans to work with her husband to improve his diabetic control and maintain a healthier lifestyle.

The nurse gives John an overview of the available treatments for erectile dysfunction, including the advantages and disadvantages of

each treatment and possible side effects. A plan is made to commence treatment with sildenafil 50 mg on demand increasing to 100 mg if necessary. John is advised to take this 1 h prior to sexual activity on an empty stomach. He is advised that sexual stimulation is required to be effective. John is supplied with eight tablets and a plan is made to see John in 3 months for follow-up. John is advised to try all eight tablets before his next review. In addition, an early morning testosterone is requested for completion and John will bring this with him when he attends his next appointment.

48.4 Conclusions

Penile erection is a complex phenomenon which is reliant upon a delicate balance of vascular, neurological, hormonal and psychological elements. ED is caused by disequilibrium within this process. There are a multitude of cause and risk factors associated with ED which can be categorised as unmodifiable or modifiable. A thorough diagnostic evaluation should elicit any modifiable risk factors, including lifestyle, medications or undiagnosed illness/conditions and these should be addressed in the first instance to optimise erectile function and improve general health. ED can have a devastating psychological impact on the sufferer and partner and therefore, it is imperative that access to treatment is not delayed.

The ED management algorithm developed by an expert panel promotes best practice in the management of this condition and should be adhered to ensure men are offered appropriate management/treatment options.

Acknowledgments With special thanks to the European Association of Urology Patient Information (https://patients.uroweb.org), for their permission to use images and illustrations in our chapter.

References

Bassett J, Rajfer J. Diagnostic and therapeutic options for the management of ischemic and non-ischemic priapism. Rev Urol. 2010;12(1):56.

Bechara A, Casabe A, Cheliz G, Romano S, Rey H, Fredotovich N. Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction. J Urol. 1997;157:2132.

Cookson MS, Nadig PW. Long-term results with vacuum constriction device. J Urol. 1993;149(2):290–4.

Davis-Joseph B, Tiefer L, Melman A. Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. Urology. 1995;45(3):498–502.

Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin N Am. 2005;32(4):379–95.

Dinsmore WW, Wyllie MG. Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction. BJU Int. 2008;102(8):933–7.

Dinsmore WW, Lopes TM, Potempa AJ, Piha J, Costa P. The role of intraurethral alprostadil as a first-choice erectile dysfunction treatment option in special populations: a proposed treatment algorithm. Clin Pract. 2014;11(2s):17–26.

Electronic Medicines Compendium. Avanafil. 2017a. https://www.medicines.org.uk/emc/medicine/28729. Last updated 31 Mar 2016). Accessed 4 Aug 2017.

Electronic Medicines Compendium. Caverject ICI Alprostadil. 2017b. https://www.medicines.org.uk/emc/medicine/1480. Last updated 25 May 2017. Accessed 5 Aug 2017.

Electronic Medicines Compendium. MUSE. 2017c. https://www.medicines.org.uk/emc/medicine/22218. Last updated 9 Jan 2014. Accessed 5 Aug 2017.

Electronic Medicines Compendium. Sildenafil. 2017d. https://www.medicines.org.uk/emc/medicine/27844. Last updated 8 Jan 2016. Accessed 4 Aug 2017.

Electronic Medicines Compendium. Tadalafil. 2017e. https://www.medicines.org.uk/emc/medicine/11363. Last updated 26 Apr 2017. Accessed 4 Aug 2017.

Electronic Medicines Compendium. Vardenafil. 2017f. https://www.medicines.org.uk/emc/medicine/24374. Last updated 27 Sep 2016. Accessed 4 Aug 2017.

Electronic Medicines Compendium. Vitaros. 2017g. https://www.medicines.org.uk/emc/medicine/28866. Last updated 2 Sep 2016. Accessed 5 Aug 2017.

Ferring. Vitaros patient support leaflet. 2016. https://www.medicines.org.uk/emc/PIL.28938.latest.pdf. Accessed 5 Aug 2017.

Glina S, Ghanem H. SOP: corpus cavernosum assessment (cavernosography/cavernosometry). J Sex Med. 2013;10(1):111–4.

Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of PDE5 inhibitors sildenafil, vardenafil, and tadalafil. Review of the literature. Eur J Med Res. 2002;7:435–46.

Gruenwald I. The ESSM syllabus of sexual medicine. Amsterdam: Medix Publishers; 2012.

Hackett G, Kell P, Ralph D, Dean J, Price D, Speakman M, Wylie K. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. J Sex Med. 2008;5(8):1841–65.

Hatzichristou DG, Hatzimouratidis K, Ioannides E, et al. Nocturnal penile tumescence and rigidity monitoring in young potent volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. J Urol. 1998;159(6):1921–6.

Hatzichristou D, Hatzimouratidis K, Bekas M, et al. Diagnostic steps in the evaluation of patients with erectile dysfunction. J Urol. 2002;168(2):615–20.

Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, Vardi Y, Wespes E. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol. 2010;57(5):804–14.

Hatzimouratidis K, Giuliano F, Moncada I, Muneer A, Salonia A, Verze P. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism. European Association of Urology. 2016. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Male-Sexual-Dysfunction-2016-3.pdf.

Heidelbaugh JJ. Management of erectile dysfunction. Am Fam Physician. 2010;81(3):305–12.

Heidenreich A, Bellmunt J, Bolla M, et al. European Association of Urology. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59(1):61–71.

Hellstrom WJ, Montague DK, Moncada I, Carson C, Minhas S, Faria G, et al. Implants, mechanical devices, and vascular surgery for erectile dysfunction. J Sex Med. 2010;7(1 Pt 2):501–23.

Hoyland K, Vasdev N, Adshead J. The use of vacuum erection devices in erectile dysfunction after radical prostatectomy. Rev Urol. 2013;15(2):67–71.

Isadori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, Porst H, Salonia A, Traish AM, Maggi A. Acritical analysis of the role of testosterone in erectile function: from pathophysiology to treatment—a systematic review. Eur Urol. 2014;65:99–112.

Le B, Burnett AL. Evolution of penile prosthetic devices. Korean J Urol. 2015;56(3):179–86.

Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. Urol Clin N Am. 2001;28(2):335–41, ix–x.

Lewis R, Witherington R. External vacuum therapy for erectile dysfunction: use and results. World J Urol. 1997;15:78–82.

Lue T, Giuliano F, Khoury S, Rosen R. Clinical manual of sexual medicine sexual dysfunctions in men. Paris: Health Publications LTD; 2004a.

Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2004b;1(1):6–23.

Martinez-Salamanca JI, Mueller A, Moncada I, et al. Penile prosthesis surgery in patients with corporal fibrosis: a state of the art review. J Sex Med. 2011;8(7):1880–9.

McMahon CG, Samali R, Johnson H. Treatment of intracorporal injection nonresponse with sildenafil alone or in combination with triple intracorporal injection therapy. J Urol. 1999;162:1992.

McVary KT. Sexual dysfunction, chapter 19. In: Jameson LJ, editor. Harrison's endocrinology. 4th ed. New York: McGraw-Hill Education; 2017. p. 241–50.

MEDA. MUSE patient support leaflet. 2011. http://www.muserx.com/hcp/muse-and-your-patients/patient-education.aspx. Accessed 5 Aug 2017.

Meuleman EJ, Diemont WL. Investigation of erectile dysfunction. Diagnostic testing for vascular factors in erectile dysfunction. Urol Clin North Am. 1995;22(4):803–19.

Montague DK. Penile prosthesis implantation in the era of medical treatment for erectile dysfunction. Urol Clin N Am. 2011;38(2):217–2. http://www.ncbi.nlm.nih.gov/pubmed/21621088

Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, Milbank AJ, Nehra A, Sharlip ID. Erectile Dysfunction Guideline Update Panel the management of erectile dysfunction: an American Urological Association update. J Urol. 2005;174(1):230–9.

Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, Sharlip I, Althof SE, Andersson KE, Brock G, Broderick G. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88.

Moreland RB, Hsieh G, Nakane M, Brioni JD. The biochemical and neurologic basis for the treatment of male erectile dysfunction. J Pharmacol Exp Ther. 2001;296(2):225–34.

Mulhall JP, Jahoda AE, Ahmed A, Parker M. Analysis of the consistency of intraurethral prostaglandin E1 (MUSE) during at-home use. Urology. 2001;58(2):262–6.

Nandipati KC, Raina R, Agarwal A, Zippe CD. Erectile dysfunction following radical retropubic prostatectomy. Drugs Ageing. 2006;23(2):101–17.

National Institute of Health. NIH Consensus Conference Impotence. NIH consensus development panel on impotence. JAMA. 1993;270(1):83–90.

Nehra A. Oral and non-oral combination therapy for erectile dysfunction. Rev Urol. 2007;9(3):99.

Nehra A, Jackson G, Miner M, et al. Aug The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78. http://www.ncbi.nlm.nih.gov/pubmed/22862865

Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. BMJ. 2000;321:499–503.

Rassweiler JJ, Knoll T, Kohrmann KU, et al. Shock wave technology and application: an update. Eur Urol. 2011;59:784–96.

Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822–30.

Sullivan M, Thompson C, Dashwood M, Khan M, Jeremy J, Morgan R, Mikhailidis D. Nitric oxide and penile erection: is erectile dysfunction another manifestation of cardiovascular disease. Cardiovasc Res. 1999;43(3):658–65.

Sussman DO. Pharmacokinetics, pharmacodynamics, and efficacy of phosphodiesterase type 5 inhibitors. J Am Osteopath Assoc. 2004;104(3 Suppl 4):S11–5.
Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low intensity extracorporeal shockwave therapy improve erectile function? A 6 month follow up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58(2):243–8.
Vitarelli A, Divenuto L, Fortunato F, Falco A, Paqliarulo V, Antonin G, Gentile V, Sciarra A, Salciccia S, Sansalone S, Di Placido MR, et al. Long term satisfaction and quality of life with AMS 700Cx unflatable penile prosthesis. Arch Ital Urol Androl. 2013;85(3):133–7.
Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. J Urol. 1993;149(5 Pt 2):1238–45.

Key Reading

1. Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of PDE5 inhibitors sildenafil, vardenafil, and tadalafil. Review of the literature. Eur J Med Res. 2002;7:435–46.
2. Hackett G, Kell P, Ralph D, Dean J, Price D, Speakman M, Wylie K. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. J Sex Med. 2008;5(8):1841–65.
3. Hatzimouratidis K, Giuliano F, Moncada I, Muneer A, Salonia A, Verze P. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism. European Association of Urology. 2016. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Male-Sexual-Dysfunction-2016-3.pdf.
4. Heidelbaugh JJ. Management of erectile dysfunction. Am Fam Physician. 2010;81(3):305–12.
5. Heidenreich A, Bellmunt J, Bolla M, et al. European Association of Urology. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59(1):61–71.
6. McVary KT. Sexual dysfunction, chapter 19. In: Jameson LJ, editor. Harrison's Endocrinology, 4th Edition. New York: McGraw-Hill Education; 2017. p. 241–50.

49 Genetic Counselling and Psychosexual Considerations in Male Health and Reproduction

Margaret G. Au and Sue Jackson

Contents

49.1 **Genetic and Ethical Considerations** 944
49.1.1 Definition and Practice of Genetic Counselling 944
49.1.2 Inheritance Patterns 944
49.1.3 Genetic Testing 947

49.2 **Psychosexual Considerations** 949
49.2.1 Psychosexual Development 949
49.2.2 Psychogenic Aspects of Sexual Function 950

49.3 **Conclusions** 952

References 952

Abstract

The chapter starts with a focus on the issues associated with genetic counselling. The process of genetic counselling is described, followed by a discussion of inheritance patterns commonly observed in reproductive disorder. Current genetic testing options with considerations for their benefits, limitations, and possible results are reviewed. The second section starts by briefly describing current theories of psychosexual development as well as highlighting some issues which suggest the limit of their utility. We then move to consider the psychogenic aspects of sexual function for men focusing mostly on those issues likely to be experienced by those with endocrine disorders. We also consider the problems men face when consulting with healthcare professionals about sexual function and make the case for the use of tools and techniques to aid the process.

Keywords

Genetic counselling · X-linked · Autosomal dominant · Autosomal recessive · Digenic · Cytogenetic · Sex · Gender identity · Mental health

M. G. Au (✉)
Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA, USA

S. Jackson
Psychology Department, University of the West of England, Bristol, UK

Wellbeing Service, Bristol, UK
e-mail: hellosue@suejackson.me.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_49

Abbreviations

BDSM	Bondage, discipline, and sadomasochism
CBAVD	Congenital bilateral absence of the vas deferens
CHH	Congenital hypogonadotropic hypogonadism
FISH	Florescence in situ hybridization
FSH	Follicle stimulating hormone
KS	Klinefelter's Syndrome
LH	Luteinizing hormone
PCR	Polymerase chain reaction

Key Terms

- **Exome sequencing:** Examining the nucleotide sequence within the protein-coding regions (exons) of all genes in the genome.
- **Genome sequencing:** Examining the nucleotide sequence of the entire genome, including the exons (protein-coding regions) and introns (segments between exons) of all genes, as well as segments of the genome between genes.

Key Points

- Reproductive disorders demonstrate a wide range of inheritance patterns. Collecting a detailed family history with a focus on reproductive and associated traits guides risk assessment and genetic test selection.
- Genetic testing can assist with confirming the aetiology of and recurrence risk for reproductive disorders. Consideration regarding appropriate test selection and possible results, including incidental findings, is an important part of pre-test genetic counselling.
- Psychosexual development is a complicated process still not completely understood. Given the increasingly fluid nature of gender identity, each person needs to be treated as an individual.
- Men face a number of obstacles to being able to seek help with problems related to sexual functioning. We need to get better at enabling men to access healthcare and psychological support.

49.1 Genetic and Ethical Considerations

49.1.1 Definition and Practice of Genetic Counselling

Genetic counselling has been defined as the process of helping others make meaning of the medical, familial, and psychosocial consequences of disease through understanding and adaptation. Key components of genetic counselling include: gathering an individual's medical history/phenotype, documenting their family history, genetic test selection, result interpretation, risk assessment, resource gathering, and psychosocial counselling. Though specific genetic counselling training programmes and certifications exist in some areas, nurses are well suited to provide many genetic services. Whether one is trained as a geneticist, genetic counsellor, physician, or nurse, key aspects of working with patients and families around genetics involve effective communication and detailed history taking (Benjamin et al. 2015; Delikurt et al. 2015).

49.1.2 Inheritance Patterns

Reproductive disorders demonstrate a wide range of inheritance patterns, so obtaining detailed medical and family histories is essential in the process of determining differential diagnoses and recurrence risk. A family history should include three generations whenever possible and constructing a family pedigree (genogram) can allow for visualization and documentation of inheritance patterns. In a pedigree, circle symbols are used for females, squares for males, and diamonds for individuals of

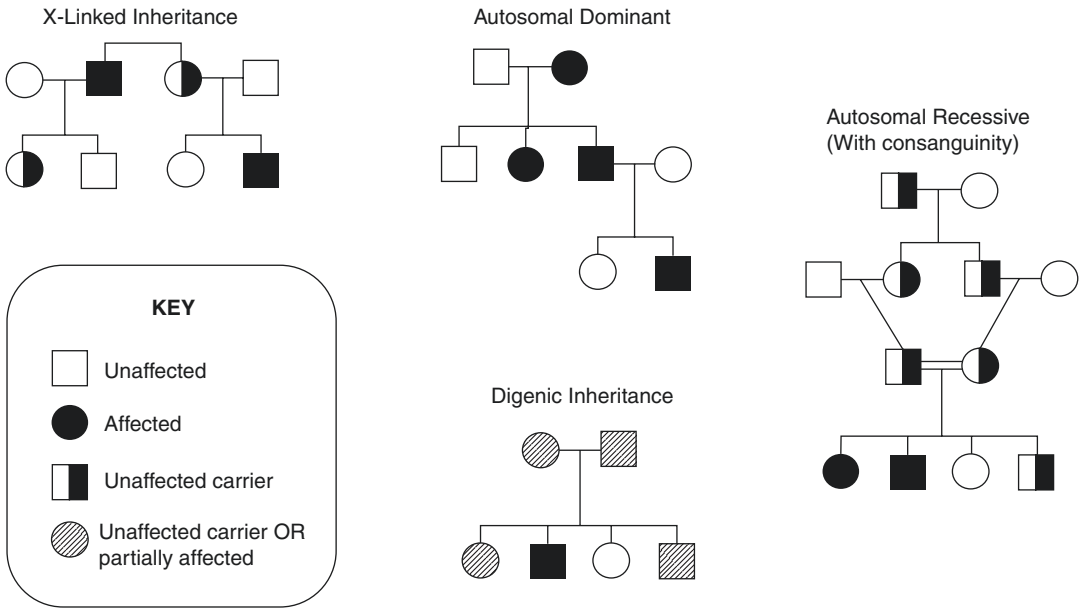


Fig. 49.1 Pedigrees demonstrating common inheritance patterns

Table 49.1 Example questions to assess family history of reproductive disorders

Fertility status	Timing of puberty	Non-reproductive phenotypes
Does a family member have biological children? If not, is it by choice?	Were any family members considered "late bloomers"?	Are there family members with congenital abnormalities (cleft lip/palate, renal abnormalities/agenesis, skeletal defects, missing or extra teeth)
Is there a family history of infertility?	At what age did women have their first menstrual period (menarche)? Did menarche occur for any female family member after the age of 16?	Does a family member have an absent or reduced sense of smell?
Has a family member required fertility treatment to conceive? If so, what treatment was used?	Did any male family members continue growing after age 18?	Any history of hearing loss among family members?
Is there a family history of recurrent miscarriage, spontaneous abortion, or stillborn babies?	Was treatment, such as oral contraceptives or testosterone, used to initiate puberty in a family member?	

unspecified gender. A male and female partner are connected in the middle with horizontal relationship line, with resulting children shown below the parents and connected with a vertical line of descent (Bennett et al. 2008). See Fig. 49.1 for example pedigrees. Relevant questions for family history focusing on reproductive conditions can be found in Table 49.1.

Reproductive disorders may present as familial cases or in sporadic forms. Familial means that more than one member of the family is affected, whereas sporadic refers to situations in which only the patient (proband) is affected. Inheritance, or how the condition is transmitted throughout a family, can take several forms.

49.1.2.1 X-Linked

Disorders related to genes on the sex chromosomes (i.e. X, Y) display a characteristic pattern of transmission as females have two X chromosomes

while men only have one X in addition to a Y chromosome. A classic X-linked family history shows affected males related through unaffected or sometimes mildly affected females. There is no male to male transmission of the condition. Examples of this include Kallmann syndrome resulting from mutations in anosmia 1 (*ANOS1,* formerly *KAL1)*, and disorders of sex development resulting from gene defects in the androgen receptor (*AR*). Affected men will have likely unaffected carrier daughters and unaffected, non-carrier sons. Female carriers of X-linked conditions have a 25% chance of having an affected son, a 25% chance of having a carrier daughter, and 50% chance of an unaffected son or non-carrier daughter.

49.1.2.2 Autosomal Recessive

Males and females are equally affected in a typical autosomal recessive pedigree. Affected individuals are often siblings with unaffected carrier parents. Parental consanguinity (meaning that the parents are related, i.e. cousins or closer) can also be a clue to support recessive inheritance. A number of genetic loci underlying congenital hypogonadotropic hypogonadism (CHH) follow an autosomal recessive inheritance pattern: *GNRHR*, *KISS1R*, *TAC3*, *TAC3R*, *PROK2*, *PROKR2*, and *GNRH1*. Mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR)* is an autosomal recessive cause for azoospermia due to congenital bilateral absence of the vas deferens (CBAVD). Carrier parents have a 25% chance of having an affected child, 25% chance of having a child who is neither affected nor a carrier, and a 50% chance of having a child who is an unaffected carrier. People with recessive conditions are only at risk of having an affected child if their partner is either affected with that condition or a carrier.

49.1.2.3 Autosomal Dominant

Autosomal dominant conditions also typically present equally in males and females. Male to male transmission occurs. Each generation can show affected individuals, though the presentation may vary (described as variable expressivity), OR a person with a pathogenic gene variant may show no signs of disease if the condition demonstrates incomplete penetrance. For CHH, *FGFR1*, *PROKR2*, *PROK2*, *CHD7*, *SEM3A1*, *NELF*, *HS6ST*, *WDR11*, and *FGF8* demonstrate autosomal dominant inheritance. CBAVD can also be due to a heterozygous pathogenic variant in *CFTR* and demonstrate dominant inheritance. An individual with an autosomal dominant condition has a 50% chance of passing on the condition/gene variant to each child and a 50% chance of having a child without the condition/gene variant.

49.1.2.4 Digenicity and Oligogenicity

Some endocrine disorders, namely Bardet–Biedl syndrome and CHH/Kallmann syndrome have been identified to include digenic and oligogenic forms. For CHH, in particular, determining the inheritance pattern can be complicated by di-/oligogenicity. This occurs when variants in two or more genes in combination appear to contribute to disease. Many of the genes associated with CHH have been reported in di-/oligogenic states, but *SEM3A1*, *NELF*, *HS6ST*, and *WDR11* variants are predominantly found in combination with other gene variants (Buck et al. 2013). The contribution of variants in multiple genes may help explain observations of incomplete penetrance and variable expressivity in family members carrying the same mutation. In some cases, the aggregation of gene defects helps explain the more severe clinical presentation (phenotypes) (Miraoui et al. 2013).

See Fig. 49.1 for pedigrees demonstrating X-linked, autosomal recessive, autosomal dominant, and digenic inheritance patterns.

49.1.2.5 Chromosomal and Cytogenetic Causes

Chromosomal/cytogenetic aetiologies of male infertility include Klinefelter syndrome (two or more X chromosomes in addition to a Y chromosome), which is typically sporadic and not seen in other family members. Microdeletions of the AZFa or AZFb regions of the Y chromosome can result in male infertility due to azoospermia. And 46, XX testicular disorders of sex development are also usually due to chromosome rearrangements involving genes that are critical for early gonadal development i.e. *SRY*, *SOX9*, or *SOX3*. Chromosome microdeletions and rearrangements

can be inherited or the result of a parental balanced chromosome rearrangement (translocation or inversion) or occur as a new (de novo) change in an affected individual.

Determination of inheritance may be derived from several sources including discussions with the patient, interviewing family members, and/or medical record review. Indeed, detailed medical record review is important for both selecting an appropriate genetic test and confirming a diagnosis. Often specific phenotypes may be useful for guiding the selection of a genetic test. For instance, CHH-associated phenotypes can be useful for targeted gene screening (Costa-Barbosa et al. 2013; Boehm et al. 2015). Similarly, clinical palpation of the vasa (i.e. absence) can help guide screening for variants in *CFTR*. Health history questions such as those noted for family history can be asked of the patient. Review of health records, including laboratory results (endocrine profiling may include testosterone, LH, FSH, prolactin, and ferritin in particular), imaging studies (pituitary MRI, ultrasound), and physical exam findings is also necessary. More regarding the evaluation and types of male reproductive disorders can be found in Chaps. 43 and 44.

49.1.3 Genetic Testing

A genetic aetiology for male infertility may be identified in up to 15% of cases (Krausz and Chianese 2014), though this number may increase with wider use of genomic testing. Clues from a patient's medical and family histories can assist in the selection of the appropriate genetic test. For CHH, a testing algorithm driven by family history and patient phenotype has been suggested (Costa-Barbosa et al. 2013; Boehm et al. 2015; Au et al. 2011). However, with increased availability and reduced cost associated with next-generation sequencing panels and exome sequencing, it may be equally economical to take a "genotype first" approach and sequence all genes associated with a particular disorder, if not the entire exome or genome (Baetens et al. 2014). Sequencing is appropriate as first-line genetic testing for CHH genes, androgen insensitivity (via the *AR* gene), and *CFTR* as sequence variants are the most common genetic aetiology. Deletion/duplication testing for these genes may be considered if sequencing is not informative. A panel of the 25 most common pathogenic *CFTR* variants is available, but the detection rate is dependent on patient race/ethnicity (i.e. it is higher in people of European and Ashkenazi Jewish descent). If the R117H pathogenic variant in *CFTR* is identified in the setting of CBAVD, further evaluation of the poly T (thymidine bases) tract is indicated (Grody et al. 2001). For individuals with possible Klinefelter syndrome or 46, XX testicular disorder of sex development, a karyotype is indicated with follow-up florescence in situ hybridization (FISH) for *SRY* or a chromosome microarray (CGH array) study if the karyotype shows 46, XX in someone with male external genitalia. CGH array could be performed instead of a karyotype as it will detect aneuploidies (like Klinefelter syndrome) and chromosome microdeletions and duplications. It may be more expensive than a traditional karyotype and will not detect balanced chromosome rearrangements (translocations, inversions). Y chromosome microdeletions of specific AZF regions may be completed with polymerase chain reaction (PCR) based copy number studies.

49.1.3.1 Inconclusive and Incidental Findings

Even with powerful genetic testing tools and careful phenotyping, results of genetic testing may be negative or uncertain. A negative genetic test result does not exclude the possibility of a genetic aetiology in many cases. Among individuals with a clinical diagnosis of CHH, the genetic cause will be identified 50% of the time (Buck et al. 2013). Genetic testing will identify SRY, SOX9, or SOX3 copy number abnormalities in ~90% of people with 46, XX testicular disorders of sex development if normal male genitalia is present, but <10% in those with ambiguous male genitalia (Baetens et al. 2014; Délot and Vilain 2015). Expanded genomic testing also increases the likelihood of identifying variants of uncertain significance. These variants may have limited or conflicting evidence that prevents them from being interpreted as either benign (normal) or

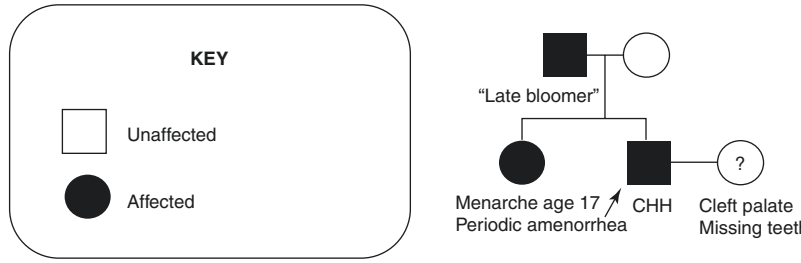


Fig. 49.2 Pedigrees demonstrating the family inheritance patterns for this patient

pathogenic (disease-causing). In some cases, studying family members to determine if the variant tracks (referred to as "segregation") with disease can be helpful to potentially resolve uncertainty. Large-scale genomic testing such as exome or genome sequencing also presents the possibility of learning unrelated or unexpected information. The American College of Medical Genetics and Genomics recommends all families proceeding with exome sequencing be given the option to learn about the presence of any disease-causing mutations in a list of 59 genes associated with conditions for which some action (mostly preventive) is available. For the most part, these conditions are related to hereditary cancer predisposition or hereditary cardiovascular diseases. This information is usually not related to the primary indication for testing and is sometimes referred to as "secondary" or "incidental" findings (Kalia et al. 2017). The European Society of Human Genetics does not have a similar policy statement at this time, but instead suggests the future guidelines take into account legal, cultural, familial, and personal factors when considering reporting incidental findings (Heihir-Kwa et al. 2015). Notably, non-paternity and parental consanguinity or possible incest can potentially be identified in the course of genetic testing. Thus, careful consideration is warranted in dealing with such sensitive issues that may reflect family secrets or culturally challenging situations.

Case Study

A 25-year-old man clinically diagnosed with CHH and his 26-year-old female partner seek genetic counselling and testing to understand their risk for having a child with a CHH. The pedigree shows the man's sister to have late menarche at age 17 and amenorrhea during stressful periods. Their father was described as a late bloomer who reached his adult height after age 18 years. The partner's personal history is significant for cleft palate and three missing adult teeth. Her family history is unremarkable. The couple are not known to be related to each other (Fig. 49.2).

1. What inheritance pattern does this pedigree suggest?
   (a) The man's family history is suggestive of autosomal dominant inheritance with variable expressivity. The woman's history of cleft palate and missing teeth could be due to sporadic congenital abnormalities OR the result of variants in genes related to CHH.
2. What genetic testing would be indicated and who would be tested first?
   (a) Testing with a panel of genes known to contribute to CHH would be most efficient. The 25-year-old man with CHH is the ideal candidate for genetic testing as he has a clinical diagnosis of CHH and appears to be the most significantly affected in his family. If other syndromic causes of cleft palate, in particular, have been ruled out in the female partner, it may also be helpful to test her for variants in genes related to CHH due to the possibility of digenic inheritance.
3. What is this couple's recurrence risk for CHH?
   (a) Based on the man's family history alone, the risk to have a child with some degree of a reproductive disorder could be as high as 50%. It will be difficult to predict how sig-

nificantly a child would be impacted by the condition due to variable expressivity. If the female partner also has a pathogenic variant in a CHH gene (and assuming an autosomal dominant genetic cause in the man), they would have a 25% chance of having a child with both genetic factors and possibly more severe phenotype, a 25% chance of having a child with the father's genetic cause of CHH only, a 25% chance of having a child with the mother's CHH-related variant only, and a 25% chance of having a child with neither CHH gene variant.

If the mother's cleft palate and missing teeth are NOT due to CHH-related factors or other syndrome, the couple would have an increased risk to have a child with a cleft palate compared to the general population risk. They may consider having a high-level foetal ultrasound after 20 weeks gestation for prenatal diagnosis of cleft palate, though cleft palate is much more difficult to detect by prenatal ultrasound than cleft lip.

49.2 Psychosexual Considerations

49.2.1 Psychosexual Development

Psychosexual development seems to flow out of theories aimed at explaining dichotomous gender identity (i.e. male/female) especially in relation to early childhood. Widely criticized for a number of failings, Boyd and Bee (Boyd and Bee 2014) describe how Freud's psychoanalytic theory has now been joined by four other theories they list as: (1) social learning (where the role of parents/caregivers is considered key); (2) cognitive-developmental (a three part process of learning about gender as being fixed); (3) information-processing (learning about gender by the generation and development of categories); and (4) biology-based (acknowledging that sex hormones can play a part in psychological functioning across the lifespan). The different theories emphasize that there are many aspects to the processes that play a part in children getting to grips with the idea of gender. Translating the theories into simpler terms, as young children we start the process of learning who we are and how we are allowed to express ourselves in the presence of others.

Children learn from their direct experience of whether they like something or not, but their caregivers also help the child to learn both what is and what is not acceptable behaviour in exploring and interacting with their environment. This trial and error approach with guidance from caregivers arguably continues throughout childhood and on into adolescence. In addition, children can be encouraged to behave in ways that are seen as gender congruent with males in particular being permitted to be lively, encouraged to be confident and play with gender appropriate toys. Males who do not do so may face serious censure or even punishment within their family and/or immediate community. Children may find these experiences to be very confusing. For many, gender is not fixed until relatively late in childhood (Kreukels et al. 2014).

Children not only learn about what is acceptable about them and their behaviour within their families, but also from their wider community, for example, at school. Junior school years are the time when children start trying out different roles, for example, playing games such as "mummies and daddies" and "doctor and nurse". Usually these are innocent enough and tend to involve hand-holding and inept kissing. Children at this age tend to be fairly blunt in their communications and will ostracize others who are perceived as being different. Such public and private experiences of censure about self-expression can lead the affected child to feel anxiety about whether they are acceptable to others. Such anxiety can grow to the point where the child will have few friends and may experience overt or covert bullying from peers.

Both age-inappropriate sexualized behaviour and non-conformity of behaviour to gender norms in young children can take many forms. In respect of the former, sensitive investigations will need to be undertaken to determine the cause of

the troubling behaviour; while in respect of the latter the book by Kruekels, Steensma, and de Vries (2014) has many useful chapters detailing the methods by which issues of gender identity can be identified in children. Their book is an ode to caution, however, as they make clear that gender confusion in children's behaviour is not necessarily indicative of anything that requires something as serious as sex-reassignment surgery. Their chapter authors provide examples of children's presentation at clinic, their care over time by the multi-disciplinary team with details of the outcomes, as well as the various questionnaires and methods employed both with the children and their caregivers to determine the extent of the issues to be addressed.

There is a certain amount of debate about the extent to which sexual identity and gender congruent behaviour are socially constructed (Giordano 2014), a key issue in adolescence when the public world starts to matter more than that of the family. It is the period of time when young people are trying out different ways of being in the world, and these can be at odds with their family/community values and lead to a great deal of conflict. For adolescents, finding a tribe/group with whom they belong is an important part of this life stage, and it is important that their behaviour fits with this tribe/group for them to be accepted and remain involved. Boyd and Bee (2014) suggest that the formation of romantic relationships at this age is dependent on the individual's self-perceived sexuality, with heterosexual and homosexual patterns of relationship formation being distinctly different and occurring on different timescales. Aron (1999) has suggested that for some adolescents the whole area of relationships can feel so daunting, that they couple up with one partner very early and stay in that relationship which then functions as a bulwark against the sexual experimenting that is common at this age. There are growing concerns that with access to the internet the experiences and expectations of young males are informed initially by pornography.

In research with males with Klinefelter's Syndrome (KS), it was clear that adolescence was a key time for them in terms of recognizing that their condition made them significantly different from the prevailing norms (Morris et al. 2009). This was both in terms of appearance (males with KS tend to look physically different to other males) and behaviour (males with KS tend to lack confidence). The research resounds with experiences of adolescent males being beaten by their fathers (to toughen them up) all the way up to reports of rape in situations where other males did not think they were sufficiently masculine enough and decided to use them as sexual subordinates. Such experiences led to a variety of responses, with some males able to learn how to act in more masculine ways, some becoming confused about their sexuality, while others experienced confusion over their gender identity. The report makes clear the ramifications of these experiences lasted a lifetime in terms of both identity and mental health issues.

49.2.2 Psychogenic Aspects of Sexual Function

Brown (2015) has written about the strait jackets that each gender wears in Western culture and how difficult, but how necessary it is, for us to recognize and move beyond them. She cites research which shows that the attributes associated with masculinity in the USA are: winning, emotional control, risk-taking, violence, dominance, playboy, self-reliance, primacy of work, power over women, disdain for homosexuality, and pursuit of status. The author (SJ) has seen many men who struggle with their identity and mental health because they do not recognize themselves in this list of masculine attributes. Their struggle is arguably made worse because men, unlike women, are not socialized to talk about their issues and compare experiences. The most common question the author (SJ) hears is, "Is this normal or am I weird?" The men quite often talk about feeling ashamed of themselves, and research by Pennebaker et al. (2001) suggests that anything associated with shame and guilt is unlikely to be talked about and the behaviour associated with it is also unlikely to be disclosed. Where there is confusion about sexual

function or gender identity, avoidance can be a common coping strategy. It can be effective to the extent that it reduces the risk of rejection and the associated stress, guilt and shame.

There are common societal discourses about Western male sexuality—shown the right visual stimulus, and assuming a suitable environment, there should be a predictable physical response. However, in men with low libido, such stimuli may be unwelcome and actively avoided. To be subjected to it unwillingly can result in feelings of entrapment and high anxiety. Some men with pituitary conditions talk about the disconnection they have from sexual feelings and sexual responses generally which can lead to tension and pressure within relationships as men try to communicate their feelings at the risk of alienating their partner who may feel they are somehow to blame for the lack of sexual desire. In men with erectile dysfunction the problem may also be associated with feelings of anxiety, in this case the stimulus is wanted, but anxiety about performance issues may create a vicious cycle where physical functioning is inhibited by the stress of the situation. Testosterone replacement therapy given to men can sometimes have unexpected outcomes, such as involuntary erections where the perceived lack of control associated with profound distress and embarrassment can lead to social anxiety, social avoidance, and in some cases profound social isolation.

If your basic relationship with your body is one of distrust because it is not performing its functions in expected ways, the levels of anxiety experienced are likely to affect any communication with others including healthcare professionals. Humans are not good with uncertainty, and anxiety will increase in the absence of explanations for occurrence, the likely duration of the problem, and the likely prognosis. The anxiety increases when we feel at odds with ourselves and are experiencing something that is socially confusing or outright unacceptable. Additionally, anxiety can be related to control; the less control you feel you have, the greater the anxiety you experience and this can lead to a strong feeling of frustration (especially if you feel you are not being heard and/or supported) which can eventually lead to feelings of anger and disappointment.

The stress, shame, and guilt associated with being different to norms of appearance, function, or behaviour activate the threat system which is associated with feelings of anxiety, anger, and depression. In such a state, as Gilbert (2010) has so well described, it is next to impossible to access the part of the brain associated with rational thought and problem-solving. The threat system requires effective soothing, but for lots of men, while they may be good at restorative hobbies and interests the soothing skills remain unlearned and they quite often rely on female family members and friends for their (mental) healthcare and support. Except when very young or much older, and unlike women, men typically do not have much contact with healthcare services which tends to reinforce the reliance on female family and friends for healthcare issues.

In primary mental health services there is a reliance on standardized questionnaires to assess need and to signpost to relevant services. Men can have problems here, too. On a lot of the standard measures used, men score significantly lower than do women. An eminent endocrinologist in discussing some research results where this pattern had been observed (yet again), commented that men are realists and women clearly exaggerate. However, an alternative interpretation is that women are realistic while men are socialized to minimize their problems (remember they are supposed to be strong and have good emotional control) and hence underreport. The short appointments in primary care mean that you have to be prepared to just "jump in" with your concerns, but medical services are predicated on the biomedical model where physical functioning takes priority over mental distress. The situation is complicated by a situation where healthcare professionals are generally not trained in the identification, assessment, or support of mental health related issues. Added to which sex has to be one of the most difficult topics to talk about. The definitions of what count as sexual behaviour can be individually or culturally very broad or very narrow, and can be gender dependent. Sex can refer to the label attached to a

particular genital configuration (i.e. penis and tests = male), it can refer to reproduction, or even a form of self-expression. For some individuals there are no differences between these things, but for others, they can be very different, for example, those involved in the world of BDSM where sexual activity might not involve penetrative sex at all. Individuals can have profound fears about how to frame their concerns in such a way as to elicit the information they need from healthcare professionals without exposing themselves to negative judgement.

In such a situation, it can be helpful for healthcare professionals to use tools and techniques aimed at empowering patients to identify their broader concerns as well as enabling a discussion about appropriate intervention and support. An example of a tool to achieve this is the Pituitary Distress Thermometer (developed by the author SJ with the Pituitary Foundation), while BATHE is an example of an appropriate consultation technique (Stuart and Lieberman 2008). Many healthcare practitioners use ICE (Ideas, Concerns and Expectations) but ICE is predominantly about data gathering and tends to relate to the first stage of the consultation (determining the presenting issue). ICE and BATHE can be used effectively together to provide a full picture of the presenting issue(s), arguably moving away from the biomedical model of symptoms and physical problems, to a biopsychosocial model where the psychological is also recognized and potentially supported.

Finally, it is important to note that we are living in a time of great change, as Pfäfflin (2014) has noted the increasingly fluid nature of gender identity means that we need to treat each person as an individual rather than relying on the outmoded dichotomously focused theories and models of psychosexual development.

49.3 Conclusions

The process of genetic counselling includes the exploration of psychosocial factors that emerge when discussing highly sensitive reproductive conditions and genetic risk. People with reproductive conditions may feel embarrassed about their altered sexual development or fertility status. Discussions of genetic/inherited disease risk also bring about feelings of guilt and shame, particularly when considering risk to children and other family members. Additionally, genetic testing may not yield an informative result, potentially leading to anxiety because the cause of disease and risk for family members remains uncertain. On the other hand, determining a genetic cause may alleviate some uncertainty. Listening, acknowledging expressed and implied feelings, sharing potentially empowering information, and clarifying as much uncertainty as possible can benefit individuals and families obtaining genetic counselling.

Psychosexual development is a complicated process still not completely understood. We should not expect that there will ever be a theory that can adequately describe and account for the variety of experiences that people have as they grow and mature. This, coupled with the increasingly fluid nature of gender identity, means that we need to have the time to treat each person as an individual. Men face a number of obstacles to being able to seek help with problems related to sexual functioning. We need to remember that their social conditioning tends to lead them to minimize their problems so we need to use tools and consultation techniques to empower them to speak up.

References

Aron EN. The highly sensitive person: how to thrive when the world overwhelms you. London: Harper Collins; 1999.

Au MG, Crowley WF, Buck CL. Genetic counseling for isolated GnRH deficiency. Mol Cell Endocrinol. 2011;346(1–2):102–9.

Baetens D, Mladenov W, Delle Chiaie B, Menten B, Desloovere A, Iotova V, Callewaert B, Van Laecke E, Hoebeke P, De Baere E, Cools M. Extensive clinical, hormonal and genetic screening in a large consecutive series of 46,XY neonates and infants with atypical sexual development. Orphanet J Rare Dis. 2014;9:209.

Benjamin CM, Thomas LH, Skirton H, Gustafson S, Coupe J, Patch C, Belk R, Tishkovskaya S, Calzone K, Payne K. Interventions to improve patient access to and utilisation of genetic and genomic counselling services. Cochrane Database Syst Rev. 2015;(11). https://doi.org/10.1002/14651858.CD011873.

Bennett RL, Steinhaus French K, Resta RG, Lochner Doyle D. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17:424–33.

Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547–64.

Boyd DG, Bee HL. Lifespan development. 6th ed. Harlow: Pearson Education Limited; 2014.

Brown B. Daring greatly: how the courage to be vulnerable transforms the way we live, love, parent and lead. London: Penguin; 2015.

Buck C, Balasubramanian R, Crowley WF. Isolated gonadotropin-releasing hormone (GnRH) deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews®. Seattle: University of Washington; 2013. http://www.ncbi.nlm.nih.gov/books/NBK1334/. Accessed 1 August 2016.

Costa-Barbosa FA, Balasubramanian R, Keefe KW, Shaw ND, Al-Tassan N, Plummer L, Dwyer AA, Buck CL, Choi JH, Seminara SB, Quinton R, Monies D, Meyer B, Hall JE, Pitteloud N, Crowley WF Jr. Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. J Clin Endocrinol Metab. 2013;98(5):E943–53.

Delikurt T, Williamson GR, Anastasiadou V, Skirton H. A systematic review of factors that act as barriers to patient referral to genetic services. Eur J Hum Genet. 2015;23(6):739–45.

Délot EC, Vilain EJ. Nonsyndromic 46,XX testicular disorders of sex development. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews®. Seattle: University of Washington; 2015. http://www.ncbi.nlm.nih.gov/books/NBK1416/. Accessed 1 August 2016.

Gilbert P. The compassionate mind. London: Constable & Robinson; 2010.

Giordano S. Medical treatment for children with gender dysphoria: conceptual and ethical issues. In: Kreukels BPC, Steensma TD, de Vries ALC, editors. Gender dysphoria & disorders of sex development. New York: Springer; 2014. p. 205–30.

Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Genet Med. 2001;3(2):149–54.

Heihir-Kwa JY, Claustres M, Hastings RJ, van Ravenswaaij-Arts C, Christenhusz G, Genuardi M, Melegh B, Cambon-Thomsen A, Patsalis P, Vermeesch J, Cornel MC, Searle B, Palotie A, Capoluongo E, Peterlin B, Estivill X, Robinson PN. Towards a European consensus for reporting incidental findings during clinical NGS testing. Eur J Hum Genet. 2015;23:1601–6.

Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT, on behalf of the ACMG Secondary Findings Maintenance Working Group. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249–55.

Krausz C, Chianese C. Genetic testing and counselling for male infertility. Curr Opin Endocrinol Diabetes Obes. 2014;21:244–50.

Kreukels BPC, Steensma TD, de Vries ALC, editors. Gender dysphoria & disorders of sex development. New York: Springer; 2014.

Miraoui H, Dwyer AA, Sykiotis GP, Plummer L, Chung W, Feng B, Beenken A, Clarke J, Pers TH, Dworzynski P, Keefe K, Niedziela M, Raivio T, Crowley WF Jr, Seminara SB, Quinton R, Hughes VA, Kumanov P, Young J, Yialamas MA, Hall JE, Van Vliet G, Chanoine JP, Rubenstein J, Mohammadi M, Tsai PS, Sidis Y, Lage K, Pitteloud N. Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are identified in individuals with congenital hypogonadotropic hypogonadism. Am J Hum Genet. 2013;92(5):725–43.

Morris M, Jackson S, Hancock J. The psychological and social impact of Klinefelter's syndrome: a report for the Klinefelter's Syndrome Association. Bristol: University of the West of England; 2009.

Pennebaker JW, Zech E, Rimé B. Disclosing and sharing emotion: psychological, social, and health consequences. In: Stroebe MS, Stroebe W, Hansson RO, Schut H, editors. Handbook of bereavement research: consequences, coping, and care. Washington, DC: American Psychological Association; 2001.

Pfäfflin F. Identity: a historical and political reflection. In: Kreukels BPC, Steensma TD, de Vries ALC, editors. Gender dysphoria & disorders of sex development. New York: Springer; 2014. p. p331–46.

Stuart MR, Lieberman JA III. The fifteen minute hour: therapeutic talk in primary care. 4th ed. Oxford: Radcliffe; 2008.

Key Reading

1. Bennett RL, Steinhaus French K, Resta RG, Lochner DD. Standardized human Pedigree nomenclature: UPDATE and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel. 2008;17:424–33.
2. Buck C, Balasubramanian R, Crowley WF. Isolated gonadotropin-releasing hormone (GnRH) deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews®. Seattle: University of Washington; 2013. http://www.ncbi.nlm.nih.gov/books/NBK1334/. Accessed 1 August 2016.

3. Délot EC, Vilain EJ. Nonsyndromic 46,XX testicular disorders of sex development. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews®. Seattle: University of Washington; 2015. http://www.ncbi.nlm.nih.gov/books/NBK1416/. Accessed 1 August 2016.
4. Boyd DG, Bee HL. Lifespan development. 6th ed. Harlow: Pearson Education Limited; 2014.
5. Kreukels BPC, Steensma TD, de Vries ALC, editors. Gender dysphoria & disorders of sex development. New York: Springer; 2014.

Part VIII

Parathyroid, Calcium and Bone Disorders

Ann Robinson and Cecilia Follin

Hyperparathyroidism and Hypoparathyroidism

50

Amy Mundy and Rachel Crowley

Contents

50.1 **Normal Parathyroid Metabolism** 959

50.2 **Primary Hyperparathyroidism** 960
50.2.1 Epidemiology, Pathophysiology, Presentation 960
50.2.2 Diagnosis of PHPT and Its Complications 961
50.2.3 Treatment 962

50.3 **Secondary Hyperparathyroidism** 964
50.3.1 Secondary Hyperparathyroidism in CKD 965
50.3.2 Management of Secondary Hyperparathyroidism 965

50.4 **Tertiary Hyperparathyroidism** 966

50.5 **Parathyroid Carcinoma** 966
50.5.1 Nursing Role/Key Learning Points from the Case 967

50.6 **Hypoparathyroidism** 967
50.6.1 Assessment of the Patient with Suspected Hypoparathyroidism 967
50.6.2 Clinical Assessment of the Patient with Potential Acute Post-surgical Hypoparathyroidism 968
50.6.3 Treatment of Hypoparathyroidism 968
50.6.4 Follow-up of the Patient with Hypoparathyroidism 969
50.6.5 Complications of Treatment of Hypoparathyroidism 969
50.6.6 Quality of Life with Hypoparathyroidism 970

50.7 **Pseudohypoparathyroidism and Pseudopseudohypoparathyroidism** 970

50.8 **Clinical Note 1: Proton Pump Inhibitors (PPIs)** 970

50.9 **Clinical Note 2: Pregnancy in Hypoparathyroid Patients** 971

A. Mundy
McGuire Veterans Medical Center,
Richmond, VA, USA
e-mail: Amy.Mundy@va.gov

R. Crowley (✉)
St. Vincent's University Hospital and University
College Dublin, Dublin, Ireland
e-mail: rcrowley@svhg.ie; R.Crowley@st-vincents.ie

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_50

50.10 Patient Experience of Hypoparathyroidism..... 971
50.11 Hypopara UK (Hypoparathyroidism and Primary Hyperparathyroidism)..... 971
50.12 Patient Story..... 972
50.13 Conclusions..... 973
References..... 973

Abstract

Parathyroid hormone and active vitamin D control calcium homeostasis; dysregulation of this system leads to abnormal calcium measurements and a spectrum of clinical disorders. Primary hyperparathyroidism can present clinically with abdominal pain from peptic ulceration or renal calculi, mood disorders, fractures and loss of height from osteoporosis or on blood tests with reduced kidney function and hypercalcemia in the setting of normal or elevated parathyroid hormone. It is managed primarily with surgery although asymptomatic patients may elect to have serial monitoring for deterioration or clinical sequelae of hyperparathyroidism. International consensus guidelines are regularly updated to reflect research on the benefits of surgery or medical management of asymptomatic patients with primary hyperparathyroidism. Parathyroid carcinoma is a rare cause of primary hyperparathyroidism that is associated with a genetic mutation causing hyperparathyroidism-jaw tumour syndrome. Secondary hyperparathyroidism is usually a complication of chronic kidney disease or vitamin D deficiency. Hypoparathyroidism is a complication of thyroid or parathyroid surgery, a manifestation of one of a number of genetic disorders or may be one of a number of autoimmune diseases in an individual patient. Patients with hypoparathyroidism suffer from lower quality of life; undertreatment manifests as symptomatic hypocalcemia and overtreatment can result in renal calculi or reduced kidney function. Pseudohypoparathyroidism is a condition of resistance to circulating PTH, which is high; this can co-exist with skeletal abnormalities described collectively as Albright's hereditary osteodystrophy. A case history, a patient perspective and clinical notes on two particular aspects of care of patients with parathyroid disorders are included with this chapter.

Keywords

Parathyroid hormone · Vitamin D · Calcium · Hyperparathyroidism · Hypoparathyroidism

Abbreviations

25OHD	25 hydroxy vitamin D
AHO	Albright's hereditary osteodystrophy
BMD	Bone mineral density
CaSR	Calcium-sensing receptor
CKD	Chronic kidney disease
CKD-MBD	Chronic Kidney Disease-Mineral Bone Disorder
DXA	Dual-energy X-ray absorptiometry
eGFR	Estimated glomerular filtration rate
FGF-23	Fibroblast growth factor 23
FHH	Familial hypocalciuric hypercalcemia
GI	Gastrointestinal
HPT-JT	Hyperparathyroidism-jaw tumour syndrome
KDIGO	Kidney Disease Improving Global Outcomes
MEN	Multiple Endocrine Neoplasia
PHPT	Primary hyperparathyroidism
PPIs	Proton pump inhibitors
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide

SERM	Selective estrogen receptor modifier
SHPT	Secondary hyperparathyroidism
SPECT	Single photon emission computed tomography
VFA	Vertebral Fracture Assessment

Key Terms

- **Hyperparathyroidism:** A disorder causing an excess of parathyroid hormone in the blood leading to elevated blood calcium levels and adverse bone, kidney, musculoskeletal, and GI effects.
- **Hypercalcemia:** an abnormally high serum calcium level.
- **Hypoparathyroidism:** A disorder causing an under-functioning of the parathyroid glands leading to low parathyroid hormone levels and low serum calcium.
- **Vitamin D:** a fat soluble vitamin responsible for increasing absorption of calcium in the intestines and essential for normal bone structure.

Key Points

- Primary hyperparathyroidism is diagnosed in the setting of hypercalcemia with high or inappropriately normal PTH measurement; it is primarily managed with surgery and there is guidance available for those asymptomatic patients who may benefit from surgical intervention.
- Hypoparathyroidism is diagnosed in the setting of hypocalcemia with low or inappropriately normal PTH; serum magnesium should be measured and hypomagnesemia corrected before the diagnosis is confirmed.
- Hypoparathyroidism is sometimes challenging to manage and requires careful assessment for complications of over- or undertreatment; it is associated with reduced quality of life.
- In recent years, more information has become available about underlying genetic disorders which predispose to parathyroid pathology including parathyroid carcinoma; consideration of genetic screening in younger patients, those with family histories suggestive of a genetic endocrinopathy and those with atypical presentations or parathyroid histology should be considered as a positive result may change clinical follow-up.

50.1 Normal Parathyroid Metabolism

Many physiologic processes depend on the precise regulation of calcium including muscle and nerve function and contractility, bone metabolism, cell signalling, and hormone release and regulation (Fraser 2009). The parathyroids, four pea-sized glands located behind the thyroid, are the master regulators of calcium homeostasis. In healthy people, these glands control calcium metabolism by releasing parathyroid hormone (PTH) in response to a fall in circulating calcium levels sensed by the calcium-sensing receptor (CaSR). PTH, an 84-amino acid peptide, is upregulated or downregulated based on the serum calcium and mediates an increase in serum calcium by its actions at bone, kidneys and gut. In bone, PTH stimulates osteoclasts to increase bone resorption to release calcium from the skeleton. In the kidneys, PTH increases reabsorption of calcium and increases excretion of phosphate from the renal tubules. In the GI tract, PTH increases the conversion of 25-hydroxyvitamin D (25OHD) to 1,25-dihydroxyvitamin D to increase calcium absorption from the gut (Fraser 2009). This is illustrated in Fig. 50.1 and discussed in more detail in Chap. 48.

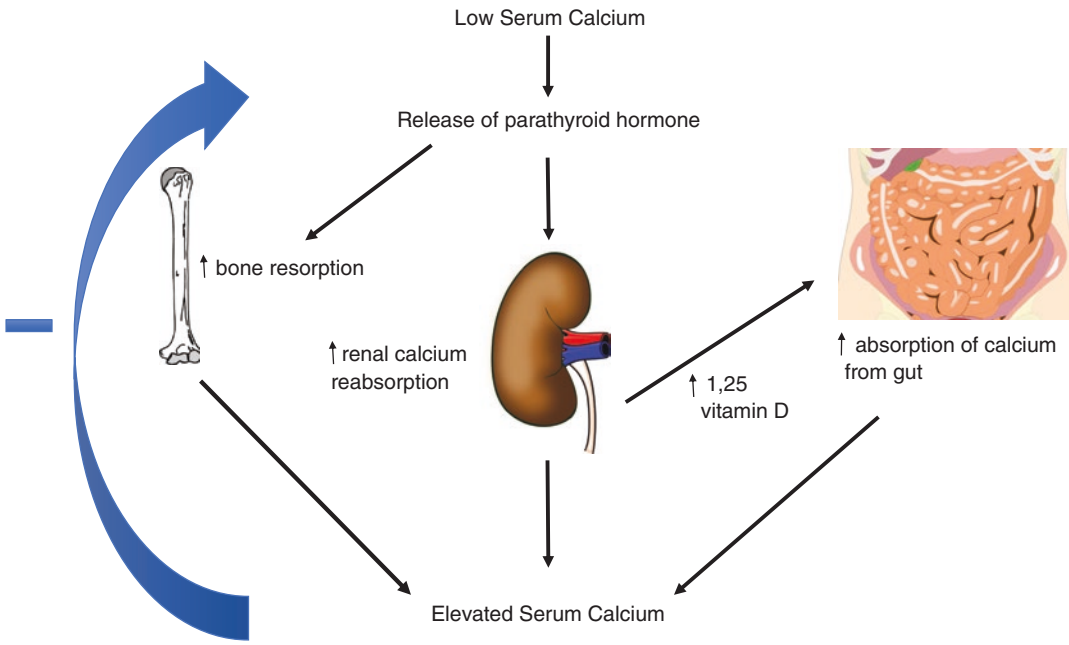


Fig. 50.1 Normal parathyroid physiology. When serum calcium is low, PTH is released from the parathyroid glands. PTH stimulates osteoclasts in the bones which releases calcium. In the kidneys, there is an increase in reabsorption of calcium from the urine. The kidney also increases the conversion of 25(OH) vitamin D to 1,25(OH) vitamin D which stimulates calcium absorption in the gut. The normalized calcium level serves as a negative feedback to stop this process

50.2 Primary Hyperparathyroidism

50.2.1 Epidemiology, Pathophysiology, Presentation

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient setting and is the third most common endocrine disorder. Women are affected about twice as often as men and the incidence increases with age. The peak incidence of PHPT is in women between 50 and 60 years old likely related to menopause. Oestrogen prior to menopause is thought to exert an inhibitory effect on the parathyroid glands. The increasing use of thiazide diuretics in this age group can also unmask the condition (Fraser 2009). The prevalence of PHPT varies based on the population studied, parameters defined and methods used, but is estimated to affect up to 5% of the general population (Crowley and Gittoes 2013).

Approximately 80% of cases of PHPT are caused by a single benign parathyroid adenoma, but there can be multiple adenomas or hyperplasia of multiple glands (Bilezikian et al. 2005). Parathyroid carcinoma is a very rare cause of PHPT occurring in only about 0.5% of cases (Bilezikian et al. 2005). Most PHPT cases are sporadic; recognised genetic causes, such as Multiple Endocrine Neoplasia (MEN) 1 and MEN 2, account for about 5% of cases. Ninety percent of patients with MEN 1 will develop 4-gland parathyroid hyperplasia and PHPT.

In the 1970s, the availability of routine laboratory chemistry gave easy access to calcium measurements and created an increase in the number of patients diagnosed with PHPT. The majority of patients in the modern day are asymptomatic and are diagnosed with mild or moderate hypercalcemia before they develop any signs or symptoms. Prior to the availability of simple biochemical screening, patients had much higher serum calcium at presentation and were often symptomatic, presenting with the classic signs and symptoms of

PHPT as described in the mnemonic 'stones, bones, groans and moans'. The most common renal manifestation of PHPT is a kidney stone, occurring in about 15–20% of patients (Mackenzie-Feder et al. 2011). Renal insufficiency, nephrogenic diabetes insipidus and nephrocalcinosis (calcium deposits in the renal parenchyma) can also occur. Bone disease associated with PHPT includes osteoporosis—particularly in cortical bone such as at the wrist—fragility fractures and osteitis fibrosa cystica. Although rarely seen in developed countries today, osteitis fibrosa cystica was once a common occurrence among those with PHPT and caused bone pain due to cyst formation in areas of subperiosteal bone resorption, 'salt and pepper' appearance of the skull, fractures and deformities. The 'Groans' of the PHPT mnemonic refer to gastrointestinal symptoms such as constipation, abdominal pain, peptic ulcers and rarely pancreatitis (usually associated with severe hypercalcemia). Neuropsychiatric symptoms or 'moans' include lethargy, impaired concentration, confusion, depression, anxiety and muscle weakness; in modern-day patients with PHPT this can manifest as subtle low mood or reduced quality of life. The cardiovascular system can also be affected by hypercalcemia, which may contribute to hypertension, cardiac and vascular calcifications, a shortened QT interval, and rarely conduction abnormalities or arrhythmias.

50.2.2 Diagnosis of PHPT and Its Complications

In patients with PHPT, serum PTH is elevated or inappropriately normal in the setting of hypercalcemia. Other causes of hypercalcemia such as malignancy, thyrotoxicosis, granulomatous diseases and immobility are usually associated with suppressed PTH measurements. A review of all the patient's medications and supplements should be performed; thiazide diuretics, vitamin D, lithium, calcium antacids and vitamin A can exacerbate hypercalcemia. Other causes of elevated PTH with or without hypercalcemia include renal insufficiency, vitamin D deficiency and familial hypocalciuric hypercalcemia (FHH).

The biochemical diagnosis of PHPT is made by measurement of serum calcium, PTH, 25OHD and urinary calcium. A finding of hypercalcemia should be confirmed by repeat laboratory testing. Thiazide diuretics should be discontinued for at least 2 weeks prior to repeating bloodwork. Calcium measurement results should be corrected to account for any abnormal measurement of albumin, since albumin is the main plasma protein that binds to calcium. Calcium correction can be provided by the local laboratory, by use of available online calculators, or by the following formula: corrected calcium = measured calcium (mg/dL) + 0.8 (4.0 − measured albumin in g/dL) or measured calcium (mmol/l) + 0.02(40 − measured albumin in g). Alternatively, an ionised calcium can be measured, but since most facilities do not have sufficient capabilities to perform this test, the corrected serum calcium is recommended (Crowley and Gittoes 2016).

Measurement of 25OHD is the estimation of choice for assessment of vitamin D status. When PHPT occurs with vitamin D deficiency, the serum calcium is often normal or lower than expected. Replacement of vitamin D is indicated in PHPT associated with vitamin D deficiency and does not cause further marked elevation in calcium in the majority of cases (Crowley and Gittoes 2013). After vitamin D replacement, and in the absence of a thiazide diuretic, 24-h urine calcium should be done to (1) exclude FHH from the differential diagnosis and (2) establish whether an elevation in urinary calcium is high enough to indicate referral for surgery (see below). In FHH, the calcium to creatinine clearance ratio is less than 0.01 mmol; it is normal or elevated in PHPT (Mackenzie-Feder et al. 2011). Ca/Cr clearance ratio is calculated by [24-h urine Ca × serum Cr] ÷ [serum Ca × 24-h urine Cr]. Confirmation of the diagnosis of FHH is by genetic testing for mutations in the *CaSR* gene.

PHPT is now most often discovered incidentally by identification of hypercalcemia on routine blood screenings, thus 80% of patients are asymptomatic on diagnosis. Those patients with asymptomatic PHPT require an additional workup to identify end-organ effects of PHPT, in

order to plan management of their disease. Some asymptomatic PHPT patients may progress over time and eventually develop symptoms—**see patient case study** (Bilezikian et al. 2005). Normocalcemic PHPT is another variant of PHPT in which calcium is normal but PTH is elevated. It is often found during the biochemical investigation of osteoporosis; surveillance of these patients over 3–8 years reveals development of hypercalcemia in 20% cases (Crowley and Gittoes 2016). Screening for end-organ disease and management planning in normocalcemic PHPT is similar to that of asymptomatic PHPT (Crowley and Gittoes 2016).

The evaluation of asymptomatic PHPT should include measurement of renal function including estimated glomerular filtration rate (eGFR), imaging for kidney stones and measurement of bone mineral density (BMD) (Table 50.1). A 24-h urine calcium level should be collected at diagnosis to exclude FHH; the degree of calciuria also informs the management plan in asymptomatic patients. Marked hypercalciuria of >400 mg/day (>10 mmol/day) is an indication to refer asymptomatic patients for surgery because of the anticipated risk of nephrolithiasis. Asymptomatic nephrolithiasis or nephrocalcinosis identified by abdominal imaging (X-ray, ultrasound, or CT scan) are indications to refer asymptomatic patients for surgical management (Bilezikian et al. 2014). Bone mineral density is evaluated by dual-energy X-ray absorptiometry (DXA) which should include measurement of the distal 1/3 radius; this area is composed of cortical bone that has a higher turnover than trabecular bone and is thus more likely to be adversely affected by PHPT (Bilezikian et al. 2014). Measurement of bone turnover markers (bone-specific alkaline phosphatase activity, CTX or urine NTX) is an optional test to evaluate skeletal involvement in asymptomatic PHPT (Bilezikian et al. 2014). Asymptomatic patients who decide not to undergo surgery at diagnosis should be monitored over time for progression of the disease.

Table 50.1 2013 guidelines for surgery in asymptomatic PHPT (Bilezikian et al. 2014)

Serum calcium measurement	1.0 mg/dL (0.25 mmol/L) above the upper limit of normal
Bone involvement	BMD with of <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius **or** Vertebral fracture seen on X-ray, CT, MRI or VFA
Renal involvement	Creatinine clearance of <60 cm^3/min **or** 24-h urine calcium >400 mg/day (>10 mmol/day) and increased stone risk by laboratory stone risk analysis **or** Presence of kidney stone on X-ray, ultrasound or CT
Patient age	<50 years
Patient preference	Patient prefers to pursue surgery despite not meeting guidelines **or** Patient is unable or unwilling to undergo medical surveillance

Adapted from Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014 Oct;99 (10):3561–9

50.2.3 Treatment

Patients with symptomatic PHPT should be referred for surgery because the only definitive cure for PHPT is excision of the parathyroid adenoma or adenomas. After surgery, the risk of kidney stones is decreased, bone mineral density improves, fracture risk may decline, and some quality of life measures may improve. Surgery may not benefit all patients with asymptomatic PHPT. One long-term observational study showed that most patients with asymptomatic PHPT could be monitored safely over a period of 15 years (Rubin et al. 2008). However, the same study showed that over 30% of asymptomatic PHPT patients had disease progression and met one or more surgical criteria at some point during the study. Additionally, decline in the BMD at the femoral neck and distal radius were present in about 60% of the untreated group (Rubin et al. 2008).

50.2.3.1 Surgical Treatment

Localising studies before parathyroid adenoma resection usually consist of two modalities such as a sestamibi single photon emission computed tomography (SPECT) scan and a neck ultrasound; the type of imaging varies between centres (Glynn et al. 2011). If an adenoma is found and imaging is concordant, a minimally invasive parathyroidectomy (combined with intraoperative PTH monitoring in some centres) can be performed. In cases of equivocal or negative imaging, either a minimally invasive surgical technique with intraoperative PTH monitoring (targeting a post-resection PTH decrement of 50%) or a bilateral neck exploration can be considered (Khan et al. 2016). Patients should be referred to an experienced endocrine surgeon for either procedure. Post-excision intraoperative PTH measurement can be falsely elevated in the setting of impaired renal function, in which case circulating PTH is cleared more slowly after excision, or if the adenoma has been stimulated to release PTH by intraoperative manipulation.

Complications of parathyroid surgery are rare but include recurrent laryngeal nerve injury, infection, hematoma and post-operative hypocalcemia. In patients with high bone resorption before parathyroid surgery, post-operative hypocalcemia can be caused by a positive bone remodelling balance as the bones recover from prolonged exposure to high PTH; this is called hungry bone syndrome and is also associated with post-operative hypophosphatemia and a rise in bone alkaline phosphatase. Post-parathyroidectomy hypocalcemia can also be secondary to hypoparathyroidism which can be transient or permanent, and is associated with higher phosphate levels than hungry bone syndrome (see section on post-operative hypoparathyroidism). Formerly, in about 5% of patients who had parathyroidectomy for PHPT, hypercalcemia recurred due to inadequate removal of diseased parathyroid tissue. However, cure rates are 96–99% with current surgical techniques (Bilezikian et al. 2005). A discussion of the risks and benefits of surgery should take place between the surgeon and the patient prior to surgery.

In 2014, an international consensus statement for the surgical management of asymptomatic PHPT was published (Bilezikian et al. 2014). These guidelines aimed to identify those asymptomatic patients with PHPT at risk for progression of the disease if untreated, or who may improve after parathyroidectomy. Patients with asymptomatic PHPT should be referred for surgery if they meet the following criteria, which are also listed in Table 50.1: under the age of 50 years, serum calcium ≥1 mg/dL (≥0.25 mmol/L) above the upper limit of normal for the local reference range; peri- or post-menopausal women and men over 50 years with *T*-score of −2.5 or less at the lumbar spine, femoral neck, total hip, or distal 1/3 radius; pre-menopausal women and men under 50 years old if *Z*-score of −2.5 or less; vertebral fracture; creatinine clearance <60 cm^3/min, 24-h urinary calcium greater than 400 mg (10 mmol)/day, presence of kidney stones, or evidence of nephrocalcinosis. Patients with asymptomatic PHPT who do not meet these criteria at the first evaluation but satisfy the referral criteria during long-term monitoring should also be referred (Bilezikian et al. 2014). If an asymptomatic patient does not meet the above criteria, but prefers to have parathyroidectomy rather than surveillance, it is acceptable to refer them for surgical management. Those patients with familial causes of PHPT, such as MEN1, have a more aggressive form of PHPT; in these cases surgery is not curative without causing hypoparathyroidism and such patients should be managed in a specialist centre.

50.2.3.2 Medical Treatment

Patients who have asymptomatic PHPT and do not meet surgical criteria should be monitored for any deterioration in their biochemistry, bone or renal status, as listed in Table 50.2. Monitoring includes serum calcium measurement every 1–2 years. BMD should be monitored, but there are no official guidelines on the interval between scans; therefore this is a decision based on the individual characteristics of the patient. Vitamin D should be supplemented to maintain a 25OHD level of at least >20 ng/dL (50 nmol/L), although

Table 50.2 2013 guidelines for observation of patients with asymptomatic PHPT who do not undergo surgery

Serum calcium	Yearly
Bone	BMD every 1–2 years and/or X-ray or VFA of spine if clinically indicated
Renal	Yearly eGFR, serum creatinine **and** If kidney stones suspected, 24-h urinary stone profile or renal imaging by X-ray, ultrasound or CT

Adapted from Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014 Oct;99(10):3561–9

there is some evidence to suggest levels >30 ng/mL may be associated with lower PTH levels (Bilezikian et al. 2014).

Patients with PHPT should meet the daily intake of dietary calcium recommended for their age. Adequate hydration should be encouraged. Drugs that may exacerbate hypercalcemia such as thiazide diuretics and lithium should be avoided. Patients should stay physically active and periods of prolonged bedrest should be avoided.

Pharmacologic treatment may be appropriate for those who meet criteria for surgery but are deemed to be poor surgical candidates or prefer to avoid surgery. However, there are insufficient long-term studies on any pharmacologic therapy in PHPT and most agents are not approved for treatment of PHPT (Bilezikian et al. 2014). Bisphosphonates improve bone density in patients with PHPT but do not significantly lower serum calcium or PTH; a reduction in fracture risk in PHPT patients has not been demonstrated (Crowley and Gittoes 2013). A discussion with the patient about the expectations for bisphosphonate therapy in PHPT is advisable. Cinacalcet reduces serum calcium and therefore may relieve symptoms in patients with symptomatic PHPT who are not fit for surgery, but does not lower PTH level, demonstrate improved BMD or reduce fracture risk. Cinacalcet is a calcimimetic which activates the calcium-sensing receptor in the parathyroid glands to decrease PTH secretion. Cinacalcet is FDA and EMA approved for treatment of severe hypercalcemia in adults with PHPT who meet criteria for surgery but are unable to undergo parathyroidectomy. It is also approved for treatment of secondary hyperparathyroidism in patients with CKD on dialysis and for the treatment of parathyroid carcinoma. It is recommended to start cinacalcet at a dose of 30 mg twice daily and titrate every 2–4 weeks as needed to normalise serum calcium. Serum calcium should be monitored within a week of initiation or dose adjustment and then every 2 months after maintenance dose is established. It is not known whether cinacalcet improves nephrolithiasis or neuropsychiatric problems associated with PHPT (Crowley and Gittoes 2013). More research is needed about the use of combination therapy bisphosphonate with cinacalcet.

Oestrogen or combination of oestrogen with progestin can improve bone density in PHPT but is not recommended as first line medical therapy for women with PHPT due to the risks for thromboembolic events, heart disease and stroke. However, if a woman with PHPT opts to take hormone replacement therapy for menopausal symptoms, it may help treat the PHPT. With raloxifene, a selective estrogen receptor modifier (SERM) that is a potential alternative to oestrogen. Neither of these drugs is approved as treatment of PHPT.

50.3 Secondary Hyperparathyroidism

Secondary Hyperparathyroidism (SHPT) occurs when elevated circulating PTH is not sufficient to maintain serum calcium in the normal range due to an underlying problem with a target organ (such as liver, kidney or gut) or because of reduced calcium availability. Causes of SHPT include malabsorption or malnutrition (celiac disease, bariatric surgery, cystic fibrosis), liver failure, vitamin D deficiency, pseudohypopara-

thyroidism, and most commonly, chronic kidney disease (CKD).

50.3.1 Secondary Hyperparathyroidism in CKD

Secondary HPT in CKD is part of a wider disorder of electrolyte and skeletal metabolism called Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) by the Kidney Disease Improving Global Outcomes (KDIGO) group, and is associated with increased morbidity and mortality (KDIGO 2009). PTH secretion in CKD is stimulated by hyperphosphatemia and vitamin D deficiency, and a rise in PTH can be measured as early as CKD stage 3. Hyperphosphatemia increases PTH in several ways as illustrated in Fig. 50.2, direct stimulation of the parathyroid glands to produce PTH, precipitation with calcium to cause a mild hypocalcemia that stimulates further PTH secretion, and stimulation of fibroblast growth factor 23 (FGF-23) secretion, the primary regulator of phosphorus. FGF-23 produced by osteocytes in response to hyperphosphatemia increases clearance of phosphorus from the proximal renal tubule and inhibits 1-alpha hydroxylase activity, thus it decreases circulating active vitamin D. Initially, this is an adaptive mechanism to maintain normal phosphate and calcium, with PTH and FGF-23 persistently elevated.

With progressive CKD and loss of nephron function, the kidney loses its ability to excrete phosphate which further stimulates PTH secretion. Although the kidney has become resistant to the effect of PTH, bone remains sensitive and continues to release calcium and phosphorus in response to PTH. The end result is a vicious cycle of escalating PTH and phosphorus in circulation which leads to bone problems such as osteitis fibrosis cystica, adynamic bone disease, osteomalacia; parathyroid hyperplasia; and is associated with vascular calcification and left ventricular hypertrophy.

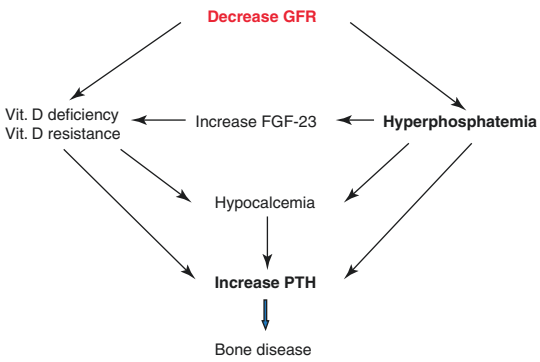


Fig. 50.2 Secondary hyperparathyroidism in renal failure. Saliba W, El-Haddad B. Secondary Hyperparathyroidism: Pathophysiology and Treatment. J Am Board Fam Med 2009 Sep; 22(5):574–581. Calcium and phosphorus metabolism in renal failure. *PTH* parathyroid hormone, *FGF-23* fibroblasts growth factor 23

50.3.2 Management of Secondary Hyperparathyroidism

Secondary HPT is managed medically in the majority of cases. For patients with CKD who do not require dialysis, the optimal target PTH for treatment is not known (KDIGO 2009). Patients with CKD who have a PTH measurement above the reference range should have measurement of calcium, phosphate and 25OHD, and any abnormality of these should be addressed. Hyperphosphatemia is managed with a low phosphate diet and phosphate binders. Vitamin D deficiency is treated with supplementation with vitamin D2 or D3. If these measures are not sufficient to maintain PTH within the normal reference range, then a vitamin D analogue or calcitriol could be added. Measurement of PTH, calcium, phosphate and 25OHD should be monitored routinely, to assess the effect of these treatments and to avoid overtreatment, for example, the development of hypercalcemia with vitamin D or calcium-based phosphate binders. Routine measurement of FGF23 is not recommended in current guidelines. Patients with CKD that have progressed to require dialysis may require cinacalcet in combination with these therapies,

although for such patients it is recommended to target a PTH within a range of twice to nine times the upper limit of the local reference range (KDIGO 2009). When medical therapy fails, parathyroidectomy may be necessary. Bone-specific therapy for renal osteodystrophy is aimed at prevention of fractures which are 2–4 times more frequent in patients with end-stage renal disease than in an age-matched population (KDIGO 2009). Patients with low BMD and advanced CKD should have replacement of calcium and vitamin D before treatment with denosumab or other anti-resorptives; the combination of CKD-MBD, untreated vitamin D deficiency and denosumab is associated with severe hypocalcemia. It can be challenging to assess the potential benefit of pharmacologic therapy for fracture prevention in CKD patients; KDIGO advises consideration of bone biopsy after correction of the abnormalities already detailed in this section (KDIGO 2009).

50.4 Tertiary Hyperparathyroidism

Tertiary HPT is a state of autonomously functioning parathyroid tissue and is usually the result of long-standing secondary HPT due to CKD. For example, a patient who undergoes successful kidney transplant but continues to have increased PTH and calcium measurements may have developed tertiary HPTH. Typically it is treated surgically.

50.5 Parathyroid Carcinoma

Parathyroid carcinoma is an extremely rare cause of primary hyperparathyroidism. It is suspected in cases with severe hypercalcemia and higher levels of PTH than are seen in benign disease, particularly when these are associated with a palpable neck mass which is unusual in benign hyperparathyroidism (McClenaghan and Qureshi 2015). The incidence of parathyroid carcinoma is equal in men and women. A small portion of carcinomas may not produce functional PTH and present with invasive local disease. Hyperparathyroidism-Jaw Tumour syndrome (HPT-JT syndrome) is caused by germline mutations in the cell division cycle 73 (*CDC73*) gene and is inherited in an autosomal dominant pattern (Li and Simonds 2015). Penetrance is incomplete therefore there is no family history in some cases. Suspected cases of HPT-JT syndrome should be discussed with the genetics laboratory conducting the genetic analysis because conventional testing may miss a complete *CDC73* gene deletion. Fibro-osseous tumours of the mandible and maxilla, Wilms tumours of the kidney and uterine fibroids are associated with this mutation. The primary management of parathyroid carcinoma is surgical, including bilateral neck dissection and cinacalcet can be used to control hypercalcaemia (Li and Simonds 2015). For members of families with known *CDC73* germline mutations, serum calcium and PTH measurement is recommended every 6–12 months with jaw imaging and renal imaging every 5 years (Li and Simonds 2015).

PHPT Case Study

Mr. S is an 80-year-old male who has been followed for asymptomatic PHPT for the last 13 years. His medical history is significant for pulmonary fibrosis, coronary artery disease, Type 2 Diabetes, hyperlipidemia and gout. He denies kidney stones or hematuria, falls or fractures, memory or mood disturbances, constipation or abdominal pain. In fact, Mr. S feels quite well. He worked up until 6 months ago as a contractor. He stays very active and appears younger than stated age.

His most recent BMD showed osteopenia with a *T*-score of −1.6 in the femoral neck but was normal at the other sites. However, BMD did show a decline from his baseline BMD several years prior.

While he remained without physical symptoms, his renal function had been worsening with a creatinine of 1.7 mg/dL (150 μmol/L), up from his baseline of 1.3 (115) (normal 0.5–1.3 mg/dL)

and calcium had risen—the highest value recorded was 11.7 mg/dL (2.93 mmol/L) (normal 8.5–10.1 mg/dL). PTH was 100 pg/mL (normal 15–88). Vit D was normal at 34 ng/mL (85 nmol/L). 24-h urine calcium was within normal limits.

The patient was sent for parathyroid SPECT which showed: 'Faint persistent uptake in the inferior posterior left thyroid bed on SPECT imaging only may represent parathyroid adenoma or hyperplasia'. Thyroid ultrasound was unremarkable.

Based on the serum calcium and the declining creatinine, the patient was counselled regarding the choice of parathyroidectomy or starting medical therapy with cinacalcet. However, he was not interested in another long-term medication and opted for surgery.

He underwent one gland parathyroidectomy with interoperative PTH monitoring. His recovery was complicated by pneumonia. He also lost weight that he has been unable to re-gain. At his 2 month post-surgery follow-up, his creatinine had improved to 1.1 mg/dL and calcium to 9.9 mg/dL.

50.5.1 Nursing Role/Key Learning Points from the Case

Renal impairment as a complication of PHPT may be missed; careful follow-up of the patient can ensure that an evolving complication is identified without delay. Co-morbidities that may influence the decision to proceed to surgery should be assessed. The specialist nurse should be aware of the individual patient's risks and indication for surgery, so that he or she can counsel the patient appropriately.

50.6 Hypoparathyroidism

Hypoparathyroidism is a disease state in which the parathyroid glands fail to produce active PTH in response to hypocalcemia or hyperphosphatemia. Some causes for hypoparathyroidism are listed in Table 50.3.

Table 50.3 Causes of hypoparathyroidism (for detailed list, see Clarke et al.) (Clarke et al. 2016; Bollerslev et al. 2015)

Congenital/genetic	Associations	Mutation
DiGeorge syndrome	Immune deficiency; congenital heart defects; ENT defects	*TBX1; NEBL*
APECED; also known as autoimmune polyglandular syndrome type 1	Addison's; chronic mucocutaneous candidiasis; malabsorption; dental abnormalities; gonadal failure; hepatitis; anaemia	*AIRE*
Sanjad-Sakati and Kenny Caffey syndromes	Short stature; cognitive impairment; seizures	*TBCE*
X-linked hypoparathyroidism	Neonatal tetany	Xq26-q27
Familial isolated hypoparathyroidism	Autosomal recessive and dominant inheritance	*PTH; GCM2*
Autosomal dominant hypocalcaemia 1 (with hypercalciuria)	Can be asymptomatic. High risk renal complications	*CASR*
	Sensorineural deafness; renal	*GATA3*
Acquired		
Surgery (damage to, or removal of parathyroid glands)	Younger age; female patients; surgery for Graves' disease or malignancy; number of parathyroids left in situ	
Infiltration	Iron/copper deposition; malignancy; sarcoid	
Neck irradiation		
Autoimmune (also see APECED, above)		
Hypomagnesaemia	PPI use; alcohol excess	

50.6.1 Assessment of the Patient with Suspected Hypoparathyroidism

Patients are diagnosed with hypoparathyroidism when albumin-adjusted serum calcium or ionised calcium concentration is less than the local lower

limit of normal, in the setting of low or inappropriately normal PTH concentration. Magnesium concentration should be measured because hypomagnesemia impairs both release of PTH from parathyroid glands and PTH action in target tissues; therefore magnesium should be replaced and bone biochemistry re-assessed in those with a low serum magnesium result. The most common aetiology of chronic hypoparathyroidism is post-surgical—up to 7% of patients who undergo total thyroidectomy develop permanent hypoparathyroidism which is defined as hypoparathyroidism persisting more than 6 months after surgery (Shoback et al. 2016). In a patient with evidence of chronic hypoparathyroidism who has no history of neck surgery or irradiation, consider an autoimmune cause followed by genetic screening (see Table 50.3) (Clarke et al. 2016). Almost half of the cases of non-surgical hypoparathyroidism are idiopathic (Astor et al. 2016). Patient and family history and clinical examination are used to guide further investigations.

50.6.2 Clinical Assessment of the Patient with Potential Acute Post-surgical Hypoparathyroidism

Hypocalcemia in the first post-operative day occurs in 30–60% of patients who undergo total thyroidectomy; this is more likely in those undergoing surgery for underlying thyroid malignancy, because they tend to have more extensive surgical clearance including lymph node dissection. Acute hypoparathyroidism can also occur after parathyroidectomy. Most centres where these procedures are performed have a protocol for monitoring patients on the post-operative ward; these protocols usually include a combination of clinical and biochemical monitoring, as outlined below.

After thyroidectomy or parathyroidectomy patients should be asked about tingling or 'pins-and-needles' sensations, usually felt in the hands, feet or face. Nursing staff should check for neuromuscular irritability by assessing Chvostek's and Trousseau's signs at the time of measurement of patient vital signs. Chvostek's sign is facial twitching elicited by lightly tapping over the patient's facial nerve. Trousseau's sign is carpopedal spasm elicited by inflating a blood pressure cuff on the upper arm to greater than the patient's systolic blood pressure for 3 min. A useful video of these signs and description of their clinical use was provided by Jesus and Landry (2012). These signs are indicators of severe hypocalcemia and should trigger urgent measurement of calcium, but do not replace routine measurement of calcium at least twice daily in this post-operative cohort of patients.

50.6.3 Treatment of Hypoparathyroidism

Hypoparathyroidism is the only endocrine deficiency state that is not routinely treated by replacement of the relevant deficient hormone. The aim of treatment of acute hypoparathyroidism is to prevent symptoms, laryngospasm and cardiac arrhythmia. It is possible that for patients with acute post-operative hypoparathyroidism, maintenance of calcium in the middle to higher end of the normal calcium reference range increases their chance of parathyroid recovery in the long term (Bollerslev et al. 2015). The aim of treatment of chronic hypoparathyroidism is to avoid symptoms of hypocalcemia, avoid complications of overtreatment and preserve a normal quality of life; in order to achieve this the biochemical targets are to keep serum calcium in the low normal or slightly low range while the patient remains free of signs and symptoms of hypocalcemia; to keep 24-h urinary calcium in the normal reference range (<0.1 mmol/kg/24 h or 4 mg/kg/24 h); to keep serum phosphate and magnesium in the normal reference range and to keep serum calcium-phosphate product less than 4.4 $mmol^2/L^2$ (55 mg^2/dL^2); this requires an individualised approach for each patient.

Standard treatment is with active vitamin D analogues and calcium supplementation, and with supplementation of cholecalciferol 400–800 IU/day to levels of at least 50 nmol/L (20 ng/mL). The vitamin D analogues commonly used are calcitriol and alfacalcidol. Oral calcium

supplements relieve mild symptoms of hypocalcemia such as fatigue. Some patients feel better at a higher serum calcium level, and it is reasonable to maintain calcium at this level if they do not develop hypercalciuria or renal stones. Oral calcium supplements also bind phosphate. The guidelines for dietary calcium intake for the general population apply to patients with hypoparathyroidism (1000 mg/day). The capacity of the intestine to absorb calcium is saturated at 500 mg at any one time, therefore it is advisable to spread out dietary and supplement calcium intake across the day in divided doses. For patients on proton pump inhibitors, see Clinical Note 1. Dose adjustment of calcium supplementation is according to symptoms, serum calcium and phosphate and urinary calcium clearance. Dietitian review for advice about dietary calcium, phosphate and sodium is advisable (Brandi et al. 2016).

Some patients benefit from use of either teriparatide, which is PTH 1–34 (the N terminal active fragment of PTH), or intact parathyroid hormone (1–84). In 2015, the FDA approved Natpara (intact PTH 1–84) with orphan drug designation for management of hypocalcemia in hypoparathyroidism (Brandi et al. 2016). Concern about the risk of osteosarcoma has limited its use to patients with hypoparathyroidism who cannot achieve normocalcemia on activated vitamin D analogues and calcium supplementation alone. American guidelines suggest consideration of PTH 1–84 replacement therapy in the setting of difficulty maintaining stable calcium measurements; high dosing requirements for calcium (>2.5 g/day) or vitamin D (>1.5 μg for active form or >3.0 μg for 1α analogue); history of hypercalciuria, calculi or reduced eGFR; increased calcium-phosphate product or hyperphosphatemia; malabsorption and reduced quality of life (Brandi et al. 2016). If PTH 1–84 is commenced, vitamin D dose must be reduced.

50.6.4 Follow-up of the Patient with Hypoparathyroidism

Patients with hypoparathyroidism receiving stable doses of calcium, vitamin D, magnesium or diuretics should undergo measurement of serum-adjusted (or ionised) calcium, magnesium, phosphate and creatinine (for estimated GFR) every 3–6 months and this frequency should be increased in the event of prescription changes. The frequency of testing after a calcium or vitamin D dose change depends on how high the dose of the supplement was prior to change (higher doses require longer time to achieve steady-state and electrolyte response), and upon the clinical status of the patient. Measurement of 24-h urinary calcium should be done annually or every second year, and renal imaging should be considered if urinary calcium is high or if estimated glomerular filtration rate is decreasing. Bone imaging is not routinely indicated during follow-up.

50.6.5 Complications of Treatment of Hypoparathyroidism

Undertreatment of hypoparathyroidism can result in symptomatic hypocalcemia which manifests as mood disorders, cognitive problems, paresthesiae, muscle cramp, sleep disturbance, fatigue, cardiac arrhythmia and laryngospasm. Some of these symptoms may go un-noticed or their significance may not be recognised by the patient—for example the authors have seen life-threatening laryngospasm present initially as an irritating cough—therefore patient education is extremely important. Patients with post-surgical hypocalcemia who experience a rapid drop in calcium may be quite symptomatic while those with hypocalcemia of more insidious onset can tolerate lower serum calcium levels without symptoms. In patients with non-surgical hypoparathyroidism, an increased risk of cataract, intracerebral calcification, ischemic heart disease and proximal humeral fracture has been reported (Bollerslev et al. 2015).

Over-replacement of calcium leading to hypercalcemia may also present with cognitive problems, muscle pain, nephrogenic diabetes insipidus and arrhythmia, as well as renal colic from nephrolithiasis where hypercalciuria is long-standing. Both hypo- and hypercalcemia can be acute emergencies, and both electrolyte

imbalances can complicate acute illness in patients with hypoparathyroidism. Hypercalciuria is a risk factor for renal stone formation in patients with hypoparathyroidism; this may be managed by reduction of calcium supplementation (with compensatory increase in vitamin D replacement), restriction of dietary sodium and use of high-dose thiazide diuretics. Patients with hypoparathyroidism who are known to have renal stones should be managed as per guidelines for the general population with renal calculi.

50.6.6 Quality of Life with Hypoparathyroidism

Patients with hypoparathyroidism report lower quality of life than members of the general population, and those with post-surgical hypoparathyroidism appear to suffer more than those with a non-surgical aetiology; this has recently been confirmed in a Norwegian study which reported lower quality of life in post-surgical patients using the Short Form 36 and Hospital Anxiety and Depression scale (Astor et al. 2016). Patients with combined post-surgical hypothyroidism and hypoparathyroidism report more physical symptoms than patients with hypothyroidism alone (Sikjaer et al. 2016). An open-label Italian study of twice daily PTH(1–34) in 42 patients with post-surgical hypoparathyroidism demonstrated improvement in quality of life measured by the SF36 (Santonati et al. 2015), and a study of PTH(1–84) therapy in patients with hypoparathyroidism of mixed aetiologies also demonstrated improvement in SF36 domains (Cusano et al. 2013); these suggest that poor quality of life is treatable in this patient cohort. See Patient Experience.

50.7 Pseudohypoparathyroidism and Pseudopseudohypoparathyroidism

Pseudohypoparathyroidism is resistance to PTH, characterised by low calcium and high phosphorus in the setting of high PTH measurements. Serum hypomagnesaemia should be excluded before the diagnosis of pseudohypoparathyroidism is made. Careful examination and biochemical assessment of response to PTH is required to diagnose the subtype of pseudohypoparathyroidism (Levine 2012). Albright's hereditary osteodystrophy (AHO) is a clinical syndrome that includes short stature, round face, obesity, heterotopic ossification, shortening of the third, fourth and fifth metacarpals and shortening of the distal phalanx of the first digit and can be observed both with and without endocrinopathy.

AHO, pseudohypoparathyroidism and the coexistence of other endocrine resistant states (thyroid stimulating hormone/gonadotrophin resistance) suggests pseudohypoparathyroidism type 1a or 1c. Type 1a and 1c can be differentiated by molecular testing of the *GNAS* gene. Type 1b is usually associated with renal PTH resistance alone and with mild brachydactyly. Pseudohypoparathyroidism type 2 is a renal resistance to PTH in which cyclic AMP is generated in response to PTH infusion but PTH does not cause phosphaturia; this is associated with severe hypocalcemia and vitamin D deficiency.

Patients with a clinical examination consistent with Albright's hereditary osteodystrophy who have normal endocrine function and PTH action have a condition called pseudopseudohypoparathyroidism caused by mutations in the GNAS gene inherited from the patient's father.

Detailed description of the genetic basis for these conditions is reported elsewhere (OMIM) (Levine 2012).

Treatment of type 1 pseudohypoparathyroidism is with calcium and either calcitriol or alfacalcidol supplementation. Correction of underlying vitamin D deficiency is also recommended. Other endocrine disorders should be identified and treated appropriately.

50.8 Clinical Note 1: Proton Pump Inhibitors (PPIs)

PPIs are associated with hypomagnesemia which can cause reduction in PTH release or resistance to PTH at the level of target tissues. PPI use

should be checked in the medication history of patients with newly diagnosed hypoparathyroidism and serum magnesium should be measured.

In patients receiving calcium supplementation for hypoparathyroidism, it should be remembered that PPIs raise the gastric pH, which interferes with absorption of calcium carbonate. If it is not possible to change the patient's antacid prescription, calcium supplementation should be given in the form of calcium citrate.

50.9 Clinical Note 2: Pregnancy in Hypoparathyroid Patients

Pregnant women with hypoparathyroidism require special consideration because of the changes in calcium metabolism that occur during pregnancy. The placenta produces 1,25 $(OH)_2D$ which drives increased intestinal absorption of calcium; parathyroid hormone-related peptide (PTHrP) production in later pregnancy and breastfeeding drives increased calcium resorption from the bone. The combined increased activity of 1,25 $(OH)_2D$ and PTHrP can lead to hypercalcemia complications for the mother and hypocalcaemia in the neonatal period for the infant. Conversely untreated maternal hypocalcemia can lead to foetal loss or skeletal abnormalities in the infant. Treatment of hypoparathyroidism with calcium and vitamin D analogues should continue in pregnancy but women with hypoparathyroidism should have serum calcium measurement (adjusted or ionised) every 2–3 weeks during pregnancy and breastfeeding, and the obstetrician should be aware of the diagnosis of hypoparathyroidism (Bollerslev et al. 2015).

50.10 Patient Experience of Hypoparathyroidism

A hypopara patient can feel both physically and emotionally at odds with a 'normal' blood test result so the key to management is to maintain calcium levels high enough to be symptom-free but low enough to prevent kidney damage. Good levels of serum magnesium and Vitamin D3 are important to help reduce symptoms and maintain stability. Patients with brittle hypopara or patients having their medication adjusted will need extra support and more frequent and accessible blood tests. Hypopara clinical guidelines should be consulted.

Hypopara is a very complicated condition to live with (especially without a home tester), so patients and their medical teams need to work together for best results. Self-management is also essential to avoid crises. Calcium levels fluctuate in response to many factors throughout the day and can affect the patient at every level—physical, emotional and neurological. Understanding how certain factors such as exercise, menstrual cycles and sleep levels affect levels; how to get calcium from dietary sources; and how and when to take medication can help the patient to feel better. Hypopara patient support groups also play a great role in educating and supporting hypopara patients and their families and raising awareness of patient needs to the medical profession.

The hardest part about being a hypopara patient is the invisibility of the illness. There is an assumption that because you look OK on the outside and your bloods might come back in the OK range that everything is fine. Family and friends can forget that you have the illness (and make unreasonable demands on your energy levels) and well-meaning people underestimate the seriousness of the illness and advise you to drink more milk!

50.11 Hypopara UK (Hypoparathyroidism and Primary Hyperparathyroidism)

Hypopara UK is a national patient organisation working to improve the lives of people living with conditions caused by parathyroid gland disorders.

Hypopara UK was founded in 2005 by Liz Glenister, a former teacher, after a 12 year search for information about her unnamed and unacknowledged condition following her operation for thyroid cancer in 1992. Liz continues to run

Hypopara UK today with the help of a committed band of patients, all volunteers like herself and a clinical advisory team of specialist healthcare professionals. Hypopara are proud founders of the World Hypopara Awareness Day and the Hypopara Europe Network and we continue to set up new groups around the world.

Hypopara UK offers support and information to empower patients and their families to become involved and active in the management of their condition through its informative website, award winning patient information leaflets, telephone helplines and online support groups. Making contact is often a life changing moment for patients who may have been struggling alone to understand their condition or find appropriate treatment, as Sarah's story describes.

Hypopara UK works closely with our Clinical Advisory Team in the UK and Ireland, as well as international HCPs with a particular interest in calcium homeostasis and bone metabolism. Together they work to raise awareness, develop new protocols and advance research into more effective treatment.

Hypopara UK is honoured to have been involved in some ground-breaking work including the BTA guideline for the 'Management of Thyroid Cancer' Guidelines (2014), the ESE guideline on the 'Treatment of Chronic Hypoparathyroidism in Adults' (2015), 'Living with Chronic Hypoparathyroidism'(2017) and 'Burden of Illness Among Patients With Chronic Hypoparathyroidism Not Adequately Controlled With Standard Therapy by Self-Perception' (2018).

Hypopara UK is very keen to work with nurses (particularly those in endocrine clinics, A&E, post-surgical wards and GP practices) wishing to learn more about supporting and educating patients with these challenging conditions. Hypopara UK attends meetings and training events to network and share information, and provides free resources for clinics and surgeries available to order or download from our website.

For further information, please visit our website at www.hypopara.org.uk, email us on mailto:info@hypopara.org.uk or call us on +44 (0)1342 316315.

50.12 Patient Story

Currently 75% of our membership (and 6–7% of all thyroid surgery cases in the UK) are living with permanent post-surgical hypoparathyroidism due to thyroid, parathyroid or laryngeal surgery. The problems of achieving calcium homeostasis, particularly without monitoring, are very challenging and, being a rare condition, symptoms may not be recognised or properly treated, even in a crisis.

Sarah H is a 51-year-old registered nurse who had a total thyroidectomy to remove a large multinodular goitre in London, in October 2017. Two days later she was readmitted with hypocalcaemia (and a haemorrhage and tracheal tear) and was finally diagnosed with permanent post-surgical hypoparathyroidism in April 2018.

Sarah writes: It has been an emotional and physical struggle, mainly because my endocrinologist had little experience of this rare condition. She couldn't understand why I was so symptomatic despite my serum calcium being within 'normal' range and did not monitor me after increasing my medication. This led to dangerously high calcium levels (>3.2) but, despite feeling extremely ill, I was told to continue on the same medication just cut the calcium slightly and retest in 3 days.

Hypopara UK was invaluable in giving me the confidence to disregard this dangerous advice and to go to A&E for urgent care. I did this and was immediately admitted for a week for IV fluids and potassium replacement. Hypopara UK later advised me to take magnesium supplements which has dramatically reduced my symptom burden further.

I have since asked Hypopara UK to recommend a specialist in calcium metabolism which they did and he is now expertly planning and monitoring my condition. I am thrilled. They also advised me to ask for altered employment hours and am now back at work with only one night shift a week.

I don't know where I'd be now without the help and support from Hypopara UK. They gave me the tools to educate myself about the condition, and above all, the confidence to be my own advocate in order to receive appropriate care. I'm in a much better place now.

50.13 Conclusions

1. Primary hyperparathyroidism (PHPT) is diagnosed in the setting of hypercalcemia with high or inappropriately normal PTH measurement; it is primarily managed with surgery. Some asymptomatic patients may benefit from surgical intervention.
2. PHPT can be complicated by osteoporosis and fractures; by nephrolithiasis, nephrocalcinosis and reduced renal function; by peptic ulcer disease and by psychiatric disturbance.
3. Hypoparathyroidism is diagnosed in the setting of hypocalcemia with low or inappropriately normal PTH; serum magnesium should be measured and hypomagnesemia corrected before the diagnosis is confirmed. The most common aetiology of hypoparathyroidism is post-surgical.
4. Hypoparathyroidism requires careful assessment for complications of over- or under-treatment with monitoring of serum and urinary calcium and imaging in certain patients; it is associated with reduced quality of life.
5. Genetic disorders which predispose to parathyroid pathology including parathyroid carcinoma have been identified in recent years; consideration of genetic screening in younger patients, those with family histories suggestive of a genetic endocrinopathy (e.g. MEN) and those with atypical presentations or atypical parathyroid histology should be considered as a positive result may change clinical follow-up.

Acknowledgements Special thanks to Liz Glenister, Chief Executive Officer, HypoparaUK (www.hypopara.org.uk), for her contribution to this chapter with case studies, patient resources, and information on the Patient Advocacy Group.

References

Astor MC, Lovas K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and health-related quality of life in hypoparathyroidism in Norway. J Clin Endocrinol Metab. 2016;101(8):3045–53.

Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med. 2005;257(1):6–17.

Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9.

Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, et al. European Society of Endocrinology Clinical Guideline: treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1–20.

Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101(6):2273–83.

Clarke BL, Brown EM, Collins MT, Juppner H, Lakatos P, Levine MA, et al. Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab. 2016;101(6):2284–99.

Crowley RK, Gittoes NJ. When would I use medical therapies for the treatment of primary hyperparathyroidism? Clin Endocrinol. 2013;79(6):770–3.

Crowley RK, Gittoes NJ. Elevated PTH with normal serum calcium level: a structured approach. Clin Endocrinol. 2016;84(6):809–13.

Cusano NE, Rubin MR, McMahon DJ, Irani D, Tulley A, Sliney J Jr, et al. The effect of PTH(1-84) on quality of life in hypoparathyroidism. J Clin Endocrinol Metab. 2013 Jun;98(6):2356–61.

Fraser WD. Hyperparathyroidism. Lancet. 2009;374(9684):145–58.

Glynn N, Lynn N, Donagh C, Crowley RK, Smith D, Thompson CJ, et al. The utility of 99mTc-sestamibi scintigraphy in the localisation of parathyroid adenomas in primary hyperparathyroidism. Ir J Med Sci. 2011;180(1):191–4.

Jesus JE, Landry A. Images in clinical medicine. Chvostek's and Trousseau's signs. N Engl J Med. 2012;367(11):e15.

KDIGO. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int. 2009;76(Suppl 113):S1–130.

Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2016;28(1):1–19.

Levine MA. An update on the clinical and molecular characteristics of pseudohypoparathyroidism. Curr Opin Endocrinol Diabetes Obes. 2012;19(6):443–51.

Li Y, Simonds WF. Endocrine neoplasms in familial syndromes of hyperparathyroidism. Endocr Relat Cancer. 2015;23(6):R229–47.

Mackenzie-Feder J, Sirrs S, Anderson D, Sharif J, Khan A. Primary hyperparathyroidism: an overview. Int J Endocrinol. 2011;2011:251410.

McClenaghan F, Qureshi YA. Parathyroid cancer. Gland Surg. 2015;4(4):329–38.

Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008;93(9):3462–70.

Santonati A, Palermo A, Maddaloni E, Bosco D, Spada A, Grimaldi F, et al. PTH(1-34) for surgical hypoparathyroidism: a prospective, open-label investigation of efficacy and quality of life. J Clin Endocrinol Metab. 2015;100(9):3590–7.

Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab. 2016;101(6):2300–12.

Sikjaer T, Moser E, Rolighed L, Underbjerg L, Bislev LS, Mosekilde L, et al. Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. J Bone Miner Res. 2016;31(7):1440–8.

Calcium Disorders

51

Arthur D. Conigrave
and Marsha M. van Oostwaard

Contents

51.1 **Introduction** 977

51.2 **Calcium and Phosphorus Metabolism and Testing** 977
51.2.1 Calcium 977
51.2.2 Phosphate 978
51.2.3 Disorders of Phosphate Metabolism 978

51.3 **Dietary Calcium and Calcium Supplementation** 978

51.4 **Hypocalcaemia** 979
51.4.1 Diagnosis of Hypocalcaemia 979
51.4.2 Laboratory Contribution to Diagnosis of Hypocalcaemia 980
51.4.3 Causes of Hypocalcaemia 980

51.5 **Hypercalcemia** 980
51.5.1 Familial Hypocalciuric Hypercalcemia 981
51.5.2 Forms of FHH That Do Not Arise from Mutations of the CaSR 982

51.6 **Other Disorders of the Calcium-Sensing Receptor** 982
51.6.1 Neonatal Severe Hyperparathyroidism (NSHPT) 982
51.6.2 Autosomal Dominant Hypocalcaemia 982
51.6.3 A Form of ADH That Does Not Arise from Mutations of the CaSR 982

A. D. Conigrave (✉)
University of Sydney, Sydney, NSW, Australia

Department of Endocrinology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia
e-mail: arthur.conigrave@sydney.edu.au

M. M. van Oostwaard
Centre for Metabolic Disorders, Department of Internal Medicine, VieCuri Medical Centre, Venlo, The Netherlands
e-mail: mvoostwaard@viecuri.nl

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_51

51.7 **Hypercalcemia of Malignancy** 983
51.7.1 Hypercalcemia in the Context of Bone Metastases 983
51.7.2 Humoral Hypercalcemia of Malignancy 983
51.8 **Calcium Disorders in Renal Disease** 983
51.9 **Milk Alkali Syndrome** 984
51.9.1 Management 984
51.10 **Nursing Process** 984
51.10.1 Assess 984
51.10.2 Diagnose 985
51.10.3 Plan 985
51.10.4 Implement 985
51.10.5 Evaluate 985
51.11 **Conclusions** 987
References 987

Abstract

The plasma levels of calcium and inorganic phosphate are controlled by homeostatic mechanisms. The plasma level of calcium is particularly tightly controlled. Parathyroid hormone (PTH) raises calcium via actions on: bone cells (osteoclasts and osteocytes) to promote mineral resorption; the renal distal tubule to enhance calcium reabsorption; and renal proximal tubule cells to promote 1,25-dihydroxyvitamin D synthesis. Calcium-sensing receptors lower calcium dependent on plasma membrane expression in cells of: the parathyroid gland to suppress PTH secretion and thus serum PTH levels; the renal cortical thick ascending limb to promote urinary calcium losses; and other tissues including thyroid calcitonin-secreting C-cells and osteoclasts. Hypocalcaemia arises as a consequence of a failure of one of the normal homeostatic mechanisms that act to raise the plasma calcium level. Hypocalcaemia may be symptomatic or asymptomatic. Key early clinical features of hypocalcaemia include perioral or peripheral paresthesiae or numbness, and various manifestations of neuromuscular excitation including carpo-pedal spasm. Later, more severe manifestations of hypocalcaemia include convulsions, including febrile convulsions in children. Dietary calcium requirements for adults are around 1–1.5 g/day, reflecting relatively low levels of intestinal absorption efficiency, even in vitamin D replete individuals. Calcium supplements are of particular benefit in patients with osteoporosis on anti-resorptive medications, which impair calcium release from bone, thereby promoting the risk of hypocalcaemia. Hypercalcemia arises as a consequence of a failure of one or more of the normal homeostatic mechanisms that act to lower the plasma calcium level.

Keywords

Calcium metabolism · Calcium-sensing receptor · Hypercalcemia · Hypocalcaemia Hypophosphatemia · Parathyroid hormone Phosphate metabolism

Abbreviations

ADH	Autosomal dominant hypocalcaemia
ATP	Adenosine 5′-triphosphate
CaSR	Calcium-sensing receptor
DXA	Dual energy Xray absorptiometry
FGF-23	Fibroblast growth factor-23
FHH	Familial hypocalciuric hypercalcemia
NSHPT	Neonatal severe hyperparathyroidism
PTH	Parathyroid hormone

Key Terms

- **Hydroxyapatite:** is a key bone mineral composed of Calcium and phosphate.
- **Ionized calcium:** is free calcium in blood that is not attached to proteins.
- **Calcium sensing receptor:** regulates calcium metabolism by regulating parathyroid hormone secretion and urinary calcium excretion.
- **Osteomalacia:** an end-stage bone disease of chronic and severe vitamin D or phosphate depletion of any cause.

Key Points

- Bone is composed of collagen protein fibres strengthened by a mineral phase. Calcium and inorganic phosphate are the two key chemical components of bone mineral, also known as crystalline hydroxyapatite.
- Calcium ions via both the extracellular and several intracellular pools are critical for various important cell functions including interactions between key proteins. Inorganic phosphate ions are also critical for normal cell function.
- The metabolisms of calcium and inorganic phosphate are subject to homeostatic control mechanisms. One key element of the control mechanism is parathyroid hormone (PTH) from the parathyroid gland, which elevates the plasma calcium concentration and suppresses the plasma phosphate concentration. The calcium-sensing receptor lowers the plasma calcium concentration by mediating negative feedback control of PTH secretion and promoting urinary calcium excretion.
- Vitamin D exists in several forms in the body, primarily as metabolites of vitamin D_3 (cholecalciferol). 25-Hydroxyvitamin D is the primary circulating form and is used to assess the whole body vitamin D store. 1,25-Hydroxyvitamin D is the active hormonal form, which stimulates calcium absorption from the small intestine and renal distal tubule.
- Disorders of calcium metabolism leading to hypercalcemia or hypocalcaemia arise from disturbances of the homeostatic mechanisms.

51.1 Introduction

Calcium and phosphate are the two main components of the key bone mineral, hydroxyapatite. In addition, the extracellular ionised Ca^{2+} concentration is a key determinant of neuromuscular excitability and is required for coagulation, and control mechanisms that up- or down-regulate the intracellular Ca^{2+} concentration drive or suppress key cell functions including muscle contraction and the secretion of key hormones including insulin and even digestive enzymes. Inorganic phosphate, on the other hand, plays major roles in reactions that are critical for human biochemistry acting, for example, to enable the storage of chemical energy as ATP, facilitate many of the reactions of intermediary metabolism, and shift the activation states of enzymes and proteins via reversible phosphorylation. For these reasons, the plasma levels of both calcium and phosphate are subject to tight regulation. The plasma ionised Ca^{2+} concentration is subject to particularly tight control. In this chapter, we consider the normal plasma levels of both calcium and phosphate as well as causes of disturbances in their levels, focusing in particular on key mechanisms that underlie hyper- and hypocalcaemia.

51.2 Calcium and Phosphorus Metabolism and Testing

51.2.1 Calcium

The normal range for the plasma total calcium concentration in humans is around 2.2–2.6 mmol/L, distributed between three major fractions:

1. One in which calcium is bound to plasma proteins, chiefly albumin (representing around 45%).
2. One taking the form of filterable complexes including calcium citrate (around 5%).
3. A free, ionised fraction (i.e. Ca^{2+} ions; around 50%).

As a result the normal range for plasma ionised Ca^{2+} concentration, which may be measured by a suitable Ca^{2+}-selective electrode, is 1.1–1.3 mmol/L. It is the ionised Ca^{2+} concentration that controls the coagulation cascade and modulates cell and tissue function. For example, low extracellular Ca^{2+} concentration enhances excitability at the neuromuscular junction. Thus, any factor that perturbs the ionised Ca^{2+} concentration can perturb cell function. One important factor is a change in pH leading to a change in Ca^{2+} binding to albumin; an increase in pH increases Ca^{2+} binding to albumin and thereby acutely lowers the ionised Ca^{2+} concentration. A drop in the plasma albumin concentration is typically accompanied by a drop in the total plasma calcium concentration so that the ionised Ca^{2+} concentration does not change.

The ionised Ca^{2+} concentration is protected by several key factors (review: Brown and MacLeod 2001):

1. Ca^{2+} ion sensing by cells of the parathyroid gland to suppress the secretion of a peptide hormone parathyroid hormone (PTH) that promotes calcium transfers into the extracellular fluid and, thus, the blood.
2. Ca^{2+} ion sensing by cells of the thick ascending limb of the renal tubules to suppress Ca^{2+} reabsorption from the tubular fluid.
3. Ca^{2+} ion sensing by parafollicular C-cells of the thyroid to activate the secretion of a peptide hormone, calcitonin that suppresses osteoclastic-dependent bone resorption.
4. Ca^{2+} ion sensing by the proximal tubule to suppress the synthesis of 1,25-dihydroxyvitamin D_3.

51.2.2 Phosphate

The plasma inorganic phosphate concentration lies in the range 0.8–1.4 mmol/L present as the free ion distributed between two main species HPO_4^{2-} and $H_2PO_4^-$, dependent upon the pH. At normal plasma pH 7.40, the ratio of HPO_4^{2-}:$H_2PO_4^-$ is around 5:1. The ratio falls as the pH drops and increases as the pH rises. $CaHPO_4$ is poorly soluble and, as might be expected, the problem is exacerbated at high pH as the concentration of HPO_4^{2-} increases.

Table 51.1 Causes of hypophosphatemia

Primary disturbances of mineral metabolism
1. Acquired
• Primary hyperparathyroidism
• Vitamin D deficiency
2. Inherited
• Autosomal dominant hypophosphatemic rickets (mutant stable form of FGF-23)
• X-linked (dominant) hypophosphatemic rickets (mutant PHEX; defective negative regulation of FGF-23 production)
• X-linked recessive hypophosphatemic rickets (various forms including mutations in renal Na-phosphate co-transporters)
Nutritional causes
• Acute alcoholism
• Refeeding after prolonged under nutrition
• Diabetic ketoacidosis (recovery phase)
Miscellaneous
• Severe burns
• Diuretic use

51.2.3 Disorders of Phosphate Metabolism

Hypophosphatemia is associated with proximal myopathy and cardiomyopathy. It is also associated with various forms of rickets and osteomalacia. Hypophosphatemia arises in some important nutritional disorders. A number of inherited and acquired conditions are also associated with hypophosphatemia (see Table 51.1).

Hyperphosphatemia typically occurs in chronic kidney disease and contributes to vascular mineralisation and associated peripheral, coronary and cerebral vascular disease. In this setting, the plasma calcium level may be low. Hyperphosphatemia also occurs in hypoparathyroidism and parathyroid hormone resistance states (pseudohypoparathyroidism) as well as disorders of FGF-23 metabolism, in which the serum levels of FGF-23 are suppressed and the serum levels of 1,25-dihydroxyvitamin D are elevated (review: Conigrave 2012).

51.3 Dietary Calcium and Calcium Supplementation

Dietary calcium intakes vary considerably dependent on dietary composition. Foods rich in calcium include various dairy products including

Table 51.2 Calcium-rich foods

• Dairy products (including milk, yoghurt, cheese and ice cream)
• Salmon or sardines (containing edible bones)
• Tofu (set with calcium salts)
• Almonds
• Broccoli, cabbage, soy-beans, tahini (sesame seeds), bok-choy, celery
• Dried figs, dried apricots, oranges

whole milk, skim milk, yoghurt and cheese. Some forms of fish, nuts, vegetables and fruit are also rich sources of calcium (see Table 51.2).

Recommended daily allowances of calcium are based on balance studies and suggest that optimal calcium intakes are around 1.0 g/day during childhood and around 1–1.5 g/day during adolescent growth, and during pregnancy and lactation. Lower calcium intakes are required in adult men and in women post-lactation and in the peri- and postmenopausal stages but are still around 1.0 g/day. The relatively high levels of recommended calcium intake reflect, in part, the low efficiency of intestinal calcium absorption, which is around 10–20% even when vitamin D levels are replete (Conigrave 2012).

Until recently, almost all patients, men and women, with osteoporosis have been prescribed both calcium and vitamin D supplements at doses of around 1.0–2.0 g/day and 1000–2000 IU/day, respectively. In the presence of anti-resorptive therapy with one of the oral or intravenous bisphosphonates, subcutaneous denosumab, selective estrogen receptor modulator (SERM) raloxifene or even oestrogen therapy, the benefits of supplementation with calcium and vitamin D are relatively straightforward. They prevent the development of acute symptomatic hypocalcaemia. Hypocalcaemia can develop in this setting as a result of anti-resorptive-induced impairment of osteoclastic bone resorption and the unopposed formation and mineralisation of new bone. In patients taking anti-resorptive therapy, increased intakes of calcium and vitamin D prevent acute hypocalcaemia by increasing the amount of calcium absorbed by the small intestine each day.

In the absence of anti-resorptive therapy, the value of calcium and vitamin D supplements in adults is less certain and benefits in terms of improved bone mineral density and muscle mass and function are at best modest. Two additional circumstances in which calcium and vitamin D supplements should be considered even in the absence of therapy with anti-resorptive agents are:

1. Low serum vitamin D levels (<40 nmol/L). Defining the normal range for serum 25-hydroxyvitamin D_3 in adults has proved difficult. However, the risk of osteomalacia increases markedly at serum concentrations below 30 nmol/L and serum PTH levels are suppressed at serum 25-hydroxyvitamin D_3 levels up to 80 nmol/L.
2. Evidence of secondary hyperparathyroidism and high bone turnover (high serum PTH in the presence of a low plasma calcium concentration with elevated bone turnover markers including the pro-collagen breakdown product P1NP and ostase reporting bone formation and the plasma CTX and urinary level of deoxypyridinoline cross-links reporting bone resorption).

51.4 Hypocalcaemia

51.4.1 Diagnosis of Hypocalcaemia

Two main sources of information are: (1) the plasma calcium levels reported by the biochemistry laboratory and (2) the patient's clinical state. The former requires careful consideration of key related information including the plasma albumin concentration and plasma pH. The latter can be somewhat unpredictable: patients who experience a relatively small but acute drop in plasma calcium concentration can be symptomatic and exhibit many of the clinical features of hypocalcaemia. On the other hand, patients with long-standing moderate-severe hypocalcaemia can be asymptomatic or only mildly symptomatic and display only modest clinical features indicating that appropriate physiological adjustments are made in the presence of persistently low calcium levels (Brown and MacLeod 2001).

The clinical features of hypocalcaemia include enhanced neuromuscular excitability including fasciculations and tetanic contractions of isolated muscle groups, which may be either spontaneous or elicited by tapping directly over nerves, e.g. the facial nerve at the angle of the mandible

(Chvostek's sign), or by inflating a blood pressure cuff to a level above the systolic pressure for 2–3 min to induce local hypoxemia (Trousseau's sign). Other clinical features include perioral or peripheral numbness, bronchospasm and even convulsions.

51.4.2 Laboratory Contribution to Diagnosis of Hypocalcaemia

As noted above, hypocalcaemia is defined by two ranges: one for plasma total calcium concentration (2.2–2.6 mmol/L) and one for plasma ionised Ca^{2+} concentration (1.1–1.3 mmol/L). In terms of pathophysiological significance, a low ionised Ca^{2+} concentration is more important but assays for ionised Ca^{2+} are not always available. In the presence of hypoalbuminemia (e.g. in the context of uncompensated chronic liver disease), the plasma ionised Ca^{2+} concentration is frequently normal despite the presence of a low plasma total calcium concentration. This arises from a significant reduction in the plasma protein calcium binding capacity. To confirm that the plasma calcium concentration is normal in this setting either (1) the plasma ionised Ca^{2+} concentration can be measured and/or (2) a correction can be made to the total calcium concentration using an appropriate formula (Payne et al. 1973).

An example of such a formula is as follows:

$$\text{Plasma total Ca}\left(\text{corrected; mmol / L}\right) = \text{plasma total Ca}\left(\text{measured; mmol / L}\right) + [0.025\ \text{mmol / g} \times \left(40\text{g / L}^{*} - \text{plasma albumin concentration g / L}\right]).$$

* plasma albumin concentration (mid-normal range)

In a case in which a plasma total calcium concentration was 2.0 mmol/L, for example, the value would be hypocalcemic if the plasma albumin concentration was in the mid-normal range, around 40 g/L. However, in the presence of a low plasma albumin concentration (30 g/L), the corrected plasma total calcium concentration would be 2.25 mmol/L, i.e. normal.

51.4.3 Causes of Hypocalcaemia

The most common cause of acute hypocalcaemia is post-operative hypoparathyroidism, typically in the context of major thyroid surgery. Untreated, the plasma total and ionised calcium concentrations both drop, typically into the plasma total calcium range 1.8–2.0 mmol/L (ionised 0.9–1.0 mmol/L) and the patients exhibit acute symptoms and clinical features of hypocalcaemia. Other causes of hypocalcaemia are provided in Table 51.3.

51.5 Hypercalcemia

As noted above, the normal range for the plasma total calcium concentration is 2.2–2.6 mmol/L (8.8–10.2 mg/dL). Therefore, hypercalcemia is defined by a total calcium concentration >2.6 mmol/L and an ionised Ca^{2+} concentration >1.3 mmol/L. The clinical features of mild hypercalcemia include lethargy, anorexia and constipation. More severe features include muscle weakness, abdominal pain that may be associated

Table 51.3 Causes of hypocalcaemia

Nutritional or metabolic
• Severe vitamin D deficiency
• Chronic kidney disease
Parathyroid dysfunction
• Hypoparathyroidism (surgical or primary)
• Autosomal dominant hypocalcaemia
• PTH resistance states (pseudohypoparathyroidism)
Miscellaneous
• Hungry bone syndrome (e.g. in response to anti-resorptives)
• Acute pancreatitis

Table 51.4 Causes of primary hyperparathyroidism

Benign adenoma: 80%
Benign hyperplasia (all four glands): 20%
Parathyroid carcinoma: <1%
Ectopic PTH (e.g. lung ca): <1%

Table 51.5 Non-PTH-related causes of hypercalcemia

Familial hypocalciuric hypercalcemia
Malignancy
• Multiple myeloma
• Metastatic disease affecting bone (e.g. breast)
• Humoral hypercalcemia of malignancy (PTHrP secreting tumours)
Vitamin D toxicity
Granulomatous disease
• Sarcoidosis
• Tuberculosis
• Inhalation-related granulomas: e.g. talc
Milk Alkali syndrome
Pituitary/adrenal failure

with peptic ulcer disease or pancreatitis, polyuria, and even confusion, convulsions and coma.

In practice, there are two main clinical scenarios according to whether the serum PTH concentration (normal range 1–6 pmol/L) is elevated. If the serum PTH level is elevated, the patient has primary hyperparathyroidism (see Chap. 47) due most commonly to a benign adenoma of a single parathyroid gland (see Table 51.4). If the serum PTH is normal or low, the patient has one of a relatively large number of uncommon causes of hypercalcemia (see Table 51.5). Appropriate investigations for hypercalcemia in the context of (1) raised or (2) normal or low serum PTH levels are provided in Box 51.1 and Box 51.2, respectively. Immobilisation and dehydration can exacerbate hypercalcemia in various contexts including primary hyperparathyroidism.

Box 51.1 Investigations for Hypercalcemia Associated with Elevated Serum PTH Levels

Plasma biochemistry: sodium, potassium, calcium, phosphate, bicarbonate, creatinine, 25-hydroxyvitamin D_3

Urine biochemistry: calcium: creatinine (Ca/Cr ratio)

Serum hormones: PTH

Bone density: DXA

Imaging for parathyroid tumour: Sestamibi scan (neck and thorax); Ultrasound of neck; 4D CT scan (neck and mediastinum)

Box 51.2 Investigations for Hypercalcemia Associated with Normal or Low Serum PTH Levels

Plasma biochemistry: sodium, potassium, calcium, phosphate, bicarbonate, creatinine, 25-hydroxyvitamin D_3. 1,25-dihydroxyvitamin D_3, Angiotensin Converting Enzyme (ACE), ACTH, Cortisol

Urine biochemistry: calcium: creatinine (Ca/Cr ratio)

CXR: granulomas or tumour

Bone density: DXA

51.5.1 Familial Hypocalciuric Hypercalcemia

Familial Hypocalciuric hypercalcemia (FHH) is an uncommon condition that should be considered in patients who present with mild-moderately severe hypercalcemia (total plasma calcium 2.7–3.0 mM) and serum PTH levels that are either normal or at the upper limit of normal. The calcium disturbance is typically benign and does not require medical or surgical intervention. It arises in the context of hyperplasia of all four parathyroid glands. Parathyroid surgery is not indicated. Two key disturbances of calcium metabolism are: (1) impaired inhibitory feedback control of PTH secretion and (2) impaired inhibitory control of renal calcium reabsorption. The elevated serum PTH level arises from impaired calcium-sensing receptor-mediated inhibition of PTH secretion from the parathyroid glands. Hypocalciuria (most easily assessed as the

urinary calcium: creatinine ratio) arises from impaired calcium-sensing receptor (CaSR)-mediated inhibitory control of renal calcium reabsorption. The inappropriately elevated serum PTH concentration and enhanced rate of renal calcium reabsorption act together to raise the plasma calcium concentration. Most commonly, impaired calcium-sensing receptor function in FHH arises from an inactivating mutation of the receptor (Brown et al. 1998).

51.5.2 Forms of FHH That Do Not Arise from Mutations of the CaSR

Recently, two additional genes have been linked to FHH: the alpha subunit of G11 (FHH2) and the sigma subunit of the endosomal sorting protein AP2 (FHH3) (Hannan et al. 2016). FHH has also been described in the context of circulating anti-CaSR antibodies that suppress receptor function.

51.6 Other Disorders of the Calcium-Sensing Receptor

51.6.1 Neonatal Severe Hyperparathyroidism (NSHPT)

Whereas FHH typically arises in individuals who are heterozygous for inactivating mutations of the CaSR, individuals that are, very rarely, homozygous or compound heterozygous for inactivating mutations of the CaSR present early in postnatal life with severe hypercalcemia (plasma total calcium >3.5 mmol/L) and markedly elevated serum PTH concentrations arising from near total failure of Ca^{2+}-dependent feedback control of PTH secretion. This disorder, neonatal severe hyperparathyroidism (NSHPT), requires early four gland parathyroidectomy to correct the disturbance in calcium metabolism, reverse skeletal demineralisation and prevent pathological fractures in the first weeks of life.

51.6.2 Autosomal Dominant Hypocalcaemia

Autosomal dominant hypocalcaemia (ADH) arises from heterozygous activating mutations of the CaSR, which promote renal Ca^{2+} excretion and inappropriately suppress PTH secretion in the context of hypocalcaemia (Brown et al. 1998). Plasma total calcium concentrations typically fall into the range 1.0–1.8 mmol/L (plasma ionised Ca^{2+} 0.5–0.9 mmol/L). Untreated, this condition is usually benign and patients typically report only mild symptoms of hypocalcaemia. Some will report a history of one or more episodes of childhood convulsions. In asymptomatic adults, correction of the plasma calcium concentration into the normal range is not required and is potentially very harmful. Aggressive treatment with oral calcium supplements and active forms of vitamin D such as calcitriol (1,25-dihydroxyvitamin D_3) to restore the plasma calcium to normal, results in marked elevations in renal calcium and phosphate excretion, nephrocalcinosis and associated chronic kidney disease. Some patients treated in this way progress to dialysis and even renal transplantation. For this reason, it is generally accepted that the plasma calcium concentration in patients with ADH should be adjusted, if possible with calcium salts alone, to lie just below the normal range, e.g. between 1.8 and 2.0 mmol/L.

51.6.3 A Form of ADH That Does Not Arise from Mutations of the CaSR

Recently, activating mutations of the alpha subunit of the G-protein G_{11} have been linked to a form of ADH (ADH2) (Hannan et al., 2016).

51.7 Hypercalcemia of Malignancy

51.7.1 Hypercalcemia in the Context of Bone Metastases

Hypercalcemia occurs in the context of osteolytic metastases from various cancers including notably breast cancer and certain forms of leukemia. It arises primarily from markedly enhanced osteoclastic bone resorption in response to cytokines released by the tumour cells in the bone microenvironment. In this context hypercalcemia responds to anti-resorptive therapy, e.g. with the bisphosphonates pamidronate or zoledronate. A similar situation arises in patients with multiple myeloma, a malignancy of plasma cells that arises in the bone marrow and drives enhanced osteoclastic bone resorption.

51.7.2 Humoral Hypercalcemia of Malignancy

In addition to the impact of cancer cells via locally derived cytokines to drive osteoclastic bone resorption in the bone microenvironment, enhanced bone resorption also arises in response to certain cancers that do not metastasise to bone. In these cases (e.g. associated with certain squamous cell carcinomas, renal carcinoma, carcinoma of the ovary, and some lymphomas) markedly enhanced production of cytokines by tumour cells converts peptides that have restricted local roles in certain tissues under normal physiological conditions to factors with endocrine effects. One of these, parathyroid hormone related protein (PTHrP) induces osteoblast-dependent osteoclastic bone resorption via type-1 PTH receptors on osteoblasts (McCauley and Martin 2012). In part, the mechanism involves enhanced osteoblast expression of RANK-ligand and decreased expression of its decoy receptor osteoprotegerin. Under these conditions, RANK-ligand induces osteoclastogenesis, a process in which the number of mature bone-resorbing osteoclasts markedly increases together with the bone-resorbing surface.

51.8 Calcium Disorders in Renal Disease

As chronic kidney disease (CKD) develops there is progressive loss of glomerular filtration, disturbances of renal tubular function and impaired synthesis of key hormones including 1,25 dihydroxyvitamin D_3 and erythropoietin. Elevated plasma phosphate concentration is one early mineral disturbance that arises in the context of the CKD and the plasma phosphate level continues to rise as renal function deteriorates. This is partially offset by increases in the serum FGF-23 and PTH concentrations, at least initially, since FGF-23 and PTH both promote renal phosphate excretion (Uribarri 2007). The plasma calcium concentration is normal initially but falls as the disorder progresses. This promotes the development of secondary hyperparathyroidism, which takes the form of markedly elevated serum PTH levels, including intact PTH as well as various inactive C-terminal fragments, and hyperplasia of all four parathyroid glands. The low plasma calcium concentration, low serum 1,25-dihydroxyvitamin D_3 concentration, high serum PTH levels, and retention of toxic N-containing metabolites, act together to promote the development of renal osteodystrophy, a form of skeletal disease with features of osteoporosis and osteomalacia. Cinacalcet, a positive modulator of the calcium-sensing receptor is used to lower serum PTH levels in CKD to reduce the severity of renal osteodystrophy and reduce bone resorption. To avoid the development of inappropriately low bone turnover rates and thus reduced bone formation rates and repair (‘frozen bone’), the doses of cinacalcet are selected to lower serum PTH concentrations to around 100 pmol/L but not lower. In some CKD patients, hypercalcemia develops late in the disorder (tertiary hyperparathyroidism). In some cases, this arises due to uncontrolled hyperplasia of all four parathyroid glands. In others, single parathyroid adenomas develop.

51.9 Milk Alkali Syndrome

This condition arises typically in the context of high oral dosing with calcium carbonate salts (calcium intakes >4 g/day) (Medarov, 2009). The prevalence of the condition has fallen due to the replacement of calcium carbonate antacids with histamine H_2 receptor antagonists, proton pump inhibitors, and anti-*Helicobacter pylori* antibiotic therapy in the treatment of peptic ulcer disease.

Key features of the condition are hypercalcemia, which can be severe (plasma total calcium concentration >3.0 mmol/L), high plasma bicarbonate levels (>35 mmol/L), alkalosis (arterial or venous pH >7.5), low plasma chloride levels, and renal impairment (plasma creatinine >120 μmol/L). Plasma inorganic phosphate levels are normal rather than low, thereby enhancing the conditions for ectopic mineralisation, and renal calcium excretion levels are inappropriately normal or low, thereby promoting hypercalcemia. Serum PTH and 1,25-dihydroxyvitamin D_3 levels are typically low. The condition may present either acutely or chronically. While the link to the ingestion of both calcium and alkaline salts is clear, the pathogenesis is not well understood. High pH promotes small intestinal Ca^{2+} absorption via the epithelial Ca^{2+} channel Trpv6 and renal Ca^{2+} reabsorption via the epithelial Ca^{2+} channel Trpv5. In addition, high plasma Ca^{2+} levels are reported to suppress glomerular filtration and to promote proximal tubular reabsorption of water and bicarbonate. Finally, chronically elevated plasma concentrations of calcium and bicarbonate together promote the deposition of calcium salts in various tissues including the arterial system, the brain, various structures in the eye including the cornea and lens, and in the kidneys (nephrocalcinosis). Nephrocalcinosis can progress to end-stage renal failure requiring dialysis or renal transplantation.

51.9.1 Management

The approach is relatively simple:

- Stop the calcium and alkaline salts.
- Promote hydration.
- Use frusemide to induce calciuresis if the plasma calcium level is markedly elevated.

In acute cases, the renal function can completely recover. In chronic cases, renal function may be permanently impaired and progression to end-stage kidney disease may occur.

51.10 Nursing Process

51.10.1 Assess

Evaluate all aspects of patient health status, including aspects relating to health promotion, protection and disease prevention, as well as signs and symptoms of calcium disorders.

Hypocalcaemia

– Take a detailed medical history, including specific questions on recent thyroid surgery, osteoporosis and a family history of known calcium disorders or parathyroid dysfunction.
– Assess patient's nutritional state and dietary intake of calcium or vitamin D, sun exposure or recent use of anti-resorptive therapy.
– Inquire about enhanced neuromuscular excitability including fasciculation and tetanic contractions of muscles.
– Examine clinically relevant signs, such as fasciculation and tetanic contractions of isolated muscle groups, by tapping directly over the facial nerve at the angle of the mandible (Chvostek's sign) or by inflating a blood pressure cuff to a level above the systolic pressure for 2–3 min to induce local hypoxemia (Trousseau's sign).

Hypercalcemia

– Assess first on symptoms, especially confusion and lethargy as they are signs of sudden-onset and severe hypercalcemia effecting the nervous system (acute care is needed!)
– Take a detailed medical history including specific questions on kidney stones, chronic kidney disease or renal insufficiency, malignancies and a family history of known calcium disorders.

- Assess patient's nutritional state and dietary intake of calcium or vitamin D and use of supplements or use of calcium and alkaline salts.
- Assess on the mnemonic 'stones, bones, abdominal moans, and psychic groans' (kidney stones, osteoporosis or fractures, pain in abdomen, obstipation and/or depression (and use of lithium)).
- Inquire about urine output, fluid intake and increased thirst.
- Examine clinically relevant signs such as hypotonic muscles, weight loss, dehydration, faecal impaction (from constipation), arrhythmias and or hyper/hypotension.

51.10.2 Diagnose

Work collaboratively to plan appropriate screening tests based on recommendations in patients presenting with calcium disorders.

- Identify patient knowledge on deficits as areas for therapeutic education.
- Ensure appropriate, accurate collection of urine or blood samples for diagnostic or evaluation purpose.
- Ensure appropriate guidance if there is a suspicion of a malignant disease.
- Collaborate with endocrine colleagues to determine if treatment is conform evidence-based guidelines.
- Facilitate additional specialist referrals as needed.

51.10.3 Plan

Interpret test results, recognise abnormal findings and help communicate results and implications to the patient and family.

- Provide disease-specific education to the patient on the long-term effects of the diagnosis and management.
- Advise patient of risks and benefits associated with the various treatment options, including medical and surgical management, and engage the patient in shared decision-making.
- Monitor calcium levels, encourage taking oral fluids, weight-bearing exercises and smoking cessation.
- Instruct what symptoms to report.
- Discuss the expectations of the therapeutic interventions on patient related outcome (what are the patients goals of the treatment) and explain the medical goals.
- Identify patient resources including websites, refer to patient support groups if appropriate.

51.10.4 Implement

Initiate treatment and inform the patient of appropriate monitoring and follow-up.

- Provide therapeutic education (holistic approach) to ensure comprehension of the effects of the diagnosis and management.
- Provide education, support and practical arrangements regarding pre- and post-operative care, make additional referrals as needed (e.g. pre-operative assessment).
- Provide emotional support to patient and family based on condition-specific psychological issues.
- Teach proper administration of medication.
- Plan and coordinate initial and subsequent follow-up appointments.

51.10.5 Evaluate

Assess the effectiveness of interventions and revise the plan of care as appropriate.

- Evaluate biochemical response to treatment.
- Inquire about potential unwanted side effects of the treatment.
- Monitor adherence and compliance to the treatment.
- Assess actual and potential effects on patient-reported outcomes (patients goals, medical goals).
- Monitor for other psychological comorbidities (e.g. anxiety, depression) and coping behaviours.

– Monitor condition-specific issues such as constipation, abdominal pain and fractures.
– Evaluate dietary fluid and calcium intake.
– Evaluate achievement of goals regarding weight-bearing exercises and cessation of smoking.

Case Study Hypercalcemia

A 53-year-old postmenopausal woman who experienced a distal radius fracture was referred to the Fracture Liaison Service (FLS) for investigation of increased fracture risk due to osteoporosis. As part of the screening a DXA scan was performed. She had a consultation with a FLS nurse who took a detailed medical history, explained the results of the DXA scan, assessed the risk for fractures and inquired about other health problems.

Medical history: Kidney stones. Mild depression. Mild hypertension.

Patient-reported health problems: obstipation, dry mouth, anxiety attacks and fear of falling.

Risk factors for fracture (non-modifiable) are:

– Recent fracture
– Age > 50 years
– Mother with hip fracture

Modifiable risk factors:

– Sedentary lifestyle
– Smoking

The results of the DXA scan:

Lumbar spine L1–L4	*T* score −3.2
Femoral neck	*T* score −2.6
Vertebral fracture assessment (Th4-L5)	No significant vertebral fractures

Diagnosis conform WHO criteria: Severe osteoporosis

The nurse explains the implications of having an increased fracture risk and the need for further investigation. She orders a chemistry panel to screen for underlying causes of osteoporosis, including: electrolytes, 25OH vitamin D, Serum calcium, Albumin, Creatinine, PTH, TSH, Alkaline phosphatase and Serum phosphate. And refers the patient to the endocrinologist (who is participating in the FLS programme).

Lab results:

Electrolytes, albumin, creatinine, TSH: within normal range
25OH vitamin D: 97 nmol/L,
Serum calcium: 2.93 mmol/L
PTH: 17 pmol/L
Alkaline phosphatase: 130 IU/L
Serum phosphate: 2.6 mg/dL

Additional investigation of calcium excretion in 24H urine sample shows increased levels of calcium. Physical investigation shows no abnormalities besides a mild hypertension. There are no signs of malignant diseases.

These results suggest primary hyperparathyroidism.

The next step in the diagnostic process is to perform a sestamibi scan and an ultrasound. These diagnostic imaging tests show hyperplasia of one of the parathyroid glands diagnosed as a solitary parathyroid adenoma.

Because there is a symptomatic primary hyperthyroidism and (secondary) osteoporosis, the patient is referred to the head-neck surgeon who performs an extirpation of the parathyroid gland. The PTH levels normalise completely after surgery. The osteoporosis is treated with a weekly dosed oral bisphosphonate.

The patient experienced difficulties coping with these three diagnoses (fracture, osteoporosis and hyperparathyroidism) and their treatment (surgery, medication). Although she was thankful for finding the probable cause of multiple health problems, it was a lot to deal with. The patient is guided by a Nurse Practitioner (NP) who provides practical and emotional support. Three months after surgery the patient reports an increased quality of life and is completely symptom free. The patients next challenges are cessation of smoking and staying compliant to the bisphosphonates.

51.11 Conclusions

Calcium and phosphate are subject to homeostatic control mechanisms due to their importance as key chemical components of the bone mineral hydroxyapatite and key roles as important ionic species in physiologically important cell functions. In plasma calcium is present in three main forms, its ionised form Ca^{2+} (normally around 50% of the total), an albumin-bound form that is pH-sensitive (around 45% of the total), and as complexes with small organic molecules such as citrate (around 5% of the total). For this reason, the ionised Ca^{2+} concentration (normal range 1.1–1.3 mM) is only around half of the total plasma calcium concentration (normal range 2.2–2.6 mM). Inorganic phosphate is present in plasma in two main forms, the dibasic form HPO_4^{2-} and the monobasic form $H_2PO_4^-$ in a ratio of around 5:1 at physiological pH, 7.4. The calcium concentration in plasma is tightly regulated dependent on the operation of calcium-sensing receptors (CaSRs) in the parathyroid gland and in several tubular segments in the kidneys. The key role of CaSRs in both parathyroid and kidney is to lower the plasma calcium concentration. The key role of PTH is to prevent and/or correct hypocalcaemia. Once activated, the key role of vitamin D is to promote calcium and phosphate absorption from the intestine and to promote calcium reabsorption from the kidneys. The daily requirements of calcium approximate 1.0 g for adults but this increases in certain circumstances, e.g. pregnancy and lactation.

There are a large number of causes of hypocalcaemia and hypercalcemia. Careful investigation is required to identify the cause and select an appropriate plan of management. In general, acute disturbances of the plasma calcium concentration require early intervention. Acute *hypocalcaemia* arises chiefly in the context of thyroid or parathyroid surgery due to the inadvertent removal/damage of normal parathyroid tissue, or in the context of anti-resorptive therapy in patients with osteoporosis, who are vitamin D deficient (serum 25-hydroxyvitamin D <40 nmol/L). Acute pancreatitis is another important cause. Acute *hypercalcemia* arises in the context of malignancy (bone metastases or HHM), vitamin D toxicity and milk alkali syndrome. Factors that can exacerbate hypercalcemia include immobilisation, dehydration and treatment with thiazide diuretics.

References

Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev. 2001;81:239–97.

Brown EM, Pollak M, Hebert SC. The extracellular calcium-sensing receptor: its role in health and disease. Annu Rev Med. 1998;49:15–29.

Conigrave AD. Regulation of calcium and phosphate metabolism. In: Licata AA, Lerma EV, editors. Diseases of the parathyroid glands. New York: Springer; 2012. p. 13–53.

Hannan F, Babinsky V, Thakker R. Disorders of the calcium-sensing receptor and partner proteins: insights into the molecular basis of calcium homeostasis. J Mol Endocrinol. 2016;57:R127–42.

McCauley L, Martin T. Twenty-five years of PTHrP progress: from cancer hormone to multifunctional cytokine. J Bone Miner Res. 2012;27:1231–9.

Medarov B. Milk-alkali syndrome. Mayo Clin Proc. 2009;84:261–7.

Payne R, Little A, Williams R, Milner J. Interpretation of serum calcium in patients with abnormal serum proteins. Br J Med. 1973;4:643–6.

Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. Semin Dial. 2007;20:295–301.

52 Congenital and Acquired Bone Disorders in Children and Adults

Kirtan Ganda, Klaus Sommer, and Anne L. Ersig

Contents

52.1 **Part A: Congenital and Acquired Bone Disorders in Adults** 991
52.1.1 Introduction 991

52.2 **Chronic Kidney Disease-Mineral and Bone Disorder** 991
52.2.1 Diagnosis and Pathophysiology 991
52.2.2 Management 992

52.3 **Paget's Disease** 992
52.3.1 Prevalence 992
52.3.2 Clinical Features 993
52.3.3 Management 993

52.4 **Osteopetrosis** 995
52.4.1 Clinical Features 995
52.4.2 Diagnosis 995
52.4.3 Treatment 995

52.5 **McCune–Albright Syndrome** 995
52.5.1 Epidemiology 995
52.5.2 Pathogenesis 996
52.5.3 Clinical Features 996
52.5.4 Investigations 996
52.5.5 Management 996

A. Ersig has authored Part B, the paediatric section of this chapter.

K. Ganda (✉)
Concord Hospital, Sydney, NSW, Australia

University of Sydney, Sydney, NSW, Australia
e-mail: kirtan.ganda@sydney.edu.au

K. Sommer
Concord Hospital, Sydney, NSW, Australia
e-mail: Klaus.sommer@sswahs.nsw.gov.au

A. L. Ersig
University of Wisconsin-Madison School of Nursing, Madison, WI, USA
e-mail: anne.ersig@wisc.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_52

52.6 **Osteogenesis Imperfecta** 997
52.6.1 Prevalence 997
52.6.2 Clinical Features 997
52.6.3 Diagnosis 997
52.6.4 Management 997

52.7 **Rickets** 997
52.7.1 Clinical Features 998
52.7.2 Pathophysiology 998
52.7.3 Management 998

52.8 **Part B: The child with a Congenital Bone Disorder** 999
52.8.1 Pathophysiology and Genetics of Congenital Bone Disorders 999
52.8.2 Genetic and Clinical Evaluation 999
52.8.3 Evaluation of Congenital Bone Disorders 1000
52.8.4 Treatment and Management of Congenital Bone Disorders 1000

52.9 **Exemplar Congenital Bone Disorders** 1001

52.10 **Conclusions** 1002

References 1003

Abstract

Congenital and acquired bone disorders generally increase the risk of low trauma fractures due to their impact on the formation and maintenance of bone microarchitecture. Bone deformity can also develop which can result in symptoms such as pain. The formation of the collagen bone matrix can be disrupted, as in osteogenesis imperfecta (OI) or replaced in focal areas by fibrous tissue, as seen in fibrous dysplasia. Alternatively the mineralization of the bone matrix can be affected in conditions such as rickets or there could be marked changes in bone turnover, as in Paget's disease and osteopetrosis. Chronic kidney disease-mineral and bone disorder can manifest as a wide spectrum of bone abnormalities ranging from low to high turnover states, impaired mineralization of bone, and or reduced bone volume.

The diagnosis of congenital and acquired bone disorders is made through a combination of clinical, radiological, genetic, and laboratory investigations. Management may simply involve vitamin D replacement in the case of rickets, or may involve anti-resorptive therapy to decrease bone turnover, improve bone strength, and reduce pain. Management may be symptompatic if there is no known cure. This chapter is a review for endocrine nurses, providing a summary of congenital and acquired bone disorders and the potential role of nurses in the care of these patients.

Keywords

Bone fragility · Anti-resorptive therapy Monostotic · Polyostotic · Osteoid mineralization · Bone deformity

Abbreviations

AD	Autosomal dominant
ALP	Alkaline phosphatase (bone marker)
AR	Autosomal recessive
BMD	Bone mineral density
CKD	Chronic kidney disease
COL1A	Mutation in the alpha chains of collagen gene
FD	Fibrous dysplasia
GFR	Glomerular filtration rate
HSCT	Hematopoietic stem cell transplantation
IPMN	Intra-ductal pancreatic mucinous neoplasia
MAS	McCune–Albright Syndrome
OI	Osteogenesis imperfecta
PTH	Parathyroid hormone

Key Terms

- **Chronic Kidney Disease-Mineral and Bone Disorders**: mineral and bone abnormalities associated with chronic kidney disease.
- **Fibrous dysplasia**: an excessive formation of fibrous tissue in bone marrow and destruction

of normal bone in conjunction with abnormal bone formation and increased osteoclast activity.
- **McCune-Albright syndrome**: triad of fibrous dysplasia of bone, endocrine hyperfunction and café-au-lait skin hyperpigmentation.
- **Osteogenesis imperfecta**: genetic disorder of increased bone fragility and low bone mass.
- **Osteopenia**: is a loss of bone mass by bone densitometry and expressed as a *T* score −1 to −2.0.
- **Osteopetrosis**: genetic condition characterized by increased bone mass.
- **Osteoporosis**: is a loss of bone mass by bone densitometry and expressed as a *T* score >−2.0.
- **Paget's disease**: disease with marked increase in bone turnover in localized part of skeleton.
- **Rickets**: Disorder of mineralization of the bone matrix.

Key Points
- Bone is a metabolically active tissue that responds to congenital and environmental triggers in various ways.
- Bone disorders, whether congenital or acquired usually result in increased bone fragility, potential bone deformity, and an increased risk of fractures.
- Rickets is an example of an acquired bone disorder which results from a deficiency of vitamin D and is mostly preventable.
- Osteogenesis imperfecta is a congenital bone disorder of increased bone fragility and low bone mass, with a broad clinical phenotype, depending on the genes involved.

52.1 Part A: Congenital and Acquired Bone Disorders in Adults

52.1.1 Introduction

The skeleton is a metabolically active unit, which is critical for an individual to maintain optimal health. It consists of acellular components, i.e., the bone matrix (collagen), mineral (hydroxyapatite) and cellular components, i.e., osteoblasts, osteoclasts, and osteocytes, which all interact to culminate in an integrated unit that functions to protect organs and enable a person to mobilize. Although osteoporosis is the most common disorder affecting bone, there are a number of less common acquired and congenital conditions, which affect bone strength and quality. Acquired disorders include Chronic Kidney Disease-Mineral and Bone Disorder as well as vitamin D deficiency leading to rickets in children and osteomalacia in adults. Genetic/congenital disorders include osteopetrosis, osteogenesis imperfecta, and fibrous dysplasia. The pathogenesis of Paget's disease is likely due to a combination of acquired and heritable mechanisms. These disorders will be discussed in the following sections.

52.2 Chronic Kidney Disease-Mineral and Bone Disorder

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a term coined by the KIDOQI group in 2009 (Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group 2009) in order to encompass the spectrum of mineral and bone abnormalities associated with chronic kidney disease that is usually seen in stage IV and V CKD (eGFR <30 mL/min). Thus, patients with CKD-MBD could manifest bone fragility through fractures but have very different underlying pathologies such as a low turnover state (characterized by low or normal PTH, low bone specific ALP), i.e., adynamic bone disease. Alternatively it may present as a high turnover state (characterized by high bone specific ALP, PTH more than 6× the upper limit of normal), i.e., osteitis fibrosa cystica, and/or osteomalacia.

52.2.1 Diagnosis and Pathophysiology

The diagnosis of osteoporosis amongst patients with CKD requires exclusion of the aforementioned conditions, especially in the setting of stage IV

(GFR 15–29 mL/min) and stage V CKD (<15 mL/min). CKD is associated with elevated PTH due to an elevated serum phosphate, a degree of PTH resistance, and elevated metabolites of PTH, which are detected in the PTH assay. These biochemical abnormalities, in particular the changes in PTH are correlated with the presence of different types of bone disorders and are most often seen amongst those with stage IV and V CKD. Ultimately however the gold standard for the exclusion of adynamic bone disease and osteomalacia is a bone biopsy with tetracycline labeling.

52.2.2 Management

Osteoporosis management should be similar to those without CKD amongst those with stage I–III CKD and absence of evidence of mineral disorders, i.e., normal calcium, phosphate, and PTH. On the other hand, in the setting of CKD stage IV and V, anti-resorptive therapy (bisphosphonates, denosumab, selective estrogen receptor modulators) should be used with caution and after the exclusion of adynamic bone disease and osteomalacia in particular. The latter conditions could be exacerbated by anti-resorptive therapy. Furthermore, treatment of osteoporosis with anti-resorptive agents is problematic as bisphosphonates are contraindicated in the setting of an eGFR <30 mL/min due to the possibility of acute kidney injury. Furthermore, there is a paucity of data from RCTs relating to treatment of osteoporosis with anti-resorptives in Stage IV and V CKD. Denosumab therapy has been used in those with stage IV and V CKD in a limited number of patients, with no effect on renal function. It has been thought of a useful agent in this setting as it is not excreted by the kidneys (unlike bisphosphonates). However denosumab should be used with caution as there have been several case reports of hypocalcemia post-denosumab therapy despite normal 25-OH-vitamin D levels. Anabolic therapy with teriparatide has not been studied in those with stage IV and V CKD and therefore any use would be off-label. However, in clinical practice, it may be worth considering amongst those with adynamic bone disease.

Nurses can play a key role in the management of this condition, supporting patients and families, facilitating communication within the multidisciplinary team, providing educational resources and patient-focused, coordinated care.

52.3 Paget's Disease

Paget's disease is a disorder in which there is a marked increase in bone turnover in localized parts of the skeleton. Subsequently, over a period of many years this results in enlarged weakened bone, manifesting with chronic pain, bone deformity, and fracture.

Since the initial report from Sir James Paget in the nineteenth century, knowledge of the disorder has grown considerably. Paget's disease occurs most frequently in the skull, pelvis, lower spine, and long bones of the leg. One (monostotic) or more (polyostotic) sites may be involved, but any bone can be involved and any number of sites can be affected at the same time. It starts from a single focus in each bone and is thought to advance about 1 cm per year (Hooper and Lang, n.d.). Patients with Paget's disease are usually diagnosed over the age of 50 years, which is consistent with the slow evolution of the disease (Singer 2015).

52.3.1 Prevalence

The prevalence of Paget's disease is highest in the UK and in countries where a large number of residents have ancestors from the UK. Currently in many countries, the prevalence of the disorder has decreased in recent decades. In addition to the reduction in prevalence, the severity of the disorder has been observed to be decreased, as revealed by a reduction in the extent of skeletal involvement and an increasing age of onset (Singer 2015).

Although the cause is not yet fully understood, it appears to be the result of both a genetic predisposition and a factor from the environment, possibly a virus. Some researchers consider that this virus may be related to a group of viruses that includes measles. The decreasing prevalence of Paget's could be attributed to measles vaccination over the past 40–50 years. A considerable

number of affected patients have a family history of Paget's disease. A large number of mutations in the SQSTM1 gene seem to account for susceptibility in some families. That gene and others are currently under investigation (Singer 2015).

52.3.2 Clinical Features

In mild cases of Paget's disease, people may have few or no symptoms and frequently these may be vague and difficult to distinguish from other conditions. Many people do not know they have the disease and attribute their symptoms to arthritis or other conditions. The most common symptom is pain, usually localized to the affected bone. A sensation of heat over the affected bone may occur, which is caused by an increase in blood flow through the abnormal bone. Deformity of the bone may lead to fracture or bowing of a limb, especially weight bearing limbs. With enlargement of the skull, compression of various nerves may cause symptoms such as hearing loss and headache (Hooper and Lang, n.d.).

52.3.3 Management

The diagnosis is usually made on the results of X-rays, bone scans, and biochemical markers of bone turnover. X-rays confirm that there is Paget's disease in a particular bone, to assess how much bone is involved and to look for complications. Isotope bone scans are more sensitive than X-ray in the identification of pagetic lesions. This test is used primarily to establish the full extent of skeletal involvement for a patient (Hooper and Lang n.d.). Paget's disease is associated with increased bone turnover. It is therefore expected that markers of bone turnover (such as ALP) will be increased in active disease (Selby et al. 2002).

The aim of treatment of Paget's disease is to relieve pain, to prevent or reduce future complications (deformity, fractures, and nerve compression by pagetic bone), and to maintain mobility (Selby et al. 2002). Treatments have advanced considerably following the introduction of bisphosphonates, in particular intravenous zoledronate. Bisphosphonates are the treatment of choice in Paget's disease and are capable of inducing suppression of the disease which may persist for years after treatment is stopped. Suppression of disease activity is expected to minimize the development of complications. The goal of treatment is to achieve remission, which is generally defined as a bone turnover result below the midpoint of the reference range of the specific bone turnover marker (Healy et al. 2015). Influenza-like side effects associated with a patient's first dose of intravenous bisphosphonate are relatively common (about 1 in 3 patients), but usually mild and transient. Influenza-like symptoms usually occur within the first 48 h but are temporary and can usually be managed with regular paracetamol. It is unusual for these effects to happen again with later doses (Hooper and Lang, n.d.).

Nurses are often part of the multidisciplinary team caring for these patients, supporting patients and their families, providing educational resources and administering intravenous bisphosphonates (Fig. 52.1).

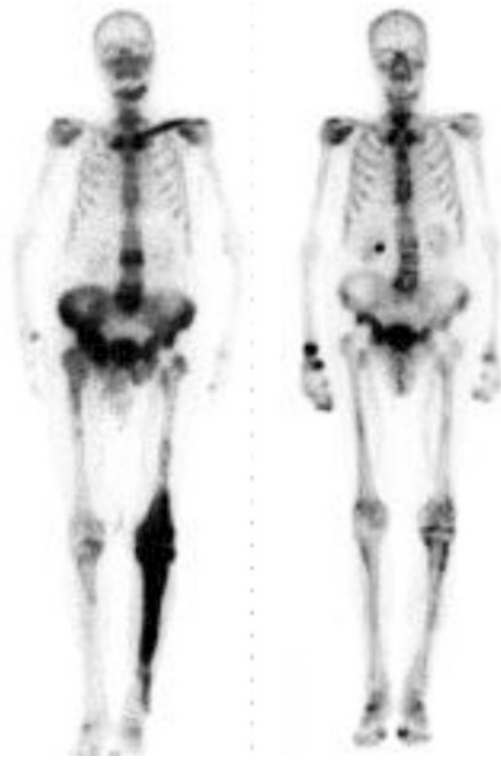


Fig. 52.1 Radionucleotide scan appearance in a patient with polyostotic disease affecting the left clavicle, spine, pelvis, femora, and tibia before (left) and after (right) bisphosphonate therapy

Case Study 1 (Fig. 52.2)

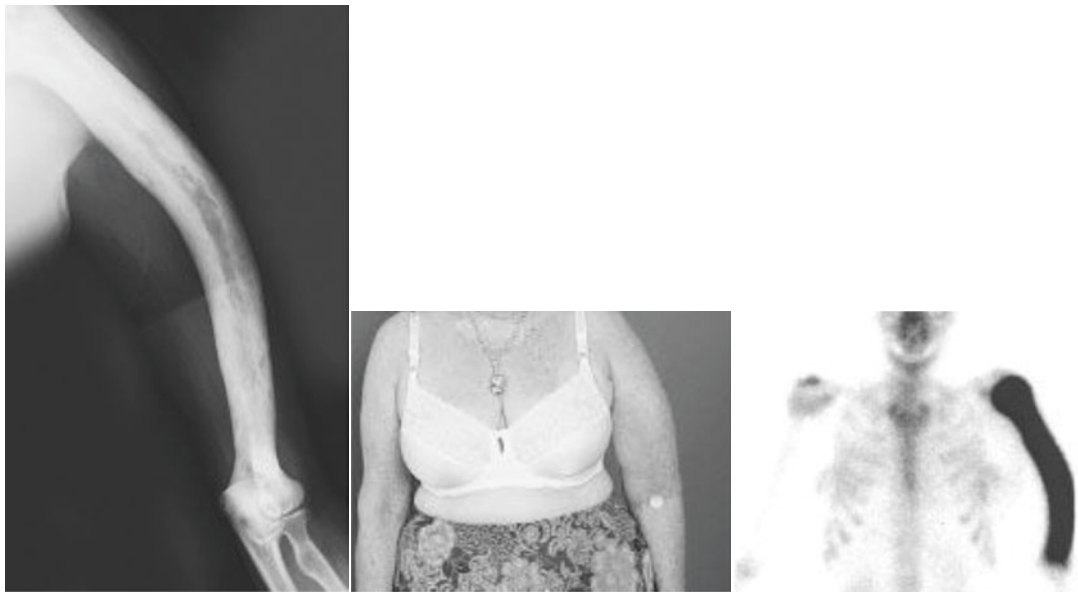


Fig. 52.2 The left humerus is extensively involved with Paget's disease. There is gross deformity and there is loss of the normal bone architecture. The disease extends from the elbow joint to the upper end of the humerus. It is unusual for Paget's not to involve the end of a long bone if other areas are diseased. Effective early treatment with bisphosphonates can be expected to prevent deformity and other complications

Case Study 2 (Fig. 52.3)

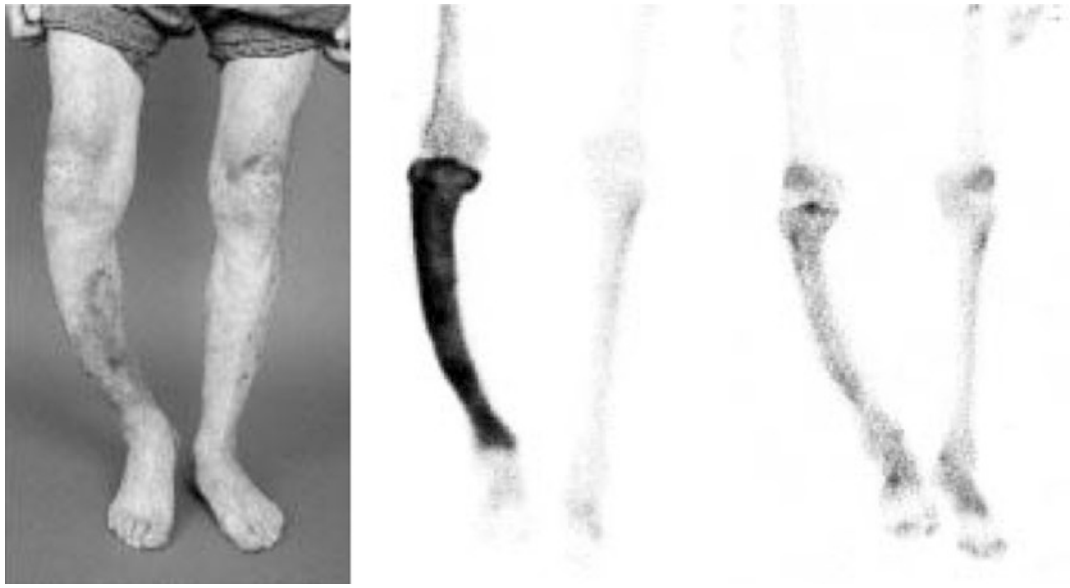


Fig. 52.3 Right tibia—effect of disease and treatment. The tibia is extensively deformed by Paget's disease which extends throughout the bone. The bone is expanded and bowed. Severe pain was a feature of the disease and the overlying skin was hot and the bone tender to pressure. With bisphosphonate therapy, the patient's pain resolved, the skin temperature returned to normal, the biochemical indices of activity of the disease returned to normal, and there was marked improvement on the bone scan

52.3.3.1 Learning Key Points/Nursing Role

Effective early treatment with bisphosphonates can be expected to prevent deformity and other complications.

52.4 Osteopetrosis

Osteopetrosis is a genetic condition characterized by increased bone mass. It has an autosomal dominant (AD) and recessive (AR) form, which have different clinical phenotypes (Sobacchi et al. 2013; Del Fattore et al. 2008). The underlying pathogenesis involves reduced bone resorption due to decreased osteoclast activity and/or function with a number of causative genetic mutations identified.

52.4.1 Clinical Features

The AR form is often fatal in children (aka malignant infantile osteopetrosis) while the AD form is more commonly present in adulthood (previously known as Albers-Schonberg disease). However, there is a wide degree of heterogeneity in the clinical presentation with both forms.

The AD form is generally less severe than the AR form; however, there is wide heterogeneity in the clinical presentation from asymptomatic to rarely fatal. It has prevalence of 5 in 100,000. Notably, a condition formerly known as ADO type I, which manifests with osteosclerosis only, due to increased bone formation from a gain-of-function mutation in the LRP5 gene, is no longer classified as osteopetrosis as it is an osteoblast defect.

The autosomal recessive form is often lethal during infancy or childhood but has a high degree of clinical and genetic heterogeneity. It is also rare with an prevalence of 1 in 250,000. The major clinical features of osteopetrosis include increased BMD on X-ray with loss of bone marrow cavity, yet increased risk of low trauma fractures, extra-medullary hemopoiesis, hypocalcemia, neurological defects (e.g., brainstem herniation), blindness, growth retardation, impaired tooth eruption and neurodegenerative manifestations. The underlying pathogenesis can vary according to the specific gene affected, which can be divided into two broad categories: from the absence of osteoclasts ("osteoclast poor") or the presence of non-functioning osteoclasts ("osteoclast rich").

52.4.2 Diagnosis

The diagnosis is made through a combination of clinical, radiological, and genetic features.

52.4.3 Treatment

The management of patients with AD osteopetrosis is symptomatic as there is no known cure. However, if the ARO is detected early, hematopoietic stem cell transplantation (HSCT) is a potential therapeutic option amongst infants without neurological involvement. Notably, HSCT is only effective amongst those with primary osteoclast defects as osteoclasts are hematopoietic in origin. On the other hand, in a form of AR osteopetrosis, which is due to a gene defect in RANK-L (produced from osteoblasts) which is of mesenchymal origin, HSCT would be ineffective. Therefore, early diagnosis and detection of the specific gene and molecular defect is critical.

52.5 McCune–Albright Syndrome

McCune–Albright Syndrome (MAS) is characterized by a triad of fibrous dysplasia (FD) of bone, endocrine hyperfunction, and café-au-lait skin hyperpigmentation (Albright et al. 1937; Dumitrescu and Collins 2008).

52.5.1 Epidemiology

MAS is rare in that it has a prevalence of 1 in 100,000 to 1 in 1,000,000.

52.5.2 Pathogenesis

The pathogenesis involves a non-inherited mutation (which occurs during the lifespan) in the gene encoding for the alpha-subunit of stimulatory G-protein resulting in osteoblast dysfunction. The type and extent of tissue involvement is dependent upon the stage of development in which the mutation occurs. Thus, there is a wide spectrum of clinical manifestations. In fibrous dysplasia there is excessive formation of fibrous tissue in bone marrow and destruction of normal bone in conjunction with abnormal bone formation and increased osteoclast activity.

52.5.3 Clinical Features

FD may present with bone pain, fragility fracture, deformity affecting the spine (i.e., scoliosis), face, upper or lower limbs, or neurological compromise. Hyperfunctioning endocrinopathies can manifest as hyperthyroidism, growth hormone excess, Cushing's syndrome, urinary phosphate wasting (with or without rickets/osteomalacia), and/or precocious puberty. A recently described association is intra-ductal pancreatic mucinous neoplasia (IPMN).

52.5.4 Investigations

In the initial assessment of a patient with possible MAS, investigations for endocrine hyperfunction should be performed. Radiological investigations to look for fibrous dysplasia include X-rays and/or CT scans of the affected area/s. A bone scan would reveal areas of intensely increased uptake in the affected bones. Bone biopsy may be required to make a diagnosis of fibrous dysplasia; however, the diagnosis is often based upon the combination of clinical, biochemical, and radiological assessments.

52.5.5 Management

Fibrous dysplasia of the bone can cause pain. Bisphosphonate therapy may be of benefit in reducing pain; however, evidence is limited due to the rarity of the disorder. Surgical management may be necessary in the case of fracture, or for cosmetic reasons. Management of the endocrinopathies is similar to those without MAS. Endocrine nurses can play a role in the diagnosis and management of associated endocrine disorders. Nurses can also play a part in the ongoing care of these patients via education and support (Fig. 52.4).

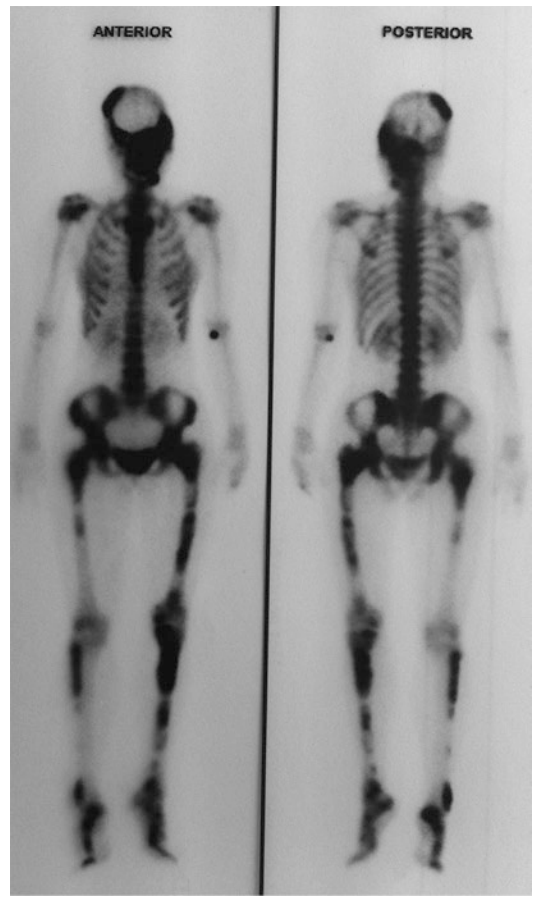


Fig. 52.4 Bone scan of a patient with polyostotic fibrous dysplasia demonstrating intense uptake in the skull, spine, ribs, femora, and tibiae

52.6 Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a genetic disorder of increased bone fragility and low bone mass.

52.6.1 Prevalence

With a prevalence of 1 in 12,000 to 15,000 children, it has a broad clinical phenotype, ranging from interuterine fractures and perinatal lethality to mild clinical forms with fractures.

52.6.2 Clinical Features

Clinical characteristics may include blue sclera, brittle teeth, and joint hypermobility. Most patients have a clinical mutation in 1 or 2 genes that encode the alpha chains of collagen type 1 (COL1A1 and COL1A2) (Rauch and Glorieux 2004). Autosomal dominant mutations in COL1A1 and COL1A2 account for approximately 90% of cases and they include OI type 1 to OI type IV. There is also rarer autosomal dominant and recessive mutations causing other forms of OI (Harrington et al. 2014).

Understanding the individual's OI type provides a starting point for understanding the person's health care needs. But due to all of the variable features, care for each person needs to be individualized. The fragility of bones in type I patients may be severe enough to limit physical activity, or so slight that individuals are unaware of any disability. Type II is lethal in the perinatal period. Type III is the most severe form in children. These patients are very short and have limb and spinal deformities due to multiple fractures. Patients with mild to moderate bone deformities and variable short stature are classified as OI type IV (Rauch and Glorieux 2004).

52.6.3 Diagnosis

The diagnosis of OI is based on typical clinical characteristics and radiological findings (including fractures and low bone density). Diagnosis can be straightforward in individuals with a positive family history or in whom several typical features are present. Though in the absence of affected family members and when bone fragility is not associated with obvious extra skeletal abnormalities, the diagnosis can be difficult. Furthermore child abuse is a frequent cause of fractures, with the highest incidence in the first year of life. Indeed clinical differentiation of mild OI from abuse can be problematic if there is no family history (Rauch and Glorieux 2004). Genetic testing can help confirm the diagnosis, though with more than 1500 dominant mutations, genetic sequencing is required (Harrington et al. 2014).

52.6.4 Management

The goals of treatment in OI are to maximize mobility, decrease bone pain and fractures. The degree of intervention needed depends on the severity of the clinical phenotype. Management should be multidisciplinary and includes surgical management, rehabilitation, and consideration of bisphosphonate therapy (Harrington et al. 2014). Endocrine nurses can play an important role for patients (and their families) with OI by helping to provide comprehensive coordinated care and promoting health and well-being.

52.7 Rickets

Although rickets was probably described some 2000 years ago, it was not until the industrial revolution and the swift movement of rural communities into heavily air-polluted and overcrowded cities of Europe that the disease became

a public health problem. The disease was rare in infants younger than 6 months of age, but with a peak prevalence of around 18 months. Early in the twentieth century the roles of cod liver oil and sunlight in the prevention and treatment of rickets was well recognized and in 1922, vitamin D was named as the factor responsible for preventing the condition (Pettifor 2005)

52.7.1 Clinical Features

Rickets is a disorder of mineralization of the bone matrix (osteoid) in growing bone before epiphyseal closure. It involves both the growth plate (epiphysis) and newly formed trabecular and cortical bone. Deficiencies of vitamin D, calcium, or phosphorus can result in defective bone mineralization (Favus 1999). The lack of mineralization results in typical appearances at the growth plate and in the gradual softening of bone, which leads to deformity in association with weight bearing (Wharton and Bishop 2003).

Signs and symptoms of rickets include muscle weakness, limb pain, increased tendency for fractures, dental problems, and skeletal deformities (esp. bowed legs once the child is walking). Changes in the skull can also occur causing frontal bossing and a distinctive "square headed" appearance (Wharton and Bishop 2003).

52.7.2 Pathophysiology

Simple nutrient deficiency, particularly of vitamin D is the most common cause of rickets. The major pathophysiological effect of vitamin D deficiency is a reduction in intestinal calcium absorption below that level need to maintain the child in a positive calcium balance large enough to meet the demands of a growing skeleton. The dietary content of vitamin D is generally insufficient to prevent vitamin D deficiency. Production of vitamin D in the skin under the influence of UV radiation is essential to maintain an adequate vitamin D status, unless foods are fortified, or supplements are taken (Pettifor 2005). Decreased calcium intake or intestinal absorption has been associated with rickets and the clinical manifestations are similar to those described for vitamin D deficiency. Phosphate deficiency has also been reported to cause rickets (Favus 1999).

The newborn infant is protected from vitamin D deficiency for the first few months of life if born to a vitamin D-replete mother as it crosses the placenta readily and has a half-life of approximately 3 weeks (Pettifor 2005). However many mothers of children with rickets have poor vitamin D status and such a mother gives her baby a low endowment of vitamin D. Her breast milk provides little of the vitamin and therefore in this situation, exclusive breast feeding can be a significant risk factor (Wharton and Bishop 2003). Children living in countries of high latitude are more at risk than those living near the equator. Additional factors include the degree of atmospheric pollution, the extent of skin coverage by clothing, the amount of skin pigmentation, and the time spent outside (Pettifor 2005).

52.7.3 Management

Prevention of rickets centers around vitamin D supplementation, public awareness, and vitamin D fortification (infant formula). These measures have been effective in dramatically reducing the prevalence of nutritional rickets in most developed countries. The mainstay of treatment for infants and children with nutritional rickets is the prompt correction of vitamin D deficiency and ensure sufficient calcium intake. As a result, symptoms can subside and healthy bones grow. Educating families at risk is critical to eradicate this preventable disease and certainly nurses have a key role in this regard with their work in community and hospital settings (Hartman 2000).

52.8 Part B: The child with a Congenital Bone Disorder

Anne L. Ersig

52.8.1 Pathophysiology and Genetics of Congenital Bone Disorders

Care of the child with a congenital bone disorder aligns with care for other conditions affecting bone and connective tissue. However, because congenital disorders are due to gene mutations, and have an earlier onset compared to other bone conditions (Bartl and Bartl 2017), there are additional considerations. Clinical signs and symptoms are not limited to bone and skeletal tissue, since the mutations causing congenital bone disorders can also affect cartilage and other connective tissue (Krakow 2015). Individuals with congenital bone disorders may present with symptoms affecting tissues other than bone, requiring careful attention to all body systems when establishing a diagnosis or evaluating the patient's current status. With earlier age at onset, congenital disorders may also have longer-term effects on growth and development, requiring additional monitoring and treatment.

Initial diagnosis typically occurs through radiologic examination, with confirmation provided by genetic analysis, particularly in families with established diagnoses and known mutations (Krakow 2015). Along with the genetic analysis, a thorough and careful history of the patient with a suspected congenital bone disorder is essential, to obtain important information on the clinical course of the patient and other potentially affected family members (Shapiro 2016). Although some signs and symptoms are common to multiple diagnoses, phenotypic variability is substantial, reflecting the specific condition and causative mutation. Mutation location and type are particularly important determinants of the clinical presentation. Phenotypes that are clinically grouped as one disease may be caused by mutations with different effects, resulting in different symptoms and presentation (Krakow 2015).

Even in families with known mutations and an established diagnosis, clinical severity and specific symptoms can vary. This requires careful evaluation of all family members at risk, since clinical manifestations in one may be more subtle compared to others. A minimum three-generation family history will provide essential information on the clinical phenotype of a family, providing guidance for future evaluations and clinical surveillance (Krakow 2015).

Somatic mosaicism, in which only a percentage of the body's cells carry the relevant mutation, is common in bone disorders, and may be one cause of variation in signs, symptoms, and severity within families (Krakow 2015). Parents who are somatic mosaics for a disease-causing mutation identified in an affected child often display more subtle clinical signs and symptoms. Gonadal mosaicism, in which a percentage of the germ cells have the mutation, is also seen. The percentage of cells with the mutation will affect risk to future pregnancies, with higher risk associated with a higher percentage of affected cells (Krakow 2015).

52.8.2 Genetic and Clinical Evaluation

While genes have been identified for many bone disorders, they are not often included in common prenatal genetic testing panels and tests; thus, when a child is the first to present with a possible congenital bone disorder, clinical identification typically occurs first, followed by genetic testing. Identifying the disease-causing mutation allows for confirmation of clinical diagnosis, and screening of potentially affected family members. One exception to this order of evaluation is in families with known mutations and a history of a congenital bone disorder; in

these cases, prenatal genetic and ultrasound screenings can help determine if a fetus is affected (Krakow 2015).

Although many cases of congenital bone disorders are seen in families with established histories, a substantial number of cases are caused by new mutations. Careful clinical evaluation and diagnosis, confirmatory genetic testing, mutation identification, and identifying a pattern of inheritance will provide essential information for the affected child and other family members. Management should also include referral to a genetic counselor.

52.8.3 Evaluation of Congenital Bone Disorders

Congenital bone disorders share some common clinical signs and symptoms, including short stature, abnormally shaped bones, and propensity to fracture (Shapiro 2016). Establishing a clinical diagnosis requires a thorough history and physical examination of all body systems. Important elements include fracture history, other skeletal and connective tissue signs and symptoms (e.g., scoliosis, hyperextensibility), pain, the neurological system, and the skin and cardiovascular systems. Neonates with a suspected congenital bone disorder will often have disproportion and skeletal abnormalities, including macrocephaly, rhizomelia, mesomelia, and brachydactyly (Krakow 2015). While fractures are common across disorders, providers should consider all possible causes, including accidental and non-accidental trauma (Bronicki et al. 2015). The shape of the skull, history of headaches, and examination of the jaw, teeth, sclerae, and ears are essential elements of the HEENT evaluation (Krakow 2015). The skin may exhibit fragility, propensity to bruise or scar easily, and changes in texture. Careful attention should also be paid to the cardiovascular system, as mutations may affect cardiac connective tissue and cause subtle signs and symptoms.

Radiological examination and evaluation provides information to support clinical diagnosis and ongoing management of a congenital bone disorder. Baseline X-rays of the entire skeleton should be acquired, for both initial evaluation and future comparison in case of injury or fracture. The spine and extremities should be examined for fractures in various states of healing, evidence of scoliosis in both planes, and growth plate abnormalities.

52.8.4 Treatment and Management of Congenital Bone Disorders

Treatment is targeted to the specific condition and its manifestations; given the wide variability in clinical presentation, there is similar variability in treatment choice and application. Treatment is often supportive and focuses on symptom and fracture management; curative treatment is not possible given the genetic cause of these conditions (Bartl and Bartl 2017). Many children with congenital bone disorders will have surgeries to correct chronic and acute bone problems; surgery may also be necessary following traumatic fracture or other events. Other common treatments across disorders include pain management, rehabilitation, physical therapy, occupational therapy, orthotic support, and gait evaluation. Depending on the specific diagnosis, referrals to other specialists (e.g., cardiovascular, pulmonary) may also be needed. In addition to pain medication, bisphosphonates are amongst the most frequently used medications for congenital bone disorders. These potent IV and oral drugs effectively raise bone density for most patients, although the clinical impact varies substantially.

52.8.4.1 Nursing Care of the Child with a Congenital Bone Disorder

Nurse practitioners play a key role in ensuring coordinated and comprehensive care for all children with chronic health conditions, including those with congenital bone disorders. Careful management by the multidisciplinary care team will support comprehensive and coordinated care for children with congenital bone disorders.

When assessing and examining a child with a congenital bone disorder, nurses and other clinicians should be aware of the high rate of fracture in these patients. Careful attention should be paid to patient position and any manipulation of the body or limbs; allowing the parent or child (depending on age) to move into a requested position will allow the nurse to avoid unanticipated movements that could result in fracture. As pain is a hallmark of many congenital bone disorders, proper positioning and cushioning during physical exams and other assessments is critical.

52.9 Exemplar Congenital Bone Disorders

Three congenital bone disorders are reviewed here as exemplar diagnoses, representing the breadth of phenotypes amongst congenital bone disorders: Paget's disease of bone, osteopetrosis, and osteogenesis imperfecta (OI). Beyond the three conditions that will be discussed in more detail below, other congenital bone disorders include Bruck syndrome, Cole-Carpenter syndrome, hypophosphatasia, idiopathic juvenile osteoporosis, and rickets (Bronicki et al. 2015).

Paget's disease of bone is typically an adult-onset condition; however, a rarer familial, inherited form of the disease presents in children. The phenotype is often severe, requiring careful management. Paget's disease is characterized by increased bone turnover due to high osteoclast activity. This leads to bone fragility and tendency to fracture; most adult cases of Paget's disease are diagnosed following fracture workup (Cundy 2016; Indumathi et al. 2009). Lytic wedges resulting from bone resorption are often evident on radiographs (Cundy 2016). High alkaline phosphatase levels also reflect higher osteoclast activity and bone resorption. Other clinical signs and symptoms include fissures and bone enlargement or other deformity; a smaller percentage of patients will experience hearing loss, leg length discrepancy, bowing of limbs, and an enlarged head (Michou and Brown 2016). Adult cases report significant impact on quality of life, usually due to pain and resulting diminished physical activity (Cundy 2016; Michou and Brown 2016). In addition to referral to rehabilitation and physical therapy, affected individuals may require assistive devices (e.g., canes). Bisphosphonates are frequently prescribed to increase bone density and reduce the number of fractures; an additional effect is relief of bone pain, which may be critical to help individuals with Paget's disease maintain movement and functionality (Michou and Brown 2016). In most cases, the number of affected bones is limited, although disease activity may increase slowly over time.

Osteopetrosis, in contrast to the other two conditions detailed here, is marked by significantly *increased* bone density. Reduced bone resorption by osteoclasts leads to high bone mass; resulting skeletal abnormalities predispose affected individuals to fractures, despite high bone density (Wu et al. 2017). Clinical presentation is similar to other bone disorders, and includes fractures, skeletal deformity, and dental abnormalities. Unique features of osteopetrosis are the associated narrowing of the marrow cavity and foramina due to bony overgrowth, potentially affecting hematologic and neurologic function (Wu et al. 2017). The highly variable clinical presentation of osteopetrosis is reflected in the clinical classifications, ranging from malignant autosomal recessive infantile to benign adult autosomal dominant, with an intermediate type also possible (Wu et al. 2017). As with many congenital bone disorders, clinical presentation can vary amongst affected family members due to incomplete mutation penetrance and variable expressivity.

Diagnosis requires, at a minimum, a skeletal survey to identify the extent of osteosclerosis. Genetic analyses should also be pursued due to the short- and long-term effects of various mutations (Wu et al. 2017). Mutation data also provide critical information on prognosis and potential clinical complications and sequelae. Additional non-genetic testing includes baseline laboratory evaluation and vision assessment. Bone density assessment is not required, nor is bone biopsy except in extreme cases.

As with other congenital bone disorders, a multidisciplinary team is best suited to manage the diverse symptoms and effects of osteopetrosis. Endocrine, ophthalmology, genetics, dentistry, orthopedic surgery, and other specialists as needed (e.g., otolaryngology, hematology, infectious disease, nephrology) should be consulted for their expertise. Other than supportive and symptom-driven treatment, most patients receive calcium and vitamin D supplementation, with transfusions only in cases of symptomatic low hemoglobin. Patients experiencing bone marrow failure due to narrowing of the marrow cavity may be considered for bone marrow transplant; however, this procedure will not be effective in all patients (Wu et al. 2017).

The final exemplar, ***osteogenesis imperfecta***, is a generalized connective tissue disorder with major manifestations in bone and a wide range of possible phenotypes. The hallmark features of OI are significant bone fragility, low bone density, and a tendency to fracture from minimal trauma. Recent advances have identified autosomal dominant and recessive mutations in multiple genes. Most cases (85–90%) are caused by mutations in one of the genes encoding type I collagen, which lead to either structural or quantitative changes in collagen, bone fragility, and high risk of fracture. The remainder are caused by mutations encoding genes that have substantial interactions with collagen, as well as genes supporting osteoblast differentiation (Forlino and Marini 2016). Mutation detection should follow a cascade pattern, starting with the genes for type I collagen, and expanding to include other genes if no mutation is identified (Forlino and Marini 2016). An exception to this is when there is more than one affected child in the family, as this indicates a greater likelihood of autosomal recessive inheritance of a non-collagen mutation. The most common structural defects in OI are caused by glycine substitution mutations in the type I collagen genes; these have varying phenotypic effects, depending on the mutation location and charge status of associated side chains. Other cases are caused by mutations in non-collagen genes that affect collagen processing and modification. While the clinical presentation may be similar, genetic analysis is critically important for family planning.

Clinical classification of OI is evolving beyond the original four types to include genetics, bone histomorphometry, and radiograph findings, and currently includes types I–VII (Biggin and Munns 2014). OI has a wide range of severity, from mild with limited impact on ambulation or stature, to lethal in the perinatal period. Regardless of clinical classification or type, careful and thorough clinical assessment is required, given the effects of OI on multiple body systems. Patients often demonstrate generalized osteopenia and other skeletal abnormalities (e.g., long bone bowing, rib deformities, vertebral compressions), blue sclerae, hearing loss, dentinogenesis imperfecta, and decreased pulmonary function (Forlino and Marini 2016). Differential diagnosis for mildly affected adults includes early-onset osteoporosis; for children with mild forms, non-accidental trauma must be considered.

As with other congenital bone disorders, the multisystem effects of OI require a multidisciplinary approach to management, including rehabilitation, physical and occupational therapy, pulmonary, cardiac, and otolaryngology specialists (Forlino and Marini 2016; Biggin and Munns 2014). Appropriate fracture management is critical, with referrals to a pediatric orthopedic surgeon for surgical intervention as needed. In addition, many patients are now treated with oral or intravenous bisphosphonates to improve bone density with positive effects on vertebral compression fractures but lack of support for prolonged use (Biggin and Munns 2014).

52.10 Conclusions

In conclusion, this chapter has detailed the wide spectrum of bone disorders, which are less common than osteoporosis; however, they need to be recognized in order to tailor appropriate therapy for the individual. While CKD-MBD has a wide spectrum of underlying pathophysiology with variable levels of bone turnover, demineralization

and quantity of bone, other disorders have a more homogenous pathophysiology, such as OI, Paget's disease, and fibrous dysplasia. The latter conditions can be managed with anti-resorptive therapy to manage associated pain in the case of Paget's and fibrous dysplasia and potentially fractures in the case of OI; however, there is a paucity of high quality evidence due to low numbers of patients with congenital disorders in particular. Thus, despite often presenting with bone pain or fractures, it is important to understand the underlying basis for the particular bone disorder, which can help tailor appropriate therapy for individuals with congenital or acquired bone disorders.

References

Albright FB, Hampton A, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. N Engl J Med. 1937;216(17):727–46.

Bartl R, Bartl C Classifying bone disorders according to pathophysiology. In Bone disorders (pp. 55–59); 2017.

Biggin A, Munns CF. Osteogenesis imperfecta: diagnosis and treatment. Curr Osteoporos Rep. 2014;12(3):279–88. https://doi.org/10.1007/s11914-014-0225-0.

Bronicki LM, Stevenson RE, Spranger JW. Beyond osteogenesis imperfecta: causes of fractures during infancy and childhood. Am J Med Genet C Semin Med Genet. 2015;169(4):314–27. https://doi.org/10.1002/ajmg.c.31466.

Cundy T. Clinical perspectives of Paget's disease of bone. In Advances in pathobiology and Management of Paget's disease of bone (pp. 1–14); 2016.

Del Fattore A, Cappariello A, Teti A. Genetics, pathogenesis and complications of osteopetrosis. Bone. 2008;42(1):19–29.

Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet J Rare Dis. 2008;3:12.

Favus M. Primer on the metabolic bone diseases and disorders of mineral metabolism. 4th ed. Philadelphia: Lippincott, Williams and Wilkins; 1999.

Forlino A, Marini JC. Osteogenesis imperfecta. Lancet. 2016;387(10028):1657–71. https://doi.org/10.1016/s0140-6736(15)00728-x.

Harrington J, et al. Update on the evaluation and treatment of osteogenesis imperfecta. Pediatr Clin N Am. 2014;61:1243–57.

Hartman J. Vitamin D deficiency rickets in children: prevalence and need for community education. Orthop Nurs. 2000;19(1):63–7.

Healy GM, et al. Paget's disease of bone: progress towards remission and prevention. Ir Med J. 2015;108(10):316–7.

Hooper, M, Lang F. Paget's disease of bone. A booklet presenting comprehensive information on Paget's disease. Sydney: Concord Hospital; n.d.

Indumathi CK, Dinakar C, Roshan R. Juvenile Paget's disease. Indian Pediatr. 2009;46:354–6.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int. 2009;76(Suppl 113):S1–S130.

Krakow D. Skeletal dysplasias. Clin Perinatol. 2015;42(2):301–19, viii. https://doi.org/10.1016/j.clp.2015.03.003.

Michou L, Brown JP. Paget's disease of bone. In Advances in pathobiology and management of Paget's disease of bone (pp. 105–18); 2016.

Pettifor JM. Rickets and vitamin D deficiency in children and adolescents. Endocrinol Metab Clin N Am. 2005;34(3):537–53.

Rauch F, Glorieux F. Osteogenesis imperfect. Lancet. 2004;363(9418):1377–85.

Selby PL, et al. Guidelines on the management of Paget's disease of bone. Bone. 2002;31(10–19):366.

Shapiro F. Skeletal dysplasias. In: Pediatric orthopedic deformities, volume 1. Basel: Springer; 2016. p. 255–409.

Singer FR. Paget's disease of the bone-genetic and environmental factors. Nat Rev Endocrinol. 2015;11:662–71.

Sobacchi C, Schulz A, Coxon FP, Villa A, Helfrich MH. Osteopetrosis: genetics, treatment and new insights into osteoclast function. Nat Rev Endocrinol. 2013;9(9):522–36.

Wharton B, Bishop N. Rickets. Lancet. 2003;362:1389–400.

Wu CC, Econs MJ, DiMeglio LA, Insogna KL, Levine MA, Orchard PJ, et al. Diagnosis and management of osteopetrosis: consensus guidelines from the Osteopetrosis Working Group. J Clin Endocrinol Metab. 2017;102(9):3111–23. https://doi.org/10.1210/jc.2017-01127.

Osteoporosis

53

Sherwin Criseno

Contents

53.1 **Background** 1007
53.1.1 Etiology of Osteoporosis 1008
53.1.2 Epidemiology 1010
53.1.3 Health and Economic Impact of Osteoporosis 1010

53.2 **Basic Pathophysiology** 1011
53.2.1 Bone Modeling and Remodeling 1011

53.3 **Diagnosis of Osteoporosis** 1014
53.3.1 Diagnostic Criteria 1014
53.3.2 Clinical Features and Complications of Osteoporosis 1014
53.3.3 Bone Densitometry 1015
53.3.4 Diagnostic Evaluation 1017

53.4 **Fracture Risk Assessment** 1017
53.4.1 Assessment of Risk 1017
53.4.2 Clinical Risk Factors 1018
53.4.3 The FRAX Tool 1019
53.4.4 Assessment Threshold for BMD Testing 1020
53.4.5 Intervention Threshold 1021
53.4.6 Assessment of Vertebral Fracture 1021

53.5 **Universal Recommendations for the Management of Osteoporosis** 1022
53.5.1 Calcium Intake 1022
53.5.2 Vitamin D Intake 1023
53.5.3 Smoking and Alcohol Intake 1024
53.5.4 Exercise 1024
53.5.5 Falls Prevention 1024

53.6 **Pharmacological Therapy** 1025
53.6.1 Bisphosphonates 1025
53.6.2 Denosumab 1027
53.6.3 Raloxifene 1027
53.6.4 Teriparatide 1028
53.6.5 Strontium Ranelate 1028

S. Criseno (✉)
University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
e-mail: Sherwin.criseno@uhb.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_53

53.6.6 Calcitriol 1028
53.6.7 Calcitonin 1028
53.6.8 Hormone Replacement Therapy (HRT) 1028

53.7 **Monitoring of Osteoporosis Treatment** 1029
53.7.1 Treatment Monitoring 1029
53.7.2 Bone Turnover Markers 1030
53.7.3 Osteonecrosis of the Jaw (ONJ) 1030
53.7.4 Atypical Femoral Fracture (AFF) 1030
53.7.5 Osteonecrosis of External Auditory Canal 1031

53.8 **Duration of Osteoporosis Treatment** 1031

References 1032

Abstract

Osteoporosis is considered as the most common bone disease in humans and represents a major public health issue as its prevalence is increasing with an aging population. Osteoporosis leads to nearly nine million fractures annually worldwide. It is a silent disease and its clinical significance lies in the fractures that arise from it. These fractures are usually sustained following minimal trauma also known as fragility fractures. It is estimated that more than one-third of adult women and one in five men will sustain one or more fragility fractures in their lifetime. Osteoporotic fragility fractures can cause substantial pain and severe disability, often leading to reduced quality of life. Additionally, hip and vertebral fractures are associated with decreased life expectancy. Hip fractures in particular, always requires hospitalization, is fatal in 20% of cases and causes permanent disability in 50% of those affected with only 30% of patients fully recover.

The substantial cost of fragility fractures is causing a significant toll on the already limited healthcare budget. In America, the cost of osteoporosis-related fractures was estimated at $17 billion in 2015 and is estimated to double and even triple by the year 2040. There are a number of effective therapies available for the prevention of fragility fracture in people thought to be at risk, or to prevent further fractures in those who have already sustained one or more fragility fractures. However, in order to effectively reduce the personal, medical, and economic burden of osteoporosis-related fractures, a robust system of fracture prevention, identification, and treatment of those who are at risk should be implemented.

Keywords

Osteoporosis · Fragility fractures · DXA
Postmenopausal · Bisphosphonate · Calcium
Vitamin D

Abbreviations

25(OH)D	25-hydroxyvitamin D
AFF	Atypical femoral fracture
BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover marker
CT	Computed tomography
DH	Department of Health, UK
DXA	Dual-energy X-ray absorptiometry
EMA	European Medicines Agency
EU	European Union
FRAX	Fracture risk assessment tool
GH	Growth hormone
GI	Gastrointestinal
GIO	Glucocorticoid-induced osteoporosis
HR-pQCT	High resolution peripheral quantitative computed tomography
HRT	Hormone replacement therapy
IGF-1	Insulin-like growth hormone factor-1
IL	Interleukin
IU	International unit
L	Liter
min	Minutes
ml/mL	Milliliter

MRI	Magnetic resonance imaging
ng	Nanogram
NICE	National Institute for Health and Care Excellence
nmol	Nanomole
NOF	National Osteoporosis Foundation
ONJ	Osteonecrosis of the jaw
pDXA	Peripheral dual-energy X-ray absorptiometry
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
QUS	Quantitative ultrasonometry
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
SD	Standard deviation
TGF	Transforming growth factor
UK	United Kingdom of Great Britain
USA	United States of America
VFA	Vertebral fracture assessment
VTE	Venous thromboembolism
WHO	World Health Organization

Key Terms

- **Bone formation**: osteoblastic activity in the formation of new bone.
- **Bone remodeling**: the process of bone growth and development involving shape and size changes.
- **Bone resorption**: osteoclastic bone breakdown with release of calcium into the blood.
- **Mineralization**: laying down minerals on a matrix of the bone.
- **Osteopenia**: is a loss of bone mass by bone densitometry and expressed as a *T* score −1 to −2.0 (NB. − is minus).
- **Osteoporosis**: is a loss of bone mass by bone densitometry and expressed as a *T* score > −2.0.
- **Reversal**: this couples bone resorption to bone formation by generating an osteogenic environment at the site of bone remodeling.
- **Vitamin D deficiency**: levels determined to increase the risk of osteoporosis and bone fracture.
- **Vitamin D insufficiency**: levels lower than recommended by endocrine clinical guidelines.

Learning Objective

This chapter focuses on the evaluation, management, and monitoring of patient with osteoporosis. Through the course of this chapter, the reader will be able to:

1. Understand the epidemiology, etiology, and basic pathophysiology of osteoporosis.
2. Identify and explore the different criteria used in assessing and diagnosing osteoporosis.
3. Understand and use the FRAX assessment tool.
4. Compare the different methods used in assessing bone mineral density.
5. Understand the currently available pharmacological and non-pharmacological therapies used in clinical practice for the management of osteoporosis.

53.1 Background

The World Health Organisation (WHO) defines osteoporosis as a "progressive skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (Kanis et al. 1994). It is a systemic skeletal disease which leads to compromised bone strength and a consequent increase in bone fragility and risk of fractures. The term osteoporosis has become synonymous with decreased bone mineral density (BMD) however; this feature is not always present. Bone strength is determined by several factors, including bone mass, size and shape of the bone, bone turnover, microarchitecture, cortical porosity, viability of osteocytes, and bone mineralization (BMJ 2018; Manolagas 2017a, b) (Fig. 53.1).

Osteoporosis is often overlooked and undertreated due mainly to the fact that it is so often clinically silent before manifesting in the form of fracture. In 2000, the Gallup survey by the National Osteoporosis Foundation found that 86% of women with osteoporosis had never discussed its prevention with their physicians, and not surprisingly, 91% wish they had known more

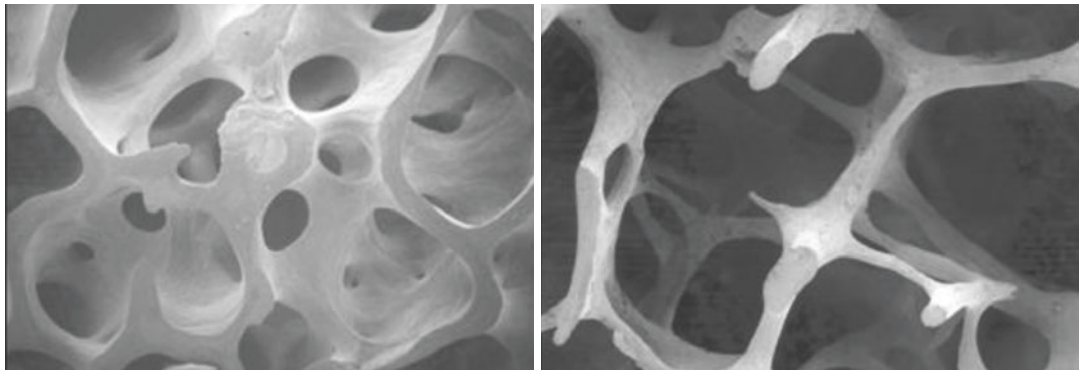


Fig. 53.1 Three-dimensional computed tomography images of cancellous bone from a normal individual (left picture) and a patient with osteoporosis (right picture). The picture illustrates how the trabeculae in patients with osteoporosis are thinner, disconnected, and further apart. Courtesy of Prof. David Dempster

Table 53.1 Types of primary osteoporosis (Source: Bethel 2017)

	Characteristics
Juvenile osteoporosis	• Usually occurs in children or young adults of both sexes • Normal gonadal function • Age of onset: usually 8–14 years • Hallmark characteristics: abrupt bone pain and/or fracture following trauma
Idiopathic osteoporosis	
(a) *Postmenopausal osteoporosis (type I osteoporosis)*	• Occurs in women with estrogen deficiency • Characterized by a phase of accelerated bone loss, primarily from trabecular bone • Fractures of the distal forearm and vertebral bodies are common
(b) *Age-associated or senile osteoporosis (type II osteoporosis)*	• Occurs in men and women as BMD gradually declines with advancing age • Represents bone loss associated with aging • Fractures occur in cortical and trabecular (wrist, vertebral, and hip)

steps to prevent this highly debilitating, yet avoidable disease (Marbury 2002). Failure to identify and educate patients at risk, and to implement preventive measures could lead to both tragic and costly consequences.

53.1.1 Etiology of Osteoporosis

Osteoporosis has been classified according to etiology and localization in the skeleton. In 1983, Riggs and Melton suggested that there are two distinct osteoporotic syndromes: type I or postmenopausal osteoporosis and type II or senile osteoporosis. Type 1 osteoporosis presents between the ages of 51 and 75 and is usually associated with vertebral crush fractures, forearm fractures, and accelerated trabecular bone loss mainly due to menopause. On the hand, type II osteoporosis presents over the age of 70 with vertebral wedging and femoral fracture, and is characterized by cortical and trabecular bone loss due to age-related factors (Riggs and Melton 1983).

While Riggs and Melton's classification may be useful in the studies of the pathogenesis and treatment of osteoporosis, its use is of limited value in the current clinical practice due to the heterogeneity and complexity of the condition. The most commonly used categories of osteoporosis are primary and secondary osteoporosis. Primary osteoporosis is the most common form of the disease and includes Rigg and Melton's type I and type II actors that can cause secondary osteoporosis as idensis (Table 53.1).

Table 53.2 Causes of secondary osteoporosis

Lifestyle factors	• Alcohol abuse • Anorexia nervosa/bulimia • Excess vitamin A • Falling • High salt intake • Immobilization • Inadequate physical activity • Low calcium intake • Malnutrition • Smoking (active or passive) • Vitamin D deficiency
Genetic factors	• Cystic fibrosis • Ehlers–Danlos syndrome • Gaucher's disease • Glycogen storage diseases • Hemochromatosis • Homocystinuria • Hypophosphatasia • Idiopathic hypercalciuria • Marfan syndrome • Menkes steely hair syndrome • Osteogenesis imperfecta • Parental history of hip fracture • Porphyria • Riley–Day syndrome
Hypogonadal state	• Androgen insensitivity • Athletic amenorrhea • Hyperprolactinemia • Klinefelter's syndrome • Premature menopause • Premature ovarian failure • Turner's syndrome
Endocrine disorders	• Adrenal insufficiency • Diabetes mellitus (Type 1 and 2) • Cushing's syndrome • Hyperparathyroidism • Central adiposity • Thyrotoxicosis
Gastrointestinal disorders	• Celiac disease • Gastric bypass • GI surgery • Inflammatory bowel disease • Malabsorption • Pancreatic disease • Primary biliary cirrhosis
Hematologic disorders	• Hemophilia • Leukemia and lymphomas • Monoclonal gammopathies • Multiple myeloma • Sickle cell disease • Systemic mastocytosis • Thalassemia
Rheumatologic and autoimmune diseases	• Ankylosing spondylitis • Lupus • Rheumatoid arthritis • Other rheumatic and autoimmune diseases
Central nervous system disorders	• Epilepsy • Multiple sclerosis • Parkinson's disease • Spinal cord injury • Stroke
Miscellaneous conditions and diseases	• Alcoholism • Amyloidosis • Chronic metabolic acidosis • Chronic obstructive lung disease • Congestive heart failure • Depression • End stage renal disease • Human immunodeficiency virus infection or AIDS • Hypercalciuria • Idiopathic scoliosis • Muscular dystrophy • Post-transplant bone disease • Sarcoidosis • Weight loss
Medications	• Aluminum (in antacids) • Anticoagulants (heparin) • Anticonvulsants (e.g., phenobarbital, phenytoin) • Aromatase inhibitor • Barbiturates • Cancer chemotherapeutic drugs • Cyclosporine A • Depo-medroxyprogesterone (Depo-Provera) • Glucocorticoid • Gonadotropin releasing hormone (GnRH) antagonists and agonists • Lithium • Methotrexate • Parenteral nutrition • Proton pump inhibitors • Selective serotonin reuptake inhibitors • Tacrolimus • Tamoxifen • Thiazolidinediones (e.g., pioglitazone [Acos]) • Thyroid hormone (in excess)

Secondary osteoporosis is characterized by having a clearly identifiable etiologic mechanism such as underlying disease, deficiency, or drug causes. There are several factors that can cause secondary osteoporosis as identified in Table 53.2.

53.1.2 Epidemiology

Osteoporosis is a major public health problem which leads to nearly nine million fractures annually worldwide (Johnell and Kanis 2006). In the United States of America (USA), the National Osteoporosis Foundation (NOF) estimated that more than ten million Americans have osteoporosis in 2004 (Cosman et al. 2014). In the UK, more than 500,000 new fragility fractures occur each year (Svedbom et al. 2013) while in Europe, all osteoporotic fractures account for 2.7 million fractures in men and women (Hernlund et al. 2013). In Australia, it was estimated that around two million people were affected by osteoporosis in 2001 (O'Neill et al. 2004).

Osteoporosis is a silent disease and its clinical significance lies in the fractures that arise. It is estimated that around 50% of white women and 20% of white men have osteoporosis-related fracture during their lifetime (Cosman et al. 2014). However, even though the risk of osteoporosis is lower amongst black men and women, the fracture risk is similar amongst those with osteoporosis (Cosman et al. 2014). In both men and women, the fracture risk increases with age (Khosla 2010). By age 60, half of white women have osteopenia or osteoporosis (Looker et al. 1997). Osteoporosis is a preventable disease and must be diagnosed and treated before any fracture occurs. Furthermore, effective treatments are available to reduce the risk of subsequent fractures following the first fractures. In primary care, prevention, diagnosis, and treatment should be the mandate when dealing with osteoporosis (Cosman et al. 2014).

Fragility fracture, also known as "low-level" or "low energy" trauma, is defined as fracture that results from mechanical force that would not normally result in fracture (Kanis et al. 2001b; NICE 2012). These fractures most commonly occur in the spine (vertebrae), hip (proximal femur), and wrist (distal radius). Fragility fractures may also occur in the arm (humerus), pelvis, ribs, and other bones. More than 20% of postmenopausal women have prevalent vertebral fractures (Melton et al. 1993). Osteoporotic fractures are fractures associated with low bone mineral density (BMD) and usually occur in the spine, forearm, hip, and shoulder (NICE 2012). In women, the lifetime probability of a fracture at any one of these sites is around 12% which exceeds that of breast cancer (Kanis et al. 2000). Collectively in Europe, all osteoporotic fractures account for 2.7 million fractures in men and women (Kanis et al. 2005a). In the USA, more than two million osteoporosis-related fractures occur annually and 70% of which occur in women (Burge et al. 2007).

53.1.3 Health and Economic Impact of Osteoporosis

Osteoporotic fragility fractures place an enormous medical and personal burden on individuals as well as economic toll on the nation. Often, patients with osteoporotic fractures suffer from substantial pain and disability which usually lead to reduced quality of life (NICE 2012). It is also well established that osteoporosis and the consequent fractures are associated with increased mortality, with the exemption of forearm fracture (Cooper et al. 1993). In Europe, in 2010, 43,000 deaths were thought to be causally related to osteoporotic fractures. It is estimated that 50% of fracture-related deaths in women were due to hip fractures, 28% to clinical vertebral and 22% to other fracture (Hernlund et al. 2013). Additionally, in Europe, osteoporosis accounts for more disability-adjusted life years compared with many non-communicable diseases including rheumatoid arthritis, Parkinson's disease, breast cancer, and prostate cancer (Johnell and Kanis 2006).

Hip fractures are associated with an 8.4–36% excess mortality within 1 year of fracture, with mortality higher in men than in women (Abrahamsen et al. 2009). Hip fractures nearly always lead to hospitalization, permanently disable 50% of those affected and are fatal in 20% of cases with only 40% of patients fully regaining their pre-fracture level of independence (USDHHS 2004; Sernbo and Johnell 1993). Most deaths following hip fracture occur in the first 3–6 months of which 20–30% are causally related to the fracture event itself (USDHHS 2004; Sernbo and Johnell 1993).

Furthermore, following a hip fracture, the risk of future fracture increases by 2.5-fold (Colón-Emeric et al. 2003). In the UK, projections suggest that the incidence of hip fracture will rise from 91,500 per year in 2015 to 101,000 in 2020 (DH 2006).

In the USA, the cost of osteoporosis-related fractures to the healthcare system was estimated at $17 billion in 2005 with hip fractures accounting for 14% of incident fractures and 72% of the total fracture costs (Burge et al. 2007). This cost is estimated to double and even triple by the year 2040. In the UK, the costs of fragility fractures to the healthcare economy were estimated at £1.8 billion in 2000, with the potential to increase to £2.2 billion by 2025, and with cost mainly relating to hip fracture care (Burge et al. 2001). In Europe, the cost of osteoporotic fractures was estimated at €38.7 billion in 2010 in 27 EU countries (Hernlund et al. 2013).

53.2 Basic Pathophysiology

The skeleton consists of specialized bone cells, water (which represents at least 25% of its wet weight), mineralized and unmineralized connective tissue matrix, and spaces that include the bone marrow cavity, vascular canals, canaliculi, and lacunae containing osteocytes. It is a highly dynamic organ that constantly undergoes changes and regeneration.

There are two major types of bone in the adult skeleton:

- Cortical bone constitutes the outer part of all skeletal structures. It is dense and compact and comprises 80% of the skeletal weight. The major function of cortical bone is to provide mechanical strength and protection. Additionally it also plays a part in metabolic responses, particularly when there is severe or prolonged mineral deficit.
- Trabecular, also known as cancellous, bone is found inside the long bones, particularly at the ends, throughout the bodies of the vertebrae, and in the inner portions of the pelvis and other large flat bones. Its main function is to provide mechanical support, particularly in the vertebrae. Compared with cortical bone, it is more metabolically active and provides the initial supplies of mineral in acute deficiency stated (Fig. 53.2).

Though dense cortical bone differs in architecture compared with spongy trabecular bone, they have the same molecular composition. Both types of bones have an extracellular matrix with mineralized and nonmineralized components. The composition and architecture of the extracellular matrix of cortical and trabecular bones determine their mechanical properties. In particular, bone strength is determined by collagenous proteins (tensile strength) and mineralized osteoid (compressive strength). The greater the concentration of calcium, the greater the compressive strength (Bono and Einhorn 2003).

53.2.1 Bone Modeling and Remodeling

The skeleton is sculpted to achieve its shape and size during growth and development. This is achieved through the process called modeling which involves complex processes that are influenced by locally and systemically produced factors and mechanical forces. Primarily, bone modeling involves the removal of bone from one site and deposition at a different site (Frost 1973). . During childhood and adolescence, linear growth occurs by the growth of cartilage at the end plates, followed by endochondral bone formation. The skeletal mass increases steadily through a combination of linear growth and changes in bone density and dimensions during childhood. During pubertal growth, there is a marked acceleration in bone mass acquisition, with 25–50% of the peak bone mass of adulthood accumulated during the pubertal growth spurt (Bailey et al. 1999, 2000). This is illustrated in Fig. 53.3, which shows the dramatic increase in the rate of bone mineral accrual in both sexes during the years of most rapid longitudinal growth.

Following skeletal maturity, the regeneration of bone continues in the form of a periodic replacement of old bone with new bone at the same location. This process is called remodeling,

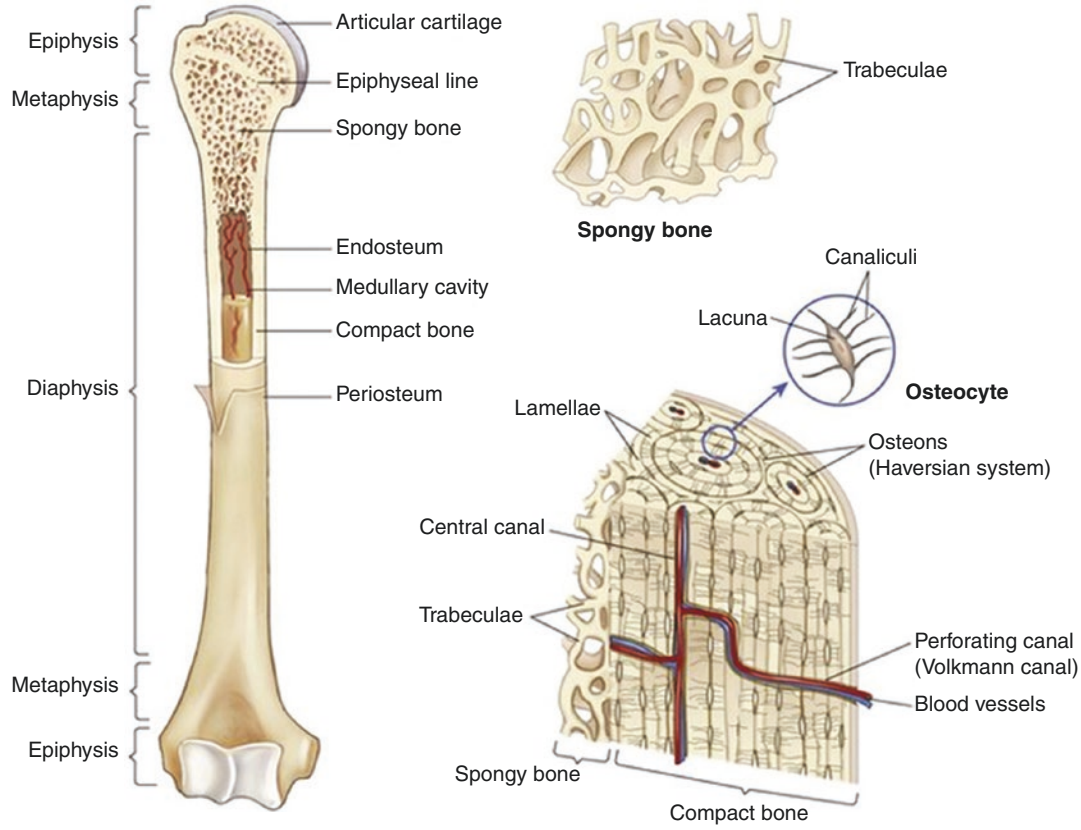


Fig. 53.2 Cortical bone and trabecular (cancellous) bone

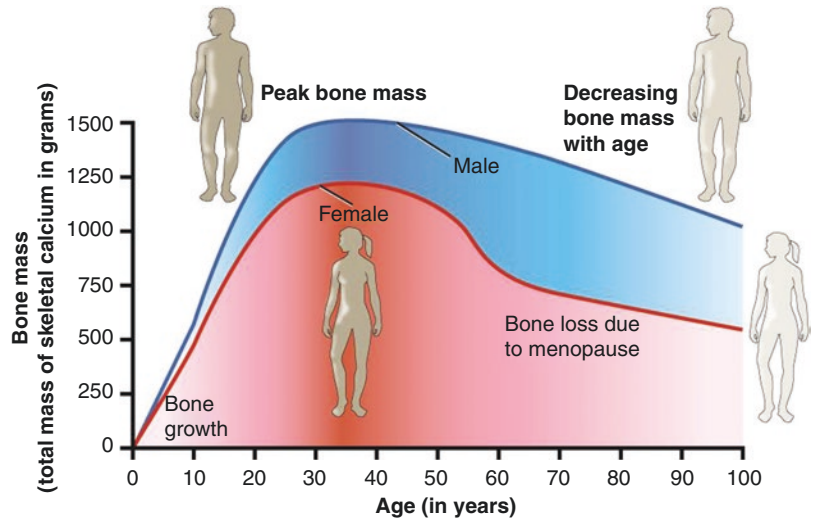


Fig. 53.3 General pattern of bone development (Bailey et al. 1999, 2000)

a complex process which is responsible for the complete regeneration of the adult skeleton every 10 years (Manolagas 2017a). The remodeling process is considered a preventive maintenance program responsible for: removing dead osteocytes; maintaining oxygen, nutrient supply and the appropriate level of matrix hydration; and repairing fatigue and damaged bone, thus preventing excessive aging and its consequences. During growth and development, remodeling also occurs in the growing skeleton with positive balance. The purpose of remodeling during this

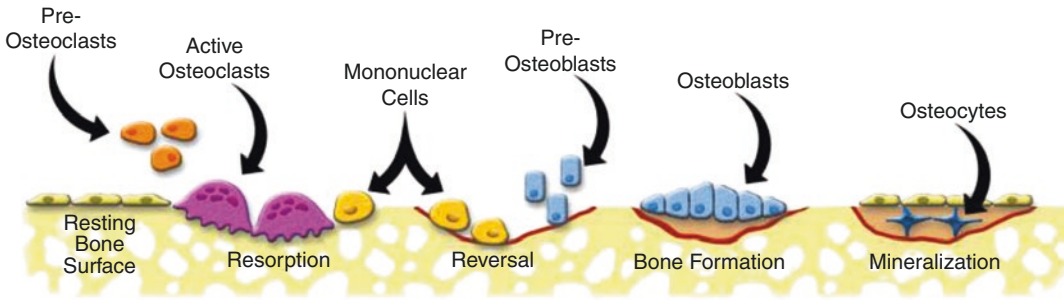


Fig. 53.4 Bone remodeling cycle

state is to expand the marrow cavity while increasing trabecular thickness (Parfitt 1994).

The remodeling cycle involves four stages: ***resorption, reversal, formation, and mineralization*** (Fig. 53.4). Each stage has different length. Resorption probably continues for about 2–3 weeks. The reversal phase may last up to 4 or 5 weeks, while formation can continue for 3–4 months until the new bone structural unit is fully formed. Bone remodeling occurs at discrete sites within the skeleton and proceeds in an orderly fashion with bone resorption always followed by bone formation, a phenomenon also known as coupling.

There are three main types of cells responsible for the bone remodeling process: ***osteoclast, osteoblast, and osteocytes***. Osteoclasts, derived from hematopoietic precursors, are responsible for bone resorption (removal of bone), whereas osteoblasts, from mesenchymal cells, are responsible for bone formation. Both of these processes are controlled by the osteocytes. Osteocytes, which are terminally differentiated osteoblasts embedded in mineralized bone, direct the timing and location of bone remodeling. Unlike osteoclasts and osteoblasts, osteocytes are deployed throughout the skeleton, are long-lived, and are far more abundant than either osteoclasts (1000 times) or osteoblasts (10 times) (Manolagas and Parfitt 2010).

There are several systemic hormones, cytokines, growth factors, and local signals that influence the birth, death, and function of bone cells. The major systemic regulators are the calcium-regulating hormones, parathyroid hormone (PTH), calcitriol, growth hormone/insulin-like growth factor-1 (IGF-1), glucocorticoids, thyroid hormones, and sex hormones. Other factors, such as IGFs, have both systemic and local effects, and some have mainly or solely local effects, particularly prostaglandins, transforming growth factor (TGF)-beta, bone morphogenetic proteins, and cytokines. The following act as Systemic and Local Regulators of Bone Cells: Parathyroid hormone, Calcitriol, Sex steroids, Calcitonin, Growth hormone and IGFs, TGF-beta, Glucocorticoids, Thyroid hormones, Cytokines, Fibroblast growth factors and other factors such as Prostaglandins, leukotrienes, and nitric oxide (Manolagas 2017a)

In osteoporosis, there is an imbalance in the coupling mechanism between osteoclasts and osteoblasts (Raisz 2005). Bone loss occurs when the balance in bone resorption and bone formation is altered, resulting in greater bone removal than replacement. Osteoclasts take weeks to resorb and osteoblasts require months to produce new bone which results in a net bone loss over time (Fig. 53.4). Rapid remodeling occurs with menopause and advancing age. During menopause, fracture risk is significantly increased because the newly produced bone is less densely mineralized, the resorption sites are temporarily unfilled, and the isomerization and maturation of collagen are impaired (Bono and Einhorn 2003).

Bone loss, together with other aging-related decline in functioning, leads to an increased risk of fracture. Fractures usually occur when weakened bone is overloaded, often caused by falls or certain activities of daily living. Figure 53.5 shows the pathogenesis of osteoporosis-related fractures which includes factors that relate to aging and sex steroid deficiency, as well as specific risk factors such as use of glucocorticoids which can cause decreased bone formation and bone loss, reduced bone quality, and disruption of micro-architectural integrity (Cosman et al. 2014).

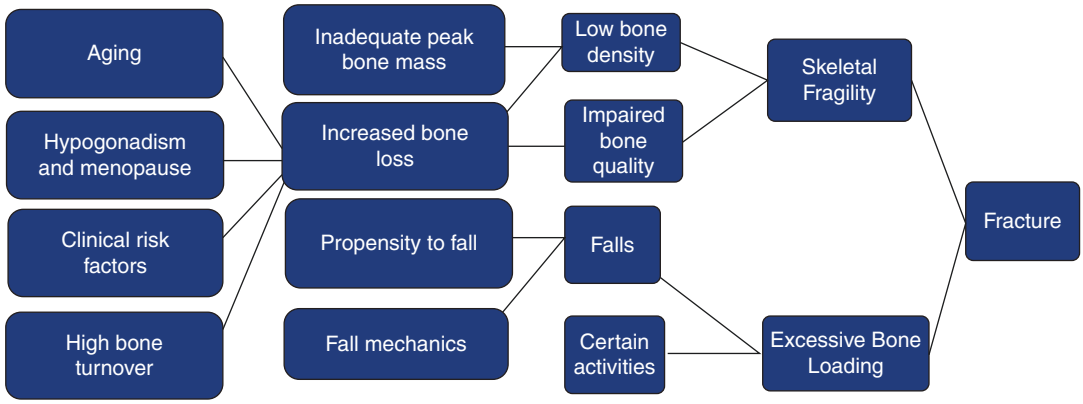


Fig. 53.5 Factors leading to osteoporosis-related fractures (Source: Cooper and Melton (2014) Epidemiology of osteoporosis. Trends Endocrinology and Metabolism. 3(6): 224–229)

53.3 Diagnosis of Osteoporosis

53.3.1 Diagnostic Criteria

Osteoporosis is diagnosed radiographically based on BMD assessment. BMD is most often described as a *T*- or *Z*-score, both of which represent units of standard deviation (SD). The *T*-score describes the number of SDs by which the BMD in an individual differs from the mean value expected in young healthy individuals. The *Z*-score on the other hand describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex. The operational definition of osteoporosis is based on the *T*-score for BMD. Based on the WHO criteria, osteoporosis is defined as a BMD, assessed at the femoral neck, that lies 2.5 standard deviations or more below the young female adult mean (*T*-score of less than or equal to −2.5 SD) (WHO 1994) (Table 53.3). These criteria, however, should not be applied in men younger than 50 years, children, or premenopausal women. The International Society for Clinical Densitometry recommends the use of the *Z*-score for these groups of individuals and *Z*-scores of −2.0 or less are considered below the expected range for age (Schousboe et al. 2013).

Clinically, osteoporosis can also be diagnosed if there is a low-trauma (e.g., fragility) fracture in the absence of other metabolic bone disease and independent of the BMD (*T*-score) value (Camacho et al. 2016).

Table 53.3 WHO criteria for classification of osteopenia and osteoporosis based on BMD

Category	BMD	*T*-score[a]
Normal	Within 1 SD of a young-adult reference population	−1.0 or above
Low bone mass (osteopenia)	Between 1.0 and 2.5 SD below that of a young-adult reference population	Between −1.0 and −2.5
Osteoporosis[b]	2.5 SD or more below that of a young-adult reference population	−2.5 or below
Severe or established osteoporosis	2.5 SD or more below that of a young-adult reference population	−2.5 or below with one or more fractures

[a]These definition and reference ranges are necessary to establish the presence of osteoporosis; however, it is important to note that they should not be used as the sole determinant of treatment decisions

[b]The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients. Decision regarding appropriate treatment should therefore be combined with clinical information as the fracture rates within this category vary widely

53.3.2 Clinical Features and Complications of Osteoporosis

Low BMD and fractures are the main clinical features of osteoporosis. As noted in the earlier section, there is a strong inverse relation between BMD and fracture risk with low BMD being the

major indicator for fracture risk. However, low BMD and/or bone loss are not associated with symptoms prior to fracture. Fracture is the single most important manifestation of postmenopausal osteoporosis (Camacho et al. 2016). In patients with osteoporosis, fractures are usually precipitated by low-energy injuries such as fall from standing height, otherwise known as fragility fracture. However, vertebral fractures may occur without a specific fall or injury even during routine daily activities.

Osteoporosis-related fractures can have serious consequences including pain, disability, deformity, and reduced quality and quantity of life (Johnell and Kanis 2006). Most major osteoporotic fractures are associated with reduced relative survival, with an impact persisting more than 5 years after the index event (Bliuc et al. 2009; Harvey et al. 2010). Hip fractures are the most serious consequence of osteoporosis with more than 50% of survivors unable to return to independent living and many require long-term nursing home care. Furthermore, women with hip fracture have an increased mortality of 12–20% during the following 2 years (Orwig et al. 2006). In Europe, osteoporosis accounts for more disability-adjusted life years than many non-communicable disease including rheumatoid arthritis, Parkinson's disease, breast cancer, and prostate cancer (Johnell and Kanis 2006).

53.3.3 Bone Densitometry

BMD is a measure of the amount of bone mass per unit volume (volumetric density), or per unit area (areal density), and both can be measured in vivo by densitometric techniques. There is a wide variety of techniques used to assess bone mineral and the most commonly used are based on X-ray absorptiometry (DXA). This technique is most widely used as the absorption of X-rays is very sensitive to the calcium content of the tissue of which bone is the important source. In bone DXA scan, the areal density (in grams per square centimeter) is measured rather than the true volumetric density as the scan is two dimensional. As determined in vitro on isolated bones, such as the vertebral body or proximal femur, areal BMD accounts for about two-thirds of the variance of bone strength (Kanis et al. 2013).

BMD measurements can provide diagnostic criteria, prognostic information on the probability of future fractures and a baseline on which to monitor the natural history of the treated or untreated patient. Table 53.4 summarizes the potential uses of BMD measurements in postmenopausal women.

DXA is versatile as it can be used to assess bone mineral density/bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fractures (Blake and Fogelman 2007). DXA can also be used for vertebral fracture assessment (VFA) as it can detect deformities of the vertebral bodies from T4 to L4. In research, DXA is also used to measure BMD of the whole bone as well as measurement of fat and lean mass. The use of DXA involves less radiation and more so, it is also less expensive compared with a conventional X-ray examination. In osteoporosis assessment, the use of bone mass measurement for prognosis depends upon accuracy. All densitometric techniques generally have high specificity but low sensitivity which varies with the cut-off chosen to designate high risk.

BMD testing is considered as the gold standard in diagnosing osteoporosis (Camacho et al. 2016). BMD has been clearly shown to correlate with bone strength and low BMD is the single best predictor of fracture risk (Camacho et al. 2016; Cosman et al. 2014). The risk of fracture increases approximately by twofold for each SD

Table 53.4 Potential uses of BMD measurements in postmenopausal women (Source: Camacho et al. 2016)

• Screening for osteoporosis
• Establishing the severity of osteoporosis or bone loss in patients with suspected osteoporosis (e.g., patients with fractures or radiographic evidence of osteopenia)
• Determining fracture risk (especially when combined with other risk factors for fractures)
• Identifying candidates for pharmacological intervention
• Assessing changes in bone density over time in treated and untreated patients
• Enhancing acceptance of, and perhaps adherence with, treatment
• Assessing skeletal consequences of diseases, conditions, or medications known to cause bone loss

Table 53.5 Indications of BMD testing (Adapted from: AACE/ACE Guidelines, 2016) (Camacho et al. 2016)

• All women ≥65 years old
• All postmenopausal women:
(a) with history of fracture(s) without major trauma
(b) with osteopenia identified radiographically
(c) starting or taking long-term systemic glucocorticoid therapy (≥3 months)
• Other peri- or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions:
(a) low body weight (<127 lb or body mass index of <20 kg/m^2)
(b) long-term systemic glucocorticoid therapy (≥3 months)
(c) family history of osteoporotic fracture
(d) early menopause (40 years old)
(e) current smoking
(f) excessive alcohol consumption
• Secondary osteoporosis

Table 53.6 Diagnostic evaluation of individuals with osteoporosis (Adapted from: Cosman et al. 2014)

A. Routine
• History and physical examination.
• Bone densitometry (DXA).
• Laboratory tests: blood cell count, sedimentation rate or C-reactive protein; serum calcium, albumin; creatinine; electrolytes; phosphate; liver enzymes; alkaline phosphatase; serum vitamin D, and thyroid function test.
B. Other test if clinically indicated may include:
b.1 Radiographic investigations:
• Lateral radiographs of lumbar and thoracic spine or DXA-based lateral vertebral imaging (VFA)
• Isotope bone scan
b.2 Laboratory investigations:
• Serum intact parathyroid hormone concentration (for possible primary or secondary hyperparathyroidism)
• Serum protein immunoelectrophoresis and urinary Bence Jones proteins (for possible myeloma)
• Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone (may indicate hypogonadism)
• Endomysial and/or tissue transglutaminase antibodies (may indicate celiac disease)
• Markers of bone turnover
• 24 h urinary free cortisol/overnight dexamethasone suppression test (for suspected cortisol hypersecretion)
• Serum tryptase, urine *N*-methylhistidine, or other tests for mastocytosis
• Genetics testing for unusual features that suggest rare metabolic bone diseases (e.g., osteogenesis imperfecta)
b.3 Bone biopsy (usually restricted to specialist centers).

decrease in BMD (Johnell et al. 2005). However, the low sensitivity of DXA is one of the reasons why widespread population-based screening with BMD is currently not widely recommended in postmenopausal women (WHO 1994). Therefore, it is crucial that the decision to measure BMD should be based on the individual's clinical risk factors and skeletal health assessment (Kanis et al. 2007). BMD measurement is not recommended in children, adolescents, or healthy young men or premenopausal women, unless there is a significant fracture history or there are specific risk factors for fracture or bone loss (e.g., long-term glucocorticoid therapy) (Camacho et al. 2016) (Table 53.5).

The preferred measurement sites for DXA are the total hip, femoral neck, and/or lumbar spine. These areas provide accurate and reproducible BMD measurements at important osteoporosis-associated fracture sites. Furthermore, most therapeutic studies, diagnostic criteria, and cost-effectiveness data have been based primarily on DXA measurements from these sites (Johnell et al. 2005; Stone et al. 2003). It is recommended that both hips are measured to prevent misclassification and to have a baseline for both hips in case a fracture or replacement occurs in one hip (Camacho et al. 2016). The distal one-third radius can also be used as a diagnostic site, especially when other preferred sites are not available. For optimal and most reliable comparative results, it is also recommended that BMD measurements are carried out using the same instruments and, ideally, by the same technician (ISCD 2015). Like any technologies, DXA has a number of limitations which should be recognized (Watts 2004). Additionally, DXA can provide inaccurate BMD readings due to several factors.

There are several other techniques available for BMD measurement, including quantitative computed tomography (QCT) for measurement of both central and peripheral sites, quantitative ultrasonometry (QUS), radiographic absorptiometry, peripheral dual-energy X-ray absorptiometry (pDXA), and single-energy X-ray absorptiometry (Table 53.6).

53.3.4 Diagnostic Evaluation

Assessment of individuals with osteoporosis should not only include BMD evaluation but also a comprehensive medical history, physical examination, exclusion of diseases that mimic osteoporosis, elucidation of the cause of osteoporosis, and the management of any associated morbidity. Some of the disorders contributing to bone loss/osteoporosis may be asymptomatic and require laboratory testing for confirmation. Due to the high prevalence of causes of secondary osteoporosis, laboratory testing should be considered for individuals diagnosed with osteoporosis (Gallagher and Sai 2010). If medical history, physical examination, or laboratory investigations suggest causes of secondary osteoporosis, additional confirmatory tests should be considered as listed in Table 53.6.

Bone turnover markers (BTMs), although cannot be used to diagnose osteoporosis, can provide a dynamic assessment of skeletal activity and can be useful predictors of fracture risk (Camacho et al. 2016). The bone formation osteoblast-derived products and the bone resorption products of collagen degradation are the most useful BTMs. BTMs are typically ordered to: aid in the decision of whether to start, continue, or stop treatment; determine medication compliance; or evaluate drug absorption or therapeutic efficacy (Vasikaran et al. 2011; Allende-Vigo 2007).

Summary

Key Points in Clinical Practice

- The diagnosis of osteoporosis is based on the BMD T-score of ≥−2.5 SD.
- BMD testing is considered the gold standard for diagnosing osteoporosis.
- The diagnostic criteria for BMD are the same in men and women because for any age and BMD at the femoral neck, the risk of hip fracture or major osteoporotic fracture is the same in both groups (De Laet et al. 1998; Johnell et al. 2005; Kanis et al. 2011).
- The T-score cannot be used interchangeably with different techniques and at different sites as the prevalence of osteoporosis, the risk of fracture, and proportion of individuals allocated to any diagnostic category vary.
- Osteoporosis in men younger than 50 years cannot be diagnosed based on BMD assessment alone (Schousboe et al. 2013).
- Low BMD and fractures are the main clinical features of osteoporosis.

53.4 Fracture Risk Assessment

53.4.1 Assessment of Risk

There is currently no universally accepted policy for population-based screening to identify patients with osteoporosis or those at high risk of fracture. Majority of patients are identified opportunistically using a case finding strategy on the discovery of a previous fracture or the presence of significant risk factors. The risk factors used for clinical assessment, as summarized in Table 53.7, are useful in assessing risk but in principle, any risk factor that alerts the clinician to the possibility of osteoporosis is a candidate (e.g., height loss, thoracic kyphosis, etc.).

Kanis et al. (2008) have proposed an approach to fracture risk assessment as shown in Fig. 53.6. The process starts with identification of clinical risk factors followed by assessment of fracture probability by FRAX®. Using this approach, patients who are categorized as high risk can be considered for treatment without the need for BMD testing. Therefore, not all individuals require BMD testing. Several guidelines in Europe and America recommend treatment in the absence of information on BMD in women with a previous fragility fracture (a prior vertebral or hip fracture in North America) (Camacho et al. 2016; Kanis et al. 2013; Papaioannou et al. 2010). Similarly, there will be instances where the probability of fracture is so low that a decision not to treat can be made without BMD. In clinical practice, BMD measurements are often requested by clinician for reasons other than to decide on treatment intervention, for example, as a baseline to monitor treatment.

Table 53.7 Clinical risk factors for fracture that are independent of age and BMD (Adapted with modification from: Compston et al. 2017)

A. Low body mass index (BMI) • Low BMI is a significant risk factor for hip fracture, but the value of BBMI in predicting other fracture is very much diminished when adjusted for BMD.
B. History of prior fracture • A history of prior fracture at a site characteristic for osteoporosis is an important risk factor for further fracture. • Fracture risk is approximately doubled in the presence of a prior fracture, including morphometric vertebral fractures. • The increase in risk is even more marked for more than one vertebral fracture.
C. Parental history of hip fracture • A parental history of hip fracture is a significant risk factor that is largely independent of BMD.
D. Smoking • Smoking is a risk factor that is part dependent on BMD.
E. Use of glucocorticoids • Glucocorticoids increase fracture risk in a dose-dependent manner. • The fracture risk conferred by the use of glucocorticoids is, however, not solely dependent upon bone loss and BMD-independent risk has been identified.
F. Alcohol • The relationship between alcohol intake and fracture risk is dose-dependent. • Where alcohol intake is on average two units or less daily, no increase in risk has been identified. • Intakes of three or more units daily are associated with a dose-dependent increase in fracture risk.
G. Rheumatoid arthritis • Rheumatoid arthritis increases fracture risk independently of BMD and the use of glucocorticoids
H. Diabetes mellitus • Recent evidence suggests that diabetes mellitus (particularly type 2) may also exert BMD-independent effects on fracture risk

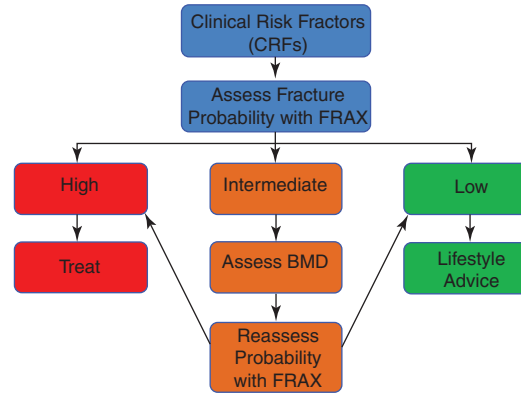


Fig. 53.6 Algorithm for the assessment of individuals at risk of fracture. (Adapted from: Kanis et al., 2008). Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. *Osteoporosis International* [online], **19**(10), pp. 1395–1408

53.4.2 Clinical Risk Factors

Osteoporosis is a preventable and treatable condition. However, as there are no warning signs prior to a fracture, majority of individuals with the condition are not diagnosed in time and therefore not given effective treatment during the early phase of the disease. A large number of risk factors for fracture have been identified but the focus of interest lies in those factors that contribute significantly to fracture risk over and above that provided by BMD and age (Table 53.7). In the case of causes of secondary osteoporosis (Table 53.2), the increase in fracture risk is presumed to be mediated by low BMD with the exception of glucocorticoid exposure and rheumatoid arthritis for which risks have been identified that are independent of BMD. Recent evidence also suggests that type 2 diabetes mellitus is an important independent risk factor (Kanis et al. 2012; Schwartz et al. 2011).

The following clinical risk factors for fracture are independent of age and BMD (Compston et al. 2017):

- Low body mass index (BM)
- History of prior fracture
- Parental history of hip fracture
- Smoking
- Use of glucocorticoids
- Alcohol
- Rheumatoid arthritis
- Diabetes mellitus

While BMD provides the foundation for the diagnosis of osteoporosis, its value in determining intervention threshold is less than optimal for several reasons. Firstly, the fracture risk varies markedly in different countries, but the *T*-score varies only by a small amount. Secondly, the signifi-

cance of any given *T*-score to fracture risk in women from any one country depends on age and the presence of clinical risk factors. Lastly, intervention thresholds will also be determined in part by the cost and benefits of treatment. These limitations have prompted the development of risk calculator engines that integrate several risk factors for fracture including the Garvan fracture risk calculator, QFracture™ and FRAX®. FRAX® is the most commonly used tool in clinical practice.

53.4.3 The FRAX Tool

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the WHO Collaborating Centre for Metabolic Bone Disease in Sheffield, UK. It calculates the 10-year probability of a major fracture (hip, clinical spine, humerus, or wrist fracture) and the 10-year probability of hip fracture. Fracture risk is calculated from known risk factors (Table 53.8) and

Table 53.8 Clinical risk factors used for the assessment of fracture probability in FRAX Tool (Source: https://www.sheffield.ac.uk/FRAX)

Age	The model accepts ages between 40 and 90 years. If ages below or above are entered, the program will compute probabilities at 40 and 90 year, respectively.
Sex	Male or female. Enter as appropriate.
Weight	This should be entered in kg.
Height	This should be entered in cm.
Previous fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors).
Parent fractured hip	This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no.
Current smoking	Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors).
Glucocorticoids	Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).
Rheumatoid arthritis	Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).
Secondary osteoporosis	Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease
Alcohol three or more units/day	Enter yes if the patient takes three or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8 to 10 g of alcohol. This is equivalent to a standard glass of beer (285 mL), a single measure of spirits (30 mL), a medium-sized glass of wine (120 mL), or one measure of an aperitif (60 mL) (see also notes on risk factors).
Bone mineral density (BMD)	(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm^2). Alternatively, enter the *T*-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center)

Notes on risk factors

- Previous fracture
  A special situation pertains to a prior history of vertebral fracture. A fracture detected as a radiographic observation alone (a morphometric vertebral fracture) counts as a previous fracture. A prior clinical vertebral fracture or a hip fracture is an especially strong risk factor. The probability of fracture computed may therefore be underestimated. Fracture probability is also underestimated with multiple fractures.
- Smoking, alcohol, glucocorticoids
  These risk factors appear to have a dose-dependent effect, i.e., the higher the exposure, the greater the risk. This is not taken into account and the computations assume average exposure. Clinical judgment should be used for low or high exposures.
- Rheumatoid arthritis (RA)
  RA is a risk factor for fracture. However, osteoarthritis is, if anything, protective. For this reason reliance should not be placed on a patient's report of "arthritis" unless there is clinical or laboratory evidence to support the diagnosis.
- Bone mineral density (BMD)
  The site and reference technology is DXA at the femoral neck. *T*-scores are based on the NHANES reference values for women aged 20–29 years. The same absolute values are used in men.

Fig. 53.7 FRAX—Fracture Risk Assessment Tool. Available at: https://www.sheffield.ac.uk/FRAX/

the femoral neck BMD can be optionally input to enhance the fracture risk prediction. The use of clinical risk factors in conjunction with BMD and age improves the sensitivity of fracture prediction without adverse effect on specificity (Kanis et al. 2007). Furthermore, the fracture probability is computed by taking into account both the risk of fracture and the risk of death. The tool has also been externally validated in independent cohorts. As the fracture probability differs markedly in different regions of the world, FRAX has been calibrated to those countries where the epidemiology of fracture and death is known. It is currently available for use in 63 countries (Table 53.8 and Fig. 53.7).

53.4.4 Assessment Threshold for BMD Testing

In clinical practice, the use of FRAX demands a consideration of the fracture probability at which to intervene, both for BMD testing (assessment threshold) and for treatment (intervention threshold). Due to the wide variation in the availability of DXA facility from country to country, most adopt a case finding strategy where individuals with clinical risk factors are identified for further assessment. However, most countries set their assessment threshold for BMD testing differently hence there is no unified recommendation for assessment threshold strategy.

53.4.5 Intervention Threshold

Similar to the assessment threshold, several strategies have been used to set the intervention thresholds with FRAX (Fig. 53.8). The intervention thresholds vary from country to country as the population risks (of fracture and death) vary and also due to several local factors including reimbursement issues, health economic assessment, willingness to pay for health care in osteoporosis, and access to DXA (Kanis et al. 2001a, 2002, 2013; Ström et al. 2011). Several guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test as a prior fracture can be considered to carry sufficient risk that warrant treatment. Using this premise, the intervention threshold can therefore be set at the "fracture threshold," an approach used in several countries including France, Switzerland, and the UK. For men, the same intervention threshold is recommended as the effectiveness and cost-effectiveness of intervention are broadly similar to that in women for equivalent risk (Kanis et al. 2011; Tosteson et al. 2008).

53.4.6 Assessment of Vertebral Fracture

Vertebral fracture is the most common osteoporotic fracture and indicates a high risk for future fractures, even when the *T*-score does not meet the threshold for osteoporosis. Hence, it is important to assess for prevalent vertebral fractures in high risk individuals as it can significantly change the diagnostic classification, estimated risk of future fractures, and clinical management (Camacho et al. 2016). However, the majority of vertebral fracture remains undetected unless specifically pursued by radiographic assessment (spine X-ray or VFA using DXA) (Lewiecki and Laster 2006). Assessment of vertebral fractures can be done using a standard lateral spine imaging or VFA by DXA. The latter delivers a significantly lower

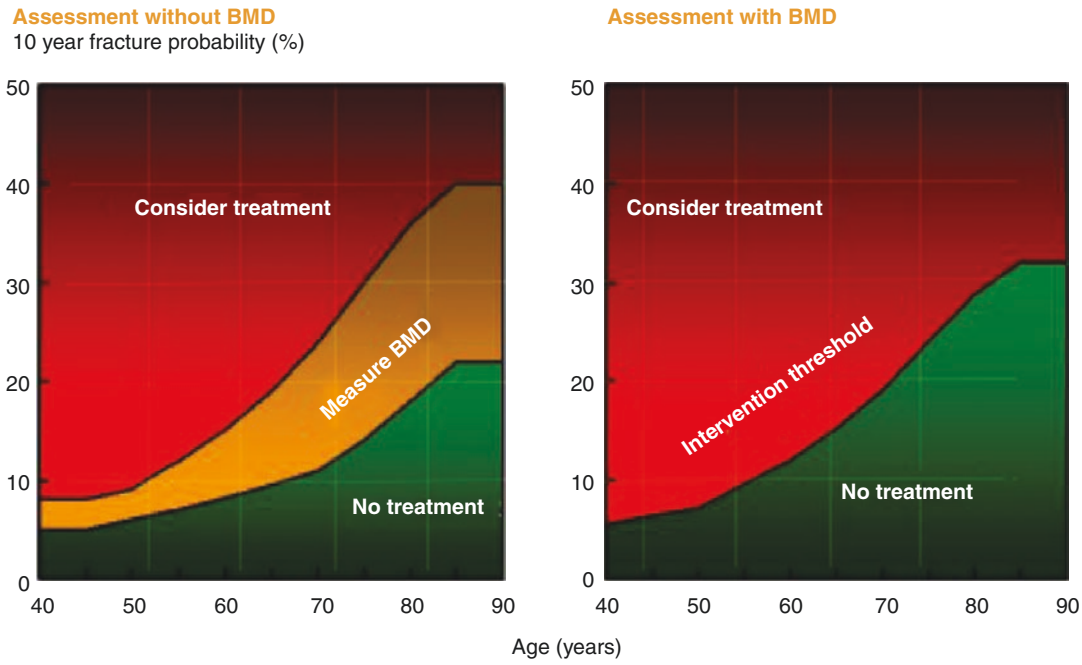


Fig. 53.8 Assessment and treatment thresholds with or without BMD (Source: Compston et al. 2009). Compston, J., Cooper, A., Cooper, C., Francis, R., Kanis, J.A., Marsh, D., McCloskey, E.V., Reid, D.M., Selby, P., Wilkins, M. and National Osteoporosis Guideline Group (NOGG) (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* [online], **62**(2), pp. 105–108

dose of radiation but performs comparably to traditional radiographs (Lewiecki 2010).

Vertebral fracture assessment should be considered in postmenopausal women and older men with:

(a) A history of ≥4 cm height loss.
(b) Self-reported but undocumented prior vertebral fractures.
(c) Kyphosis.
(d) Recent or current long-term oral glucocorticoid therapy (equivalent to ≥5 mg prednisolone per day for ≥3 months).
(e) BMD *T*-score of ≤−2.5 (In the USA, *T*-score of <−1.0 and one or more of the above as defined in a–d).

Assessment of vertebral fracture is also recommended in individuals with a history of non-vertebral fracture after the age of 50 years (Gallacher et al. 2007). In patients with back pain or unexplained height loss, vertebral fracture assessment should be considered if prevalent vertebral fractures would alter the clinical management. It is important to note that the sensitivity and reliability of standard radiography to assess BMD are poor and therefore, the technique should not be used to diagnose osteoporosis in routine clinical practice.

Summary

Key Points in Clinical Practice

- Assessment of fracture risk should be undertaken through comprehensive medical history and physical examination.
- Assessment of clinical risk factors should be completed including: history of prior fracture without major trauma after the age of 50, age ≥65, low BMI (<57.6 kg [127 lb]); family history of osteoporosis or fractures; smoking; early menopause, excessive alcohol intake (≤3 units daily); height loss or kyphosis, and risk for falling.
- Laboratory investigation to screen for secondary causes should be completed.
- Assessment of vertebral fractures by standard lateral spine imaging or VFA by DXA should be considered in high risk patients.
- BMD measurement by DXA should be considered in those at increased risk for osteoporosis and fractures and willing to consider pharmacological interventions.

53.5 Universal Recommendations for the Management of Osteoporosis

Several lifestyle interventions can be recommended to the general population to improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These lifestyle measures include increasing the level of physical activity, stopping smoking, reducing alcohol intake, reducing the risk of falls, and ensuring adequate intake of calcium and vitamin D. Some patients with osteoporosis may also benefit from physical therapy or other activities or even other non-pharmacological measures to improve strength and reduce the risk of falls and fractures.

53.5.1 Calcium Intake

Adequate calcium intake either through the diet or supplementation is a fundamental aspect of any osteoporosis management program and has been shown to result in small increase in BMD (Tai et al. 2015). However, convincing evidence that calcium alone reduces fracture risk is lacking (Bolland et al. 2015). A balanced diet rich in low-fat dairy products, fruits, and vegetables can provide the necessary calcium as well as other nutrients essential for good health. If adequate calcium cannot be achieved through dietary intake, supplementation is indicated up to the recommended daily intake. Prior to recommend-

ing calcium supplementation, it is important to obtain a dietary history to assess calcium intake. There are several simple dietary calcium intake calculators available online.

There are several preparations of calcium supplements. Generally, calcium carbonate tablet is the most commonly used in clinical practice as it requires the smallest number of tablets due to its substantial calcium content (40%). However, it is known to cause more gastrointestinal (GI) side effects (e.g., constipation and bloating) compared with calcium citrate (Camacho et al. 2016). The absorption of calcium carbonate is dependent on gastric acid concentration and is best absorbed when taken with food. Calcium citrate is usually more expensive compared with calcium carbonate and it also requires more tablets to achieve the desired dose due to its lower calcium content (21%). The absorption of calcium citrate, however, is not dependent on gastric acid and therefore less likely to cause GI side effects. It is recommended that calcium supplementation should not exceed 500–600 mg per dose to ensure optimal absorption (Camacho et al. 2016). For individuals requiring more than 600 mg calcium supplementation daily, the dose should be split accordingly. Calcium supplements are also available in chewable or soluble preparations.

53.5.2 Vitamin D Intake

Vitamin D plays a major role in calcium absorption, bone health, balance, muscle performance, and risk of falling. Evidence also suggests that optimal vitamin D status may enhance the response to bisphosphonate treatment, increase BMD, and prevent fractures (Bischoff-Ferrari et al. 2004). The recommended intake of vitamin D, as proposed by many international scientific organizations, is between 800 and 1000 IU per day for adults aged 50 years and older (Camacho et al. 2016; Compston et al. 2017; Cosman et al. 2014). For the general population, a reference intake of at least 400 IU daily for adults of all ages is recommended with 4000 IU as the safe upper limit (Ross et al. 2011; SACN 2016).

Vitamin D status is assessed by measuring serum 25-hydroxyvitamin D (25[OH]D). There is currently no international consensus on the optimal level of 25(OH)D. The American Endocrine Society recommends a serum 25(OH)D of ≥30 ng/mL (75 nmol/L) (Camacho et al. 2016) while the UK National Osteoporosis Guideline Group (NOGG) recommends a serum 25(OH)D of ≥20 ng/mL (50 nmol/L) (Compston et al. 2017). There remains a controversy as to the optimal upper limit for serum 25(OH)D and the evidence of the safety of higher levels in different populations is not conclusive. The American Endocrine Society recommends a reasonable upper limit of 50 ng/mL (125 nmol/L), a level based on the sun-exposed healthy young adults. The Institute of Medicine (IOM) and the National Osteoporosis Society, UK have proposed the following vitamin D thresholds in respect to bone health (Aspray et al. 2014; Ross et al. 2011):

- Serum 25(OH)D <30 nmol/L (12 ng/mL) is ***deficient***.
- Serum 25(OH)D of 30–50 nmol/L (12–20 ng/mL) ***may be adequate in some people.***
- Serum 25(OH)D of >50 nmol/L (20 ng/mL) is ***sufficient for almost the whole population***.

Many individuals are at high risk of vitamin D deficiency including those with malabsorption (e.g., celiac disease), other intestinal disease, chronic renal insufficiency, patient on medications that increase the breakdown of vitamin D (e.g., some anti-seizure medications), those who are housebound, chronically ill patients, with limited sun exposure, individuals with very dark skin, and obese individuals. Additionally, vitamin D deficiency is also common in patients with osteoporosis and hip fractures (Holick et al. 2005; LeBoff et al. 2008). Individuals who are vitamin D insufficient/deficient (serum 25[OH]D of <20 ng/mL [50 nmol/L]) may be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 6 weeks or 3200–5000 IU vitamin D_2 or vitamin D_3 daily for 8–12 weeks (Aspray et al. 2014; Holick et al. 2011; Ross et al. 2011). This regime should be followed by appropriate maintenance dose to maintain adequate target of

25(OH)D level. The usual maintenance dose of vitamin D is 800–2000 IU daily (Aspray et al. 2014; Camacho et al. 2016). Occasionally, a higher dose may be required of up to 4000 IU daily (e.g., obese individuals or those with malabsorption problem). When rapid correction of vitamin D deficiency is required, such as patients with symptomatic disease or those who are about to start treatment with potent antiresorptive agent (e.g., zoledronate or denosumab), a single fixed loading dose of 300,000 IU vitamin D may rapidly correct deficiency and improve vitamin D status for up to 3 months (Aspray et al. 2014; Kearns et al. 2013). This should be followed by appropriate regular maintenance therapy.

53.5.3 Smoking and Alcohol Intake

There is a strong body of evidence that proves cigarette smoking increases osteoporotic fracture risk and should therefore be avoided (Daniell 1976; Giampietro et al. 2010; Kanis et al. 2005b). All smokers should be advised to stop tobacco smoking as it is detrimental to the skeleton and to the overall health.

Excessive alcohol intake has also been associated with increased fracture risk (Kanis et al. 2005c). Patients with excessive alcohol intake should be recognized and treated. Moderate alcohol intake has been shown not to have negative effect on bone and may even be associated with slightly higher bone density or lower risk of fracture in postmenopausal women (Cosman et al. 2014). Postmenopausal women at risk of osteoporosis should be advised to consume not more than three units of alcohol daily. A unit of alcohol varies slightly in different countries from 8 to 10 g of alcohol per unit with one unit equivalent to 120 mL of wine, 30 mL of liquor, or 260 mL of beer (Kanis et al. 2005c).

53.5.4 Exercise

Strength training has been shown to result in small yet significant improvement in BMD from studies on early postmenopausal women. Regular weight-bearing and resistance exercise has several other health benefits including improving agility, strength, posture, and balance, which may also reduce the risk of falls. Therefore, regular weight-bearing exercise (e.g., walking for 30–40 min per session, 3–4 days a week) should be advocated lifelong at all ages. Other weight bearing exercises include jogging, Tai-Chi, stair climbing, dancing, and tennis (Cosman et al. 2014). Those individuals with severe osteoporosis should be advised to use caution when engaging in activities that involve forward spine flexion and rotation, lifting heavy weights, or even side bending of the trunk as these maneuvers exert compressive forces on the spine that can lead to fracture (Camacho et al. 2016).

53.5.5 Falls Prevention

Falls are the most common cause of fractures. Therefore, all patients should be assessed for falls risk and advised on fall prevention. An effective osteoporosis management program should include assessing and addressing modifiable risk factors for fall such as correcting visual impairment, minimizing the use of medications that alters alertness and balance, and improving the home environment (anchoring rugs and using non-skid mats, removing obstacles/clutter, improving lighting, installing handrails). Hip protectors may reduce the risk of hip fractures by protecting the individual in the event of a fall. However, its effectiveness due to poor acceptance and adherence by older people has not been established and evidence on its anti-fracture benefits is inconclusive (Gillespie et al. 2010).

Summary

Key Points in Clinical Practice

- Life style measures should be promoted to improve bone health including increasing the level of physical activity, smoking cessation, minimizing alcohol intake to not more three units per day, reducing the risk of falls, and ensuring

adequate dietary calcium intake and vitamin D status.
- Daily calcium intake of 700–1200 mg daily should be advised, either through diet or in the form of supplementation.
- Daily vitamin D dose of 800–1000 IU is recommended in postmenopausal women and men ≥50 years who are at increased risk of fracture.
- Falls risk assessment should be part of every osteoporosis management program including the provision of appropriate measures to reduce the risk of falling.

53.6 Pharmacological Therapy

Several pharmacological agents have been shown to be effective in reducing fracture risk in postmenopausal women with osteoporosis. Most agents used for the prevention and/or treatment of osteoporosis have been studied in women with postmenopausal osteoporosis with very limited data in glucocorticoid-induced osteoporosis and in men. Prior to initiating pharmacological treatment, clinician should counsel patient about the potential benefits as well as the potential risks of therapy. Table 53.9 summarizes the list of approved medications for the prevention and treatment of osteoporosis.

53.6.1 Bisphosphonates

Bisphosphonates are analogues of inorganic pyrophosphate that inhibit bone resorption. It was first introduced in the 1990s and is the most widely used drugs for treating osteoporosis.

53.6.1.1 Alendronate

- *Indications*: it is approved for the treatment of postmenopausal osteoporosis, prevention of postmenopausal osteoporosis, in men with osteoporosis, and for prevention and treatment of glucocorticoid-induced osteoporosis.
- *Dose and Preparation*: 70 mg tablet or effervescent/soluble tablet once weekly.
- *Special Instructions:* alendronate should be taken after an overnight fast and at least 30 min before the first food or drink (other than water) of the day or any other oral medi-

Table 53.9 Approved medications in North America and Europe by approval indication (Adapted with modification from: Adler et al. 2016)

Drug	Postmenopausal osteoporosis		Men	GIO
	Prevention	Treatment		
Anti-remodeling agents				
Alendronate	✓	✓	✓	✓
Ibandronate	✓	✓	–	–
Risedronate	✓	✓	✓	✓
Zoledronic acid	✓	✓	✓	✓
Bazedoxifene[a]	✓	✓	–	–
Lasofoxifene[a]	✓	✓	–	–
Raloxifene	✓	✓	–	–
Denosumab	✓	✓	✓	✓
Teriparatide	✓	✓	✓	✓
Denosumab	–	✓	✓	–
Estrogen	✓	–	–	–
Conjugated estrogen/bazedoxifene	✓	–	–	–
Calcitonin[b]	–	✓	–	–
Tibolone[a]	✓	–	–	–
Anabolic agents				
Teriparatide	–	✓	✓	✓
Others				
Strontium ranelate[c]	✓	✓	✓	–

Abbreviation: *GIO* Glucocorticoid-induced osteoporosis
[a]Only approved in Europe
[b]Withdrawn from EU market and available in US for restricted conditions
[c]Approved in Europe with restrictions

cations or supplementations (including calcium). Tablet should be swallowed whole with a glass of plain water (~200 mL) while the patient is sitting or standing in an upright position. Patient should not lie down for 30 min after taking the tablet.
- *Side effects:* upper gastrointestinal symptoms, bowel disturbance, headaches, and musculoskeletal pain.
- *Contraindications:* hypersensitivity to alendronate or to any of the excipients, hypocalcaemia, patient unable to follow the dosing regimen for oral use (e.g., inability to remain upright for 30 min), the presence of anatomic or functional esophageal abnormalities (e.g., active esophageal disease, achalasia, stricture, or dysmotility), and the presence of documented or potential GI malabsorption (e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.).

53.6.1.2 Ibandronate

- *Indications*: it is approved for the treatment of postmenopausal osteoporosis. Oral preparation is also approved for the prevention of postmenopausal osteoporosis.
- *Dose and Preparation*: 150 mg tablet once a month or 3 mg as an intravenous injection every 3 months.
- *Special Instructions:* ibandronate should be taken after an overnight fast and 1 h before the first food or drink (other than water) of the day or any other oral medications or supplementations (including calcium). Tablet should be swallowed whole with a glass of plain water (180–240 mL) while the patient is sitting or standing in an upright position. Patient should not lie down for 1 h after taking the tablet. Patient should note chew or suck the tablet due to the potential risk of oropharyngeal ulceration. In case of a missed dose, patient should be instructed to take one ibandronic acid 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. If the next scheduled dose is within 7 days, patient should be advised to wait until their next dose and continue taking one tablet once a month as originally scheduled.
- *Side effects:* side effects with the oral preparation include upper gastrointestinal symptoms and bowel disturbance. Intravenous administration may be associated with an acute phase reaction, characterized by an influenza-like illness; this is generally short-lived and typically occurs only after the first injection.
- *Contraindications:* hypersensitivity to ibandronic acid or to any of the excipients, hypocalcaemia, abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia, and inability to stand or sit upright for at least 60 min.

53.6.1.3 Risedronate

- *Indications*: it is approved for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture, for the treatment of established postmenopausal osteoporosis, prevention of postmenopausal women with increased risk of osteoporosis, and for the treatment of osteoporosis in men at high risk of fractures.
- *Dose and Preparation*: 5mg tablet once daily or 35 mg tablet once weekly.
- *Special Instructions:* risedronate absorption is affected by food, thus it should be taken at least 30 min before the first food or drink (other than water) of the day or any other oral medications or supplementations (including calcium). If taking the tablet before breakfast is not practical, risedronate should be taken at least 2 h before and at least 2 h after any food, medicinal product, or drink (other than plain water), or at least 30 min before going to bed. The tablet should be swallowed whole in an upright position with a glass of plain water (≥120 mL). Patient should be advised not to lie down for 30 min after taking the tablet.
- *Side effects:* side effects with the oral preparation include upper gastrointestinal symptoms and bowel disturbance. Intravenous administration may be associated with an acute phase reaction, characterized by an influenza-like

illness; this is generally short-lived and typically occurs only after the first injection.
- *Contraindications:* hypersensitivity to risedronate acid or to any of the excipients, hypocalcaemia, pregnancy and lactation, and severe renal impairment (creatinine clearance of <30 mL/min).

53.6.1.4 Zoledronic Acid

- *Indications*: it is approved for the treatment of osteoporosis in postmenopausal women and adult men at increased risk of fracture (including those with a recent low-trauma hip fracture) and treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in postmenopausal women and adult men at increased risk of fracture.
- *Dose and Preparation*: 5 mg as intravenous infusion once yearly.
- *Special Instructions:* zoledronic acid should be administered by intravenous infusion over a minimum period of 15 min. The incidence of post-dose acute phase reaction can be reduced with the administration of paracetamol or ibuprofen shortly following zoledronic acid administration.
- *Side effects:* acute phase reaction characterized by an influenza-like illness; this is generally short-lived and typically occurs only after the first infusion, and gastrointestinal symptoms.
- *Contraindications:* hypersensitivity to zoledronic acid, to any bisphosphonate, or to any of the excipients; hypocalcaemia; severe renal impairment with creatinine clearance of <35 mL/min; pregnancy; and breast-feeding.
- should be evaluated for an incomplete femur fracture.

53.6.2 Denosumab

Denosumab is a fully humanized monoclonal antibody that prevents Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) from binding to its receptor, RANK, thereby reducing the differentiation of precursor cells into mature osteoclasts and decreasing the function and survival of activated osteoclasts.

- *Indications*: it is approved for the treatment of osteoporosis in postmenopausal women and men at increased risk of fracture, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.
- *Dose and Preparation*: 60 mg as subcutaneous injection once every 6 months.
- *Special Instructions:* administration should be performed by an individual who has been adequately trained in injection techniques.
- *Side effects:* skin infection, predominantly cellulitis, and hypocalcaemia.
- *Contraindications:* hypersensitivity to the active substance or to any of the excipients and hypocalcaemia.

53.6.3 Raloxifene

Raloxifene is a selective estrogen receptor modulator and inhibits bone resorption.

- *Indications*: it is approved for the treatment and prevention of osteoporosis in postmenopausal women and for the reduction of risk of breast cancer in women with postmenopausal osteoporosis or at high risk of breast cancer.
- *Dose and Preparation*: 60 mg tablet once daily.
- *Special Instructions:* raloxifene may be taken at any time of the day without regard to meals.
- *Side effects:* leg cramps, edema and vasomotor symptoms.
- *Contraindications:* hypersensitivity to the active substance or to any of the excipients, women with child-bearing potential, active or past history of venous thromboembolic events (VTE) (including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis), hepatic impairment (including cholestasis), severe renal impairment, unexplained uterine bleeding, and patients with signs and symptoms of endometrial cancer.
- *Special Precautions and Warning:* raloxifene should be used with caution in women with a history of stroke or with risk factors for stroke.

53.6.4 Teriparatide

Teriparatide is a recombinant human parathyroid hormone (PTH) [1-34]. When administered intermittently, it has anabolic skeletal effects which are most marked in cancellous bone.

- *Indications*: it is approved for the treatment of osteoporosis in postmenopausal women and men at high risk of fracture, and for the treatment of osteoporosis associated with systemic glucocorticoid therapy in women and men at increased risk of fracture.
- *Dose and Preparation*: 20 μg as subcutaneous injection once daily. Maximum total duration of treatment is 24 months.
- *Special Instructions:* Patient must be trained to use the proper injection techniques.
- *Side effects:* nausea, pain in limb, headache, and dizziness.
- *Contraindications:* hypersensitivity to the active substance or to any of the excipients, pregnancy and breast-feeding, pre-existing hypercalcemia, severe renal impairment, metabolic bone disease (including hyperparathyroidism and Paget's disease of the bone) other than primary osteoporosis or glucocorticoid-induced osteoporosis, unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, and patients with skeletal malignancies or bone metastases.
- *Special Precautions and Warning:* in normocalcemic patients, slight and transient elevations of serum calcium concentrations have been observed following teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 h and return to baseline by 16–24 h after each dose of teriparatide. If blood samples for serum calcium measurements are taken, this should be done at least 16 h after the most recent injection. Routine calcium monitoring during therapy is not required.

53.6.5 Strontium Ranelate

Strontium ranelate is approved for treatment of osteoporosis in some countries but not in the USA. Due to evidence of increased cardiovascular risk and occurrence of severe Stevens–Johnson reaction, the European Medicines Agency (EMA) has recommended that strontium ranelate use be restricted to patients who cannot be treated with other medicines approved for osteoporosis, and that these patients be evaluated regularly by their doctor and that treatment is stopped if patients develop heart or circulatory problem such as uncontrolled high blood pressure or angina (EMA 2014).

53.6.6 Calcitriol

Calcitriol (1,25-dihydroxyvitamin D) is the active form of vitamin D and is approved for the treatment of established osteoporosis in an oral dose 0.25 μg twice daily. It acts mainly by inhibiting bone resorption. It has been shown to reduce vertebral fracture risk in postmenopausal women with osteoporosis but effects on non-vertebral and hip fractures have not been demonstrated. It is contraindicated in patients with hypercalcemia or with metastatic calcification. Serum calcium and creatinine levels should be monitored at 1, 3, and 6 months after starting treatment and at 6 monthly intervals thereafter.

53.6.7 Calcitonin

Injectable and nasal spray recombinant salmon calcitonin are approved by the FDA for the treatment of postmenopausal osteoporosis. The approved dosage of injectable calcitonin for treatment of postmenopausal osteoporosis is 100 IU daily given subcutaneously or intramuscularly. The approved dose of nasal spray calcitonin is 200 IU (1 spray) daily. The main contraindication is drug hypersensitivity and skin testing is recommended before use in patients with suspected sensitivity to the drug.

53.6.8 Hormone Replacement Therapy (HRT)

HRT is available in a wide variety of oral preparations including estrogen only, progestin only, and combination estrogen-progestin. Some of

these agents are approved for the prevention of osteoporosis in postmenopausal women at high risk of fracture. Conjugated equine estrogens 0.625 mg daily ± 2.5 mg/day of medroxyprogesterone acetate have been shown to reduce vertebral, non-vertebral, and hip fracture in postmenopausal women not selected on the basis of low bone density or high fracture risk (Rossouw et al. 2002). Due to the unfavorable risk/benefit balance in older postmenopausal women, the use of HRT for osteoporosis is generally restricted to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms (NCCWCH 2015). In women who are appropriately treated with long-term estrogen (or combination estrogen/progestin) therapy, these agents be sufficient, but they can also be used in conjunction with other medications for osteoporosis (e.g., bisphosphonate, denosumab, or teriparatide) based on clinical needs and judgment (Camacho et al. 2016).

Summary

Key Points in Clinical Practice

- There is a range of pharmacological agents currently used in clinical practice for the prevention and treatment of osteoporosis.
- The most commonly used agents are the bisphosphonates (e.g., alendronate, ibandronate, risedronate, zoledronic acid), raloxifene, agents derived from parathyroid hormone (teriparatide), RANK ligand inhibitor (denosumab), and HRT.
- Strontium ranelate is still available in some countries but its use is restricted to patients who cannot be treated with other medicines approved for osteoporosis.
- Teriparatide is the only pharmacological agent currently used that offers an "anabolic effect."

53.7 Monitoring of Osteoporosis Treatment

53.7.1 Treatment Monitoring

The goal of pharmacological therapy in a patient with osteoporosis is to significantly increase bone strength and ultimately, to prevent fractures. However, there is no treatment that can completely eliminate the risk. As discussed in the previous section, BMD is one of the major determinants of bone strength, and low BMD is an important predictor of fracture. However, there remains a controversy as to whether the long-term anti-fracture efficacy of anti-osteoporotic drugs depends on the extent to which treatment can increase or maintain BMD (Rabenda et al. 2011). A fracture during therapy with bone-targeted medication does not necessarily mean a treatment failure. The occurrence of fracture should trigger re-evaluation of risk factors for fracture and possibly a change in treatment strategies (Camacho et al. 2016).

It is important to monitor patients while receiving pharmacological therapy in order to identify those who have significant bone loss (Camacho et al. 2016). Serial BMD is commonly used to monitor the response to osteoporosis treatment. In patients on treatment, stable or increasing BMD at the spine and hips indicates a satisfactory response (Lewiecki and Watts 2008). In patients with significant reduction in BMD while on treatment should be evaluated for noncompliance, secondary causes of osteoporosis, or use of medications that might cause bone loss (Lewiecki and Rudolph 2002). The frequency of BMD testing should be individualized depending on the patient's clinical state. It is recommended that BMD monitoring occur at the same facility, using the same machine and, if possible, the same technologist as with the previous DXA. Additionally, DXA scan should involve the same regions of interest for both the spine and hip or the distal one-third radius when the spine and hip sites are not evaluable.

The definition of treatment failure remains controversial and complex. However, there is a consensus that treatment failure should be considered in patients with significant decrease on

BMD or recurrent fractures and are compliant to therapy (Lewiecki and Rudolph 2002) For this group of patients, it is recommended that they are re-evaluated for compliance with medication, secondary causes of bone loss, new medications or diseases that can cause bone loss. Particular emphasis should be given to monitoring of compliance to treatment as poor compliance usually occurs early (after 6–7 months) (Tosteson et al. 2003).

53.7.2 Bone Turnover Markers

In the last 25 years, several bone turnover markers (BTMs) have been developed that reflect the overall rate of bone formation and/or bone resorption. However, the utility of BTMs in clinical practice is limited by high in vivo and assay variability, poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision-making (Camacho et al. 2016). Nonetheless, BTMs can provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Significant reductions in BTMs are seen with antiresorptive therapy (e.g., bisphosphonates) and have been associated with fracture reduction, and significant increases indicate good response to anabolic therapy (e.g., teriparatide) (Lewiecki and Watts 2008). The most useful bone turnover markers for the monitoring of osteoporosis are procollagen I N-terminal extension peptide (P1NP) for assessing bone formation and C-telopeptide breakdown products (especially serum CTX) to assess bone resorption (Kanis et al. 2012).

53.7.3 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw occurs only very rarely in patients receiving bisphosphonate or denosumab therapy for osteoporosis. It was first reported in patients with advanced cancer receiving high-dose bisphosphonate therapy (at an annual dose ten times higher than that used to treat osteoporosis). The estimated incidence of ONJ is much lower with oral or intravenous bisphosphonate therapy for osteoporosis, on the order of 1/10,000 to 1/100,000 patients per year (Bilezikian 2006; Khan et al. 2015; Khosla et al. 2007; Woo et al. 2006). Its incidence is also low with denosumab for osteoporosis at 1–90 per 100,000 patient-years of exposure (Khan et al. 2016). Risk factors for osteonecrosis of the jaw include poor oral hygiene, dental disease, dental interventions, cancer, chemotherapy, or glucocorticoid therapy (Khan 2015).

Patients being considered for bisphosphonate or denosumab treatment should be advised to have oral examination by a dentist. For patients with significant dental issues, delaying the initiation of bisphosphonate or denosumab therapy until the dental issues have been corrected should be considered. For patients already receiving bisphosphonates or denosumab who require invasive dental procedures, there is no evidence that discontinuing or interrupting treatment will change the outcome or reduce the risk of ONJ. Nonetheless, stopping treatment should at least be considered for patients undergoing extensive invasive dental procedures (e.g., extraction of several teeth) (Camacho et al. 2016).

53.7.4 Atypical Femoral Fracture (AFF)

AFF, mainly of the subtrochanteric and diaphyseal regions of the femoral shaft, is another rare adverse event seen with long-term bisphosphonate therapy (>5 years duration) but is rarely (if at all) seen with the higher doses used in advanced cancer (Bauer et al. 2000; Lenart et al. 2009; Shane et al. 2014). Because of their radiologic appearance, such fractures are sometimes described as “chalk stick.” AFF usually occurs after little or no trauma and significant number of cases occur bilaterally (Shane et al. 2014). In a review by the American Society for Bone and Mineral Research (ASBMR) Task Force on the management of osteoporosis in patients on long-term bisphosphonates, a systematic search of the literature revealed wide variation in the

relative risk of atypical femoral fractures associated with bisphosphonate use (between 2- and 128-fold), but the absolute risk was consistently low, ranging between 3.2 and 50 cases/100,000 person-years (Shane et al. 2010). This estimate appeared to double with prolonged duration of bisphosphonate use (>3 years, median duration 7 years), and declined with discontinuation (Gedmintas et al. 2013; Shane et al. 2010, 2014).

All patients receiving bisphosphonate or denosumab therapy who present with persistent unexplained thigh, groin or hip pain should have imaging studies of the femur (X-ray, isotope scanning or MRI) (Camacho et al. 2016; Compston et al. 2017). If an atypical fracture is present, the contralateral femur should also be evaluated radiographically. In patients with confirmed AFF, bisphosphonate or denosumab therapy should be discontinued; weight-bearing activity should be restricted and alternative options considered where appropriate (Compston et al. 2017). In most cases, surgical treatment with intramedullary nailing is recommended.

53.7.5 Osteonecrosis of External Auditory Canal

In recent years, another rare side effect of long-term bisphosphonate and denosumab treatment, osteonecrosis of the external auditory canal, has been reported. This rare adverse event is not very well-known and there are currently no diagnostic methods or treatments for the condition. The previously reported cases were diagnosed based on the patients' medication history and computed tomography (CT) findings and were surgically treated via the removal of inflammatory granulation tissue and necrotic bone and the reconstruction of the ear canal with cartilage (Takahashi et al. 2017). The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates or denosumab who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate/denosumab treatment.

Summary

Key Points in Clinical Practice

- It is important to monitor patients while receiving pharmacological therapy in order to identify those who have significant bone loss.
- BMD testing and BTMs measurement are useful tools during treatment monitoring.
- In patients with significant reduction in BMD or those who continue to fracture while on treatment, should be re-evaluated for noncompliance, secondary causes of osteoporosis, or use of medications that might cause bone loss.
- Osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and osteonecrosis of auditory canal have been seen following long-term treatment with bisphosphonate and denosumab. Signs and symptoms associated with these rare complications of antiresorptive treatment should be assessed and monitored on all patients during therapy.

53.8 Duration of Osteoporosis Treatment

Due to the rare adverse effects of long-term bisphosphonate and denosumab therapy, particularly osteonecrosis of the jaw and atypical femoral fractures, the optimal duration of pharmacological therapy remains controversial. It is known that bisphosphonates are retained in bone for varying periods of time, therefore "treatment holidays" may be considered as its beneficial effects may persist for some time after cessation

of treatment. Treatment holidays involves stopping the treatment for some years and the need to reinstitute therapy is reassessed regularly (Compston et al. 2017). As most pivotal clinical trials on the use of bisphosphonate in postmenopausal women have been limited to a duration of 3 years, recommendations for longer term use and for "treatment holidays" are based on limited evidence from extension studies (Adler et al. 2016). As for men, there is currently no evidence on which to base recommendations from.

The ASBMR Task Force has proposed an algorithm for the monitoring of long-term bisphosphonate therapy in postmenopausal women. It is important to note that the optimal duration of a "treatment holiday" has not been established and guidelines vary from different countries. The UK NOGG for instance has proposed a slightly different management approach. Nonetheless, all guidelines stressed the importance of patient selection and monitoring during "treatment holidays." During "treatment holidays," consider resuming therapy in patients who experience fracture or show significant BMD decline. In some cases, the rise in bone resorption markers (e.g., CTX) to pre-treatment levels might be a signal that the "holiday" should be over; however, this may not apply to patients with osteoporosis who had low bone resorption markers before treatment initiation (Camacho et al. 2016).

References

Abrahamsen B, Van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int [online]. 2009;20(10):1633–50.

Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American society for bone and mineral research. J Bone Miner Res [online]. 2016;31(1):16–35.

Allende-Vigo MZ. The use of biochemical markers of bone turnover in osteoporosis. Puerto Rico health sciences journal [online]. 2007;26(2):91–5.

Aspray TJ, Bowring C, Fraser W, Gittoes N, Javaid MK, Macdonald H, Patel S, Selby P, Tanna N, Francis RM. National osteoporosis society vitamin D guideline summary. Age Ageing [online]. 2014;43(5):592–5.

Bailey D, McKay H, Mirwald R, Crocker P, Faulkner R. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. J Bone Miner Res [online]. 1999;14(10):1672–9.

Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. J Bone Miner Res [online]. 2000;15(11):2245–50.

Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, Musliner T, Freedholm D. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. Arch Intern Med [online]. 2000;160(4):517–25.

Bethel M. Osteoporosis 14 November 2017-last update. Medscape. 2017. https://emedicine.medscape.com/article/330598-overview#showall. Accessed 2 Jan 2018.

Bilezikian JP. Osteonecrosis of the jaw-do bisphosphonates pose a risk? N Engl J Med [online]. 2006;355(22):2278.

Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med [online]. 2004;116(9):634–9.

Blake GM, Fogelman I. Role of dual-energy X-ray absorptiometry in the diagnosis and treatment of osteoporosis. J Clin Densitom. 2007;10(1):102–10.

Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA [online]. 2009;301(5):513–21.

BMJ. Osteoporosis. BMJ Best Practice. 2018. https://bestpractice.bmj.com/topics/en-gb/85.

Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR. Calcium intake and risk of fracture: systematic review. BMJ (Clinical research ed.) [online]. 2015;351:h4580.

Bono CM, Einhorn TA. Overview of osteoporosis: pathophysiology and determinants of bone strength. Eur Spine J [online]. 2003;12(2):S90–6.

Burge RT, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK: projections for 2000–2020. J Med Econ [online]. 2001;4(1–4):51–62.

Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J Bone Miner Res [online]. 2007;22(3):465–75.

Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, Kleerekoper M, Lewiecki EM, Miller PD, Narula HS. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. Endocr Pract [online]. 2016;22(s4):1–42.

Colón-Emeric C, Kuchibhatla M, Pieper C, Hawkes W, Fredman L, Magaziner J, Zimmerman S, Lyles

KW. The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies. Osteoporos Int [online]. 2003;14(11):879–83.

Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P, Wilkins M, National Osteoporosis Guideline Group (NOGG). Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas [online]. 2009;62(2):105–8.

Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis J, McCloskey E, Poole K. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos [online]. 2017;12(1):43.

Cooper C, Melton LJ III. Epidemiology of osteoporosis. Trends Endocrinol Metab. 1992;3(6):224–9.

Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ III. Population-based study of survival after osteoporotic fractures. Am J Epidemiol [online]. 1993;137(9):1001–5.

Cosman F, De Beur S, LeBoff M, Lewiecki E, Tanner B, Randall S, Lindsay R. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int [online]. 2014;25(10):2359–81.

Daniell HW. Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. Arch Intern Med [online]. 1976;136(3):298–304.

De Laet CE, Van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Hip fracture prediction in elderly men and women: validation in the Rotterdam study. J Bone Miner Res [online]. 1998;13(10):1587–93.

Department of Health. Hospital episode statistics (England). 2006.

European Medicines Agency (EMA). Protelos/Osseor to remain available but with further restrictions. London. 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Protelos_and_Osseor/human_referral_prac_000025.jsp&mid=WC0b01ac05805c516f.

Frost HM. Bone remodeling and its relationship to metabolic bone diseases [online]. Springfield: Charles C. Thomas Publisher; 1973.

Gallacher S, Gallagher A, McQuillian C, Mitchell P, Dixon T. The prevalence of vertebral fracture amongst patients presenting with non-vertebral fractures. Osteoporos Int [online]. 2007;18(2):185–92.

Gallagher JC, Sai AJ. Bone: is screening for secondary causes of osteoporosis worthwhile? Nat Rev Endocrinol [online]. 2010;6(7):360.

Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. J Bone Miner Res [online]. 2013;28(8):1729–37.

Giampietro PF, McCarty C, Mukesh B, McKiernan F, Wilson D, Shuldiner A, Liu J, LeVasseur J, Ivacic L, Kitchner T, Ghebranious N. The role of cigarette smoking and statins in the development of postmenopausal osteoporosis: a pilot study utilizing the Marshfield Clinic Personalized Medicine Cohort. Osteoporos Int. 2010;21(3):467–77.

Gillespie WJ, Gillespie LD, Parker MJ Hip protectors for preventing hip fractures in older people. Cochrane Database Syst Rev [online]. 2010;(10):CD001255.

Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol [online]. 2010;6(2):99.

Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos [online]. 2013;8(1–2):136.

Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab [online]. 2005;90(6):3215–24.

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab [online]. 2011;96(7):1911–30. https://academic.oup.com/jcem/article/96/7/1911/2833671. Accessed 23 June 2018.

International Society for Clinical Densitometry (ISCD). 2015 ISCD official positions—adult June 18, 2015-last update Middletown, CT: ISCD. 2015. https://www.iscd.org/official-positions/2015-iscd-official-positions-adult/. Accessed 21 Apr 2018.

Johnell O, Kanis J. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int [online]. 2006;17(12):1726–33.

Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D. Predictive value of BMD for hip and other fractures. J Bone Miner Res [online]. 2005;20(7):1185–94.

Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res [online]. 1994;9(8):1137–41.

Kanis J, Johnell O, Oden A, Sernbo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B. Long-term risk of osteoporotic fracture in Malmö. Osteoporos Int [online]. 2000;11(8):669–74.

Kanis J, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int [online]. 2001a;12(12):989–95.

Kanis J, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int [online]. 2001b;12(5):417–27.

Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res [online]. 2002;17(7):1237–44.

Kanis J, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby A. The components of excess mortality after hip fracture. Bone [online]. 2003;32(5):468–73.

Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N. Assessment of fracture risk. Osteoporos Int [online]. 2005a;16(6):581–9.

Kanis JA, Johnell O, Odén A, Johansson H, De Laet C, Eisman J, Fujiwara S, Kroger H, McCloskey E, Mellstrom D. Smoking and fracture risk: a meta-analysis. Osteoporos Int [online]. 2005b;16(2):155–62.

Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture. Osteoporos Int [online]. 2005c;16(7):737–42.

Kanis J, Odén A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int [online]. 2007;18(8):1033–46.

Kanis J, McCloskey E, Johansson H, Strom O, Borgstrom F, Odén A. Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. Osteoporos Int [online]. 2008;19(10):1395–408.

Kanis JA, Bianchi G, Bilezikian JP, Kaufman J, Khosla S, Orwoll E, Seeman E. Towards a diagnostic and therapeutic consensus in male osteoporosis. Osteoporos Int [online]. 2011;22(11):2789–98.

Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD. FRAX® with and without bone mineral density. Calcif Tissue Int [online]. 2012;90(1):1–13.

Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster J. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int [online]. 2013;24(1):23–57.

Kearns M, Alvarez J, Tangpricha V. Large, single-dose, oral vitamin D supplementation in adult populations: a systematic review. Endocr Pract [online]. 2013;20(4):341–51.

Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res [online]. 2015;30(1):3–23.

Khan A, Morrison A, Cheung A, Hashem W, Compston J. Osteonecrosis of the jaw (ONJ): diagnosis and management in 2015. Osteoporos Int [online]. 2016;27(3):853–9.

Khosla S. Update in male osteoporosis. J Clin Endocrinol Metab [online]. 2010;95(1):3–10.

Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res [online]. 2007;22(10):1479–91.

LeBoff M, Hawkes W, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J. Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. Osteoporos Int [online]. 2008;19(9):1283–90.

Lenart B, Neviaser A, Lyman S, Chang C, Edobor-Osula F, Steele B, Van Der Meulen M, Lorich D, Lane J. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int [online]. 2009;20(8):1353–62.

Lewiecki EM. Bone densitometry and vertebral fracture assessment. Curr Osteoporos Rep. 2010;8(3):123–30.

Lewiecki EM, Laster AJ. Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. J Clin Endocrinol Metab [online]. 2006;91(11):4215–22.

Lewiecki E, Rudolph L. How common is loss of bone mineral density in elderly clinical practice patients receiving oral bisphosphonate therapy for osteoporosis? J Bone Miner Res [online]. 2002;17(Suppl 2):S367.

Lewiecki E, Watts N. Assessing response to osteoporosis therapy. Osteoporos Int [online]. 2008;19(10):1363–8.

Looker AC, Orwoll ES, Johnston CC, Lindsay RL, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP. Prevalence of low femoral bone density in older US adults from NHANES III. J Bone Miner Res [online]. 1997;12(11):1761–8.

Manolagas SC. Normal skeletal development and regulation of bone formation and resorption. May 06 2016-last update. Wolters Kluwer. 2017a. https://www.uptodate.com/contents/normal-skeletal-development-and-regulation-of-bone-formation-and-resorption?search=osteoporosis,%20pathophysiology&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4. Accessed 2 Jan 2018.

Manolagas SC Pathogenesis of osteoporosis. Wolters Kluwer. 2017b. https://www.uptodate.com/contents/pathogenesis-of-osteoporosis. Accessed 2 Jan 2018.

Manolagas SC, Parfitt AM. What old means to bone. Trends Endocrinol Metab [online]. 2010;21(6):369–74.

Marbury K. Strengthening communication on bone health. GALLUB News; 2002.

Melton L, Lane A, Cooper C, Eastell R, O'fallon W, Riggs B. Prevalence and incidence of vertebral deformities. Osteoporos Int [online]. 1993;3(3):113–9.

National Collaborating Centre for Women's and Children's Health (NCCWCH) (UK). Menopause, 23. London: National Institute for Health and Care Excellence (UK); 2015.

National Institute for Health and Care Excellence (NICE). Osteoporosis: assessing the risk of fragility fractures [online]. NICE CG146; 2012.

O'Neill S, MacLennan A, Diamond T, Ebeling P, Findlay D, Flicker L, Markwell A, Nowson C, Pocock N, Sambrook P. Guidelines for the management of postmenopausal osteoporosis for GPs. Aust Fam Physician [online]. 2004;33:910–9.

Orwig DL, Chan J, Magaziner J. Hip fracture and its consequences: differences between men and women. Orthop Clin North Am [online]. 2006;37(4):611–22.

Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD, Scientific Advisory Council of Osteoporosis Canada.

2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ [online]. 2010;182(17):1864–73.

Parfitt A. Osteonal and hemi-osteonal remodeling: the spatial and temporal framework for signal traffic in adult human bone. J Cell Biochem [online]. 1994;55(3):273–86.

Rabenda V, Bruyère O, Reginster J. Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. Osteoporos Int [online]. 2011;22(3):893–901.

Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Investi [online]. 2005;115(12):3318–25.

Riggs BL, Melton LJ. Evidence for two distinct syndromes of involutional osteoporosis. Am J Med [online]. 1983;*75*(6):899–901.

Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab [online]. 2011;96(1):53–8.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–33.

Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 international society for clinical densitometry position development conference on bone densitometry. J Clin Densitom [online]. 2013;16(4):455–66.

Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA [online]. 2011;305(21):2184–92.

Scientific Advisory Committee on Nutrition (SACN). Vitamin D and Health. London: Public Health England; 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf.

Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. Osteoporos Int [online]. 1993;3(3):148–53.

Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res [online]. 2010;25(11):2267–94.

Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res [online]. 2014;29(1):1–23.

Stone KL, Seeley DG, Lui L, Cauley JA, Ensrud K, Browner WS, Nevitt MC, Cummings SR. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res [online]. 2003;18(11):1947–54.

Ström O, Borgström F, Kanis JA, Compston J, Cooper C, McCloskey EV, Jönsson B. Osteoporosis: burden, health care provision and opportunities in the EU. Arch Osteopor [online]. 2011;6(1–2):59–155.

Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteopor [online]. 2013;8(1–2):137.

Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ (Clinical research ed.) [online]. 2015;351:h4183.

Takahashi M, Yamamoto Y, Kuroyanagi H, Seino Y, Kojima H. Bisphosphonate-associated ear canal osteonecrosis: a case report and review of the literature. Acta Otolaryngol Case Reports [online]. 2017;2(1):107–10.

Tosteson A, Grove MR, Hammond CS, Moncur MM, Ray GT, Hebert GM, Pressman AR, Ettinger B. Early discontinuation of treatment for osteoporosis. Am J Med [online]. 2003;115(3):209–16.

Tosteson AN, Melton L, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, Lindsay RL. Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int [online]. 2008;19(4):437–47.

US Department of Health and Human Services (USDHHS). Bone health and osteoporosis: a report of the surgeon general. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004. p. 2, 87. https://www.ncbi.nlm.nih.gov/books/NBK45513/. Accessed Jan 2018.

Vasikaran S, Eastell R, Bruyère O, Foldes A, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int [online]. 2011;22(2):391–420.

Watts NB. Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). Osteoporos Int [online]. 2004;15(11):847–54.

Woo S, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med [online]. 2006;144(10):753–61.

World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group [meeting held in Rome from 22 to 25 June 1992]. Technical Report Series 843. Geneva: WHO; 1994. http://apps.who.int/iris/handle/10665/39142.

Vitamin D Deficiency and Treatment in Children and Adults

54

Yuk Fun Chan, Kerry-Lee Milner, Chris White, and Pauline Musson

Contents

54.1 **Part A: Vitamin D Deficiency and Treatment in Adults** 1039
54.1.1 Vitamin D Repletion and Its Potential Benefits 1039
54.1.2 Vitamin D Deficiency 1043
54.1.3 High-Risk Groups for Deficiency and Special Populations 1045
54.1.4 Dosing Options 1046
54.1.5 Vitamin D Metabolites 1047
54.2 **Part B: Vitamin D Deficiency and Treatment in Children** 1051
54.3 **Bone Growth and Strength** 1051
54.4 **Calcium** 1052

P. Musson has authored Part B, the paediatric section of this chapter.

Y. F. Chan (✉)
Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia
e-mail: Yuk.Chan@health.nsw.gov.au

K.-L. Milner
Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia

University of New South Wales, Sydney, NSW, Australia
e-mail: Kerrylee.Milner@health.nsw.gov.au

C. White
Department of Endocrinology and Metabolism, Prince of Wales Hospital, Randwick, NSW, Australia

University of New South Wales, Sydney, NSW, Australia

Royal Hospital for Women, Randwick, NSW, Australia
e-mail: Christopher.White@health.nsw.gov.au

P. Musson
Southampton Children's Hospital, Southampton, UK
e-mail: pauline.musson@uhs.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_54

54.5 **Vitamin D** 1052
54.6 **Maintaining Serum Calcium** 1053
54.7 **Rickets** 1053
54.8 **Assessment of Vitamin D status** 1053
54.9 **Factors Increasing Risk of Vitamin D Deficiency** 1053
54.10 **Screening for Vitamin D Deficiency** 1054
54.11 **Vitamin D Supplementation** 1054
54.12 **Treatment of Vitamin D Deficiency** 1054
54.13 **Excluding Other Causes of Rickets** 1055
54.14 **Other Factors That Affect Bone Health** 1055
54.14.1 Nutrition 1055
54.14.2 Physical Activity 1055
54.14.3 Sex Steroids 1055
54.14.4 Inflammatory Disorders 1056
54.14.5 Liver and Renal Disease 1056
54.14.6 Drug Treatment 1056
54.15 **Learning Points/Nursing Role** 1057
54.16 **Learning Points/Nursing Role** 1058
54.17 **Conclusions** 1059
References 1059

Abstract

Vitamin D deficiency (hypovitaminosis D) has a very high prevalence worldwide. Over the last decade, there has been a growing interest in the research of vitamin D deficiency, its' metabolites and repletion regimen. Vitamin D plays an important role in maintaining human physiologic process such as calcium and phosphate homeostasis, adaptive and innate immunity. Vitamin D deficiency can cause metabolic bone diseases such as rickets in children and osteomalacia in adults, and may have a major impact on extraskeletal conditions such as diabetes, cancer, mortality, autoimmune and inflammatory disorders. Specific attention must be paid to high-risk groups such as the elderly, especially those living in institutional homes, people with limited sun exposure for various reasons such as religion, and people with darker skin. There are increasing numbers of children living with medical conditions in which either the condition or the treatment predisposes them to poor bone health and threatens their ability to attain peak bone mass. An understanding of calcium homeostasis and normal bone growth and development is essential for the paediatric endocrine nurse to be able to provide advice on lifestyle, supplement, and treatment options to this heterogeneous patient group. In adults, endocrine nurses need to understand the effects and recognise the importance of vitamin D deficiency on various organs and ensure appropriate assessment and management of vitamin D deficiency and assist in educating patients in how to improve their quality of life.

Keywords

Vitamin D deficiency · 25(OH)D $1,25(OH)_2D_3$ · Vitamin D repletion · Vitamin D metabolites

Abbreviations

$1,25(OH)_2D$	1,25 dihydroxyvitamin D
1α(OH)ase	1-Hydroxylase
24(OH)ase	24-Hydroxylase
25 (OH)D	25-Hydroxyvitamin D
BMD	Bone mineral density
CKD	Chronic kidney disease

DBP	Vitamin D binding protein
FGF23	Fibroblast growth factor 23
Pi	Phosphate and/or phosphorus
PTH	Parathyroid hormone
RCTs	Randomised controlled trials
RXR	Retinoid X receptor
VDRs	Vitamin D receptors

Key Terms

- **BMD**: Bone mineral density, bone mass per unit volume.
- **Cortical bone**: Outer part of all skeletal structures.
- **Osteoblast**: Responsible for bone formation.
- **Osteoclast**: Responsible for bone resorption.
- **Osteoporosis**: Skeletal disease with low bone mass with a consequent increase in bone fragility.
- **Trabecular**: The bone inside long bones, also known as cancellous bone.
- **T-score**: SDs by which BMD in an individual differs from the mean value expected in young healthy individuals.
- **Z-score**: SDs by which the BMD in an individual differs from the mean value expected for age and sex.
- **DXA**: Dual X-ray absorptiometry, measure bone areal density.

Key Points

- Vitamin D repletion is important and has many potential health benefits in skeletal and extra-skeletal health.
- Vitamin D deficiency is caused by limited sunlight exposure, decreased dietary intake, malabsorption, and other disorders.
- Vitamin D deficiency can be corrected with a repletion regimen to normalise serum vitamin D levels.
- Vitamin D metabolites such as 25(OH)D_3 and 1,25$(OH)_2D_3$ have important functions in many body organs.
- Endocrine nurses play an important role in the care of people with vitamin D deficiency.

54.1 Part A: Vitamin D Deficiency and Treatment in Adults

54.1.1 Vitamin D Repletion and Its Potential Benefits

54.1.1.1 Definition of Vitamin D

Vitamin D is a hormone, a fat-soluble vitamin, and a steroid like molecule derived from cholesterol which has two forms: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol (vitamin D_2) can be obtained from food such as shitake mushrooms, whereas cholecalciferol (vitamin D_3) is produced in the skin from ultraviolet light after sun exposure alters the ring of cholesterol molecule (Holick 2006; Holick et al. 2011). The circulating form of vitamin D in the blood is 25-hydroxyvitamin D (25(OH)D) which is commonly used as the indicator of the vitamin D status (The Royal College of Pathologists of Australasia, n.d.).

54.1.1.2 Recommended Daily Intake (RCI)

Normal healthy subjects produce about 4000 units of vitamin D daily, after obtaining vitamin D from various sources such as sunlight and diet (Heaney et al. 2003). According to the US Institute of Medicine in 2010, it is recommended that an 'adequate daily intake of vitamin D' is: from birth to 50 years old—200 IU; 51–70 years old: 400 IU; and >70 years old—600 IU (Dawson-Hughes et al. 2010).

Based on the 'Vitamin D and health in adults in Australian and New Zealand: A Position Statement' in 2012, it is suggested that to prevent vitamin D deficiency requires an intake of Vitamin D daily: ≥600 IU for ≤70 years old; and ≥800 IU for >70 years old (Nowson et al. 2012).

54.1.1.3 Sources of Vitamin D

54.1.1.3.1 Sunlight

It has been noted that >90% of the vitamin D body requirement comes from causal sunlight exposure (Holick 2004). The production of vitamin D_3 in the skin is affected by skin colour, application of sunscreen, time of the day, season, and latitude (Holick 2004; Holick 2007).

It's essential to have adequate sunshine exposure to maintain an optimal vitamin D level in the body. However, one must bear in mind the increased risk of skin cancer from excess sun exposure. The sun will not cause vitamin D toxicity and it is suggested that daily sunlight exposure of 15–20 min between 10:00 am and 3:00 pm will be enough for synthesis of vitamin D metabolism. It has also been found that a single body dose of ultraviolet radiation can produce 10,000 IU of vitamin D (Heaney 2005).

54.1.1.3.2 Dietary Sources

Vitamin D rich foods are presented in Table 54.1.

54.1.1.3.3 Vitamin D Supplementation

Vitamin D repletion can use either vitamin D_2 or vitamin D_3. A meta-analysis found that vitamin D_3 produces higher serum 25(OH)D levels as compared to vitamin D_2 (Hossein-nezhad and Holick 2012). Vitamin D_3 was used for vitamin D repletion since it is considered to be more effective in the prevention of non-vertebral fractures (Bischoff-Ferrari et al. 2009). Holick et al. (2008) demonstrated that a repletion regimen for 11 weeks with 1000 IU/day of vitamin D_2, 1000 IU/day of vitamin D_3, or a combination of 500 IU of vitamin D_2 and 500 IU of vitamin D_3 daily yielded the same outcome with an equal increase in serum total 25(OH)D levels in both groups (Biancuzzo et al. 2013). People taking vitamin D_2 supplements increase serum 25(OH)D levels and maintain total serum $1,25(OH)_2D$ levels compared to those taking the same dose of vitamin D_3 (Biancuzzo et al. 2013).

In Australia and New Zealand, virtually all oral vitamin D supplementation is vitamin D_3.

In clinical practice, vitamin D can be given daily or weekly or even monthly depending on the severity of vitamin D deficiency and patient preferences.

Table 54.1 Sources of Vitamin D (Holick 2007)

Source	Vitamin D_2 (D_2)/Vitamin D_3 (D_3)
Sunlight/UVB radiation	About 20,000 IU (D_3) = exposure to 1 minimal erythemal dose (MED) in a bathing suit, i.e. exposure of arms and legs to 0.5MED = ingesting about 3000 IU vitamin D_3
Cod liver oil	About 400–1000 IU/teaspoon (D_3)
Salmon, fresh	About 100–1000 IU/3.5 oz. (D_3)
Salmon, canned	About 300–600 IU/3.5 oz. (D_3)
Sardines, canned	About 300 IU/3.5 oz. (D_3)
Mackerel, canned	About 250 IU/3.5 oz. (D_3)
Tuna, canned	About 230 IU/3.5 oz. (D_3)
Shitake mushrooms, fresh	About 100 IU/3.5 oz. (D_2)
Shitake mushrooms, sundried	About 1600 IU/3.5 oz. (D_2)
Egg yolk	About 20 IU/yolk (D_2/D_3)
Fortified milk	About 100 IU/8 oz. (usually D_3)
Fortified yogurts	About 100 IU/8 oz. (usually D_3)
Fortified margarine	About 430 IU/3.5oz (usually D_3)
Fortified cheese	About 100 IU/3 oz. (usually D_3)
Fortified cereals	100 IU/serving (usually D_3)

1 oz = 30 mL

54.1.1.4 Potential Health Benefits

Over the last decade, there have been a plethora of studies assessing vitamin D and general health benefits, in addition to bone health. The skeletal and extra-skeletal health benefits in relation to vitamin D will be discussed below:

54.1.1.4.1 Skeletal Benefits

According to many randomised controlled trials (RCTs) and other studies, it has been suggested that serum 25(OH)D levels should be kept >30 ng/mL (74 nmol/L) for optimal bone health and >20 ng/mL (50 nmol/L) for normalisation of parathyroid hormone levels to ensure optimal muscle and bone health (Holick 2007; Bischoff-Ferrari et al. 2006). Similarly, it is observed that the antifracture efficacy of 25(OH)D level occurs at 30 ng/mL (74 nmol/L) suggesting a threshold for fracture protection with this optimal level (Tangpricha et al. 2006).

Hip and Non-vertebral Fractures

A meta-analysis (Boonen et al. 2007) examined postmenopausal women and men ≥50 years old taking oral vitamin D supplementation together with calcium and found that this cohort had an 18% reduction of hip fractures independent of

calcium supplementation. Research studies have demonstrated that treatment of vitamin D insufficiency can reduce the risk of hip and non-vertebral fractures (Chapuy et al. 1992; Trivedi et al. 2003).

A meta-analysis of RCT studies with 33,265 older people >65 years old taking vitamin D_3 (483–770 IU), Vitamin D_2 (800–1000 IU) or placebo (with or without calcium supplementation), after 1–7 years follow-up, showed the group taking vitamin D_3 was associated with a significant decrease (>20%) in non-vertebral fractures (Bischoff-Ferrari et al. 2009). A pooled analysis of eight RCTs indicated that serum 25(OH)D level >24 ng/mL (60 nmol/L) may be required to decrease fracture risk (Bischoff-Ferrari 2012).

Osteoporosis

Vitamin D repletion has been shown to be effective in improving bone mineral density (BMD) as illustrated in a population-based study showing a positive correlation between serum 25(OH)D and BMD (Bischoff-Ferrari et al. 2004). Another report (Adams et al. 1999) suggested that there was an increase in BMD in subjects previously with both low BMD and vitamin D deficiency after normalisation of 25(OH)D levels. Similar findings were reported in a small study of 229 subjects given vitamin D repletion of vitamin D_2 50,000 IU twice weekly with calcium supplementation for 5 weeks who normalised serum 25(OH)D and showed a significant increase in BMD (Kantorovich et al. 2000).

Fall and Muscle Strength

One of the main features of vitamin D deficiency is proximal muscle weakness (Holick et al. 2011; Holick 2007). In a systemic review and meta-analysis study, it has been shown that there is an association between muscle strength and vitamin D supplementation in older adults with significant reduction in postural sway and improved lower extremity strength (Muir and Montero-Odasso 2011). Interestingly, a recent study demonstrated that vitamin D supplementation has a small positive effect on muscle strength (Beaudart et al. 2014). In a nursing home study, the intervention group taking 800 IU of vitamin D daily together with calcium supplementation for 5 months had a 72% reduction in the risk of falls compared to the placebo group (Broe et al. 2007).

54.1.1.4.2 Extra-Skeletal Benefits

With the discoveries of vitamin D receptors (VDRs) and the 1 α-hydroxylase enzyme (CYP27B1) in various tissues, there has been growing research interests in the area of the relationship to immunity, macrophages, colon, pancreas, breast, stomach, and placenta (Plum and DeLuca 2010). Within these tissues, 25(OH)D is converted to $1,25(OH)_2D$ without changing the serum $1,25(OH)_2D$ concentrations while $1,25(OH)_2D$ affects gene expression. VDRs are a critical determinant of the ability of proliferating cells to regulate their response to various stimuli. Many observational studies have shown a reduction in risk of many disorders such as cancer, cardiovascular disease, autoimmune disease, diabetes mellitus, mental illness, and infectious disease, associated with a blood level of 25(OH) D > 28–32 ng/mL (70–80 nmol/L) (Holick et al. 2011; Nowson et al. 2012; Holick 2007).

Many research studies have been published recently in relation to extra-skeletal benefits with some still ongoing; however, the evidence of association and magnitude of the effects of these studies are not as strong as the skeletal benefits. Currently there is no consensus on the 25(OH)D levels that should be maintained for the best non-skeletal outcomes (Holick 2007).

Diabetes

There is a high prevalence of vitamin D deficiency in people with diabetes (Alam et al. 2012). The risk of type 1 and type 2 diabetes may be increased due to vitamin D insufficiency (Holick 2004; Mathieu et al. 2005).

VDRs can be found in pancreatic B cells and vitamin D may increase insulin secretion and improve insulin sensitivity. An observational study described that subjects taking vitamin D supplementation with calcium had a reduced risk of type 2 diabetes (Pittas et al. 2006). Recently a US study with a sample size of 2877 found a weak positive association between serum vitamin D levels and fasting and 2-h plasma glucose and HbA1c levels and a negative association with beta-cell function (Nielsen et al. 2016). Some small studies found that vitamin D supplementation in adults has shown an improvement of insulin sensitivity

(Mathieu et al. 2005); however, this outcome is debatable. In a recently published randomised double-blind placebo-controlled hyperinsulinemic-euglycemic glucose clamp study, taking ergocalciferol 50,000 IU weekly for 8 weeks in subjects with low vitamin D levels improved 25(OH)D levels but did not improve insulin sensitivity (Simha et al. 2012). It is still questionable whether normalisation of serum vitamin D levels with vitamin D supplementation will alter diabetic microvascular complications (Alam et al. 2016).

Infection/Autoimmune Disorder

The mechanism of the association between vitamin D deficiency and infection is thought to be due to the pleiotropic effects of 25(OH)D on human immunity with T-cell proliferation, immunoglobulin claws switching, and cytokine release (Mora et al. 2008).

Some studies findings suggested that vitamin D plays a potential role in the pathogenesis of some organ-specific autoimmune disorders such as rheumatoid arthritis (RA), Crohn's disease (CD), multiple sclerosis (MS), and type 1 diabetes. This is likely due to interference with genes, transcription factors, and signalling pathways which mediate inflammatory responses (Szekely and Pataki 2012). A systematic review and meta-analysis of 647 studies found that vitamin D deficiency (a serum 25(OH)D level <15–20 ng/mL (38–50 nmol/L)) is associated with a higher risk of infection (Upala et al. 2015).

Mortality and Cardiovascular Mortality

A meta-analysis of 18 RCTs examining all-cause mortality in postmenopausal women with vitamin D supplementation from 2000 to 3000 IU daily showed a 7% relative risk reduction of death in the intervention group of women (Autier and Gandini 2007). A Cochrane Review of 50 RCTs with a sample size of 94,000 subjects (mainly elderly women) illustrated that vitamin D_3 supplementation reduced mortality (Bjelakovic et al. 2011). It has also been reported that hospital in-patients with severe vitamin D deficiency (25(OH)D < 10 ng/mL or 25 nmol/L) and acute coronary syndrome had an increased in-hospital mortality (Correia et al. 2013).

Reduced Risk of Cancer

A meta-analysis of 11 studies has shown no association between prostate cancer and serum 25(OH)D levels. For breast cancer, a meta-analysis showed the risk of breast cancer is lower in the group with higher serum 25(OH)D levels compared to the group with the lower levels (Correia et al. 2013). A US meta-analysis suggested that every increase of 4 ng/mL (10 nmol/L) of serum 25(OH)D levels was associated with a 6% decrease in the risk of colorectal cancer (Chung et al. 2011). A RCT found a 60% decrease in all cancers, in postmenopausal women taking vitamin D_3 of 1100 IU and 1500 mg calcium daily for a duration of 4 years (Lappe et al. 2007).

Reduced Risk of Depression and Dementia

A RCT placebo trial study with obese and overweight subjects taking 20,000 or 40,000 IU vitamin D versus placebo for 12 months found the intervention group had higher serum 25(OH)D concentrations and significant improvement in depression scores (Jorde et al. 2008). In a study examining the risk of depression, there was a lower risk of depression in the middle adulthood group with serum 25(OH)D levels of 20–34 ng/mL (50–85 nmol/L) (Maddock et al. 2013). A vitamin D rich diet in animals has shown a decrease in the risk of Alzheimer's disease, and a decrease in the number of amyloid plaques and inflammation in the brains. This may imply $1,25(OH)_2D$ to have a neurological protective role (Yu et al. 2011).

Periodontal Disease

Vitamin D deficiency may be a risk factor for periodontal disease due to the effect of vitamin D on immunomodulation or bone mineral density. Periodontal disease involves inflammation with loss of periodontal attachment in the alveolar bone and ligaments. This is one of the major causes of tooth loss in the elderly. A study has shown that vitamin D supplementation with calcium decreased tooth loss and may reduce the risk of periodontal disease (Krall et al. 2001). A cross-sectional study with more than 1000 subjects concluded that in people aged ≥50 years, there is an association between lower serum 25(OH)D levels and periodontal disorders independent of BMD (Dietrich et al. 2004).

54.1.2 Vitamin D Deficiency

54.1.2.1 Epidemiology

Vitamin D deficiency is common across all ages around the world. In the USA, around 32% of the population had a serum 25(OH)D levels <20 ng/mL (50 nmol/L) (Looker et al. 2011). Whereas in the Canadian population, 60.7% of females and 57.5% of males had serum 25(OH)D levels <30 ng/mL (75 nmol/L) (Greene-Finestone et al. 2011). Australia has a similar rate as the USA, with 31% of people with vitamin D deficiency (serum 25(OH)D <50 nmol/L or 20 ng/mL) and 73% with serum 25(OH)D levels <30 ng/mL (<75 nmol/L) (Nowson et al. 2012).

In Sweden and Norway, there are higher serum 25(OH)D levels which is likely due to a higher consumption of cod liver oil and fatty fish. In contrast, there are lower serum 25(OH)D levels in Greece, Italy, and Spain, which is probably due to sun-avoiding behaviour, darker skin pigmentation, and air pollution with ozone and nitrogen dioxide (van Schoor and Lips 2011).

In a multi-centre study with 2173 adults from five cities in China, a high prevalence of hypovitaminosis D was observed, with 55.9% of subjects with serum 25(OH)D levels <20 ng/mL (50 nmol/L) and 94.6% with serum 25(OH)D levels <30 ng/mL (75 nmol/L). In addition, vitamin D deficiency was higher in inland cities compared to coastal cities such as Dalian. The reasons may be like that of Norway where people living in the coastal region of Dalian have higher daily intake (Yu et al. 2015). It has been reported that vitamin D deficiency has a high prevalence of 70–100% across the Indian subcontinent (Ritu and Gupta 2014). The reasons for this include darker skin, low dietary sources of vitamin D, such as usual unfortified milk with only 2 IU/100 mL and high phytate content in the Indian diet. Phytate is indigestible and reduces intestinal absorption of calcium due to chelation. In addition, there is a high lactose intolerance in India.

54.1.2.2 Pathophysiology

The skin absorbs vitamin D via ultraviolet B (UVB) radiation (wavelengths 290–315 nm) from sunlight. As illustrated in Fig. 54.1, 7-dehydrocholesterol in the skin is then converted to pre-vitamin D_3 which is quite unstable so then quickly undergoes thermal isomerisation to the form of vitamin D_3. Vitamin D_3 is then transported to the dermal capillary bed in the extracellular space via the vitamin D binding protein (DBP). It then enters the blood stream. DBP is a circulating alpha globulin in the same protein group as albumin and is primarily produced by the liver (Holick 2006).

Vitamin D_2 and D_3 from dietary sources after ingestion are incorporated into chylomicrons and then enter into the lymphatic system. Thereafter, the chylomicrons are transported to venous circulation, where they bind with lipoproteins and DBP.

Both vitamin D_2 (from the skin) and vitamin D_3 from the diet can then be stored in and released from fat cells. In the liver, DBP releases vitamin D which undergoes hydroxylation and is converted to 25-hydroxyvitamin D ($25(OH)D_3$) (calcidiol).

25(OH)D is the main circulating form of vitamin D. In the kidneys, 25(OH)D binding to DBP is then reabsorbed in the proximal renal tubules (Negri 2006). 25(OH)D undergoes sequential hydroxylation in the kidneys to produce 1,25 dihydroxyvitamin D [$1,25(OH)_2D$]. The hydroxylation in the kidneys is strongly regulated and is also augmented by hypocalcaemia, hypophosphatemia, and PTH; and repressed by FGF23, hyperphosphatemia, and $1,25(OH)_2D$ itself as well (Holick 2007; Nair and Maseeh 2012).

$1,25(OH)_2D$ has a half-life of 6 h, whereas 25(OH)D has 2 weeks in the circulation. This explains why the measurement of serum 25(OH)D level is used to determine vitamin D status. For non-skeletal function, 25(OH)D is also metabolised to $1,25(OH)_2D$ in other body tissues to regulate cellular growth (Holick 2007).

$1,25(OH)_2D$ is the active form of vitamin D that facilitates bone mineralisation and binds to VDRs to enhance absorption of calcium and phosphate in the intestine. It also binds to VDRs in osteoblasts which activate immature preosteoclasts as a result of the formation of mature bone-absorbing osteoclasts (Fig. 54.1). The mature osteoclasts then move calcium and phosphorous from the bone so as to maintain normal calcium and phosphorous levels in the blood stream (Holick 2006).

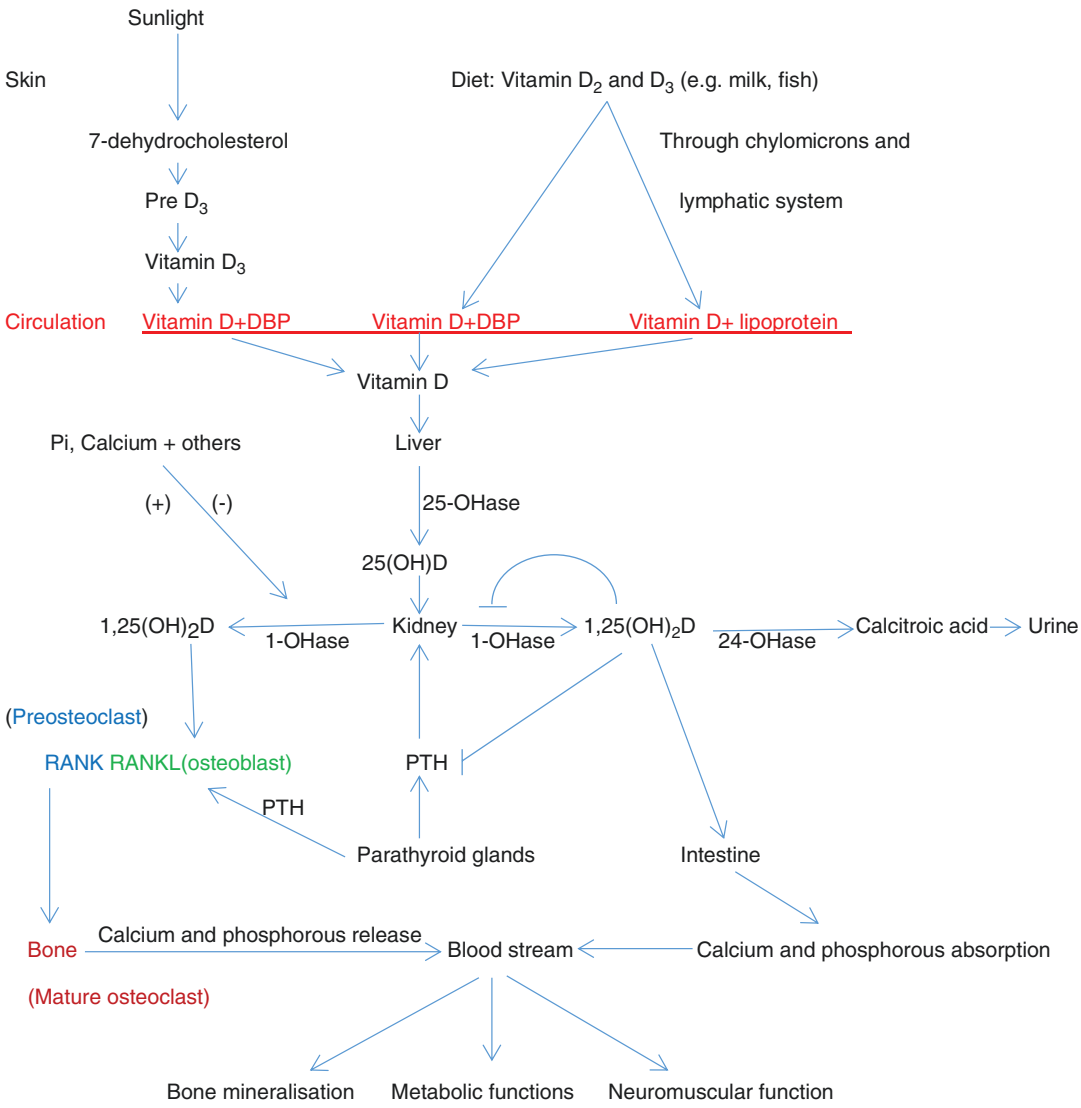


Fig. 54.1 The metabolism of vitamin D and the biologic effects of $1,25(OH)_2$ D on calcium, phosphorus, and bone metabolism (Holick 2006)

As noted early on, vitamin D plays an important role on calcium homeostasis through major interaction with bone and intestines. When serum calcium or phosphorous levels are low, the parathyroid hormone (PTH) stimulates and regulates the synthesis of $1,25(OH)_2D$ so as to: increase calcium absorption in the intestine, increase resorption of calcium by the kidneys, and stimulate the release of calcium from the bone. Apart from this, FGF23 from osteocytes inhibits the synthesis of $1,25(OH)_2D$.

Dysfunction in any of these pathways results in osteomalacia and hyperparathyroidism (Holick 2006). People with chronic kidney disease do not synthesise this active metabolite which results in hyperphosphatemia, and further impairs renal synthesis of the hormone contributing to secondary hyperparathyroidism. Alternatively, hypophosphatemia can cause osteomalacia, arising from excess FGF23 or primary renal tubule phosphate wasting disorders (Biancuzzo et al. 2013; Nair and Maseeh 2012; Shimada et al. 2004).

54.1.2.3 Diagnosis of Vitamin D Deficiency (Hypovitaminosis D)

In clinical practice, the best measurement of vitamin D status is the serum concentration of 25-hydroxyvitamin D (25[OH]D). There has not been a consensus on the cut-off points of serum 25[OH]D levels for the delineation of vitamin D deficiency. In general, it is agreed that vitamin D deficiency is defined as a serum level of 25(OH)D with <20 ng/mL (50 nmol/L) (Holick et al. 2011; Nowson et al. 2012). In clinical practice, it is common that patients with vitamin D deficiency also have an increase in PTH which indicates secondary hyperparathyroidism. An elevated serum PTH will provide a signal of the diagnosis of vitamin D insufficiency. According to The Endocrine Society's clinical practice guidelines (2011) in the USA: vitamin D insufficiency: 21–29 ng/mL (52.5–72.5 nmol/L) and vitamin D deficiency: <20 ng/mL (50 nmol/L). In addition, the guidelines also suggested that in order to prevent the risk of fracture and falls in older people, a serum level of 25[OH]D >30 ng/mL (75 nmol/L) is required (Holick et al. 2011). According to a position statement on **vitamin D and health in adults in Australia and New Zealand**: vitamin D adequacy: ≥50 nmol/L at the end of winter (level may need to be 10–20 nmol/L higher at the end of summer, to allow for seasonal decrease), mild vitamin D deficiency: 12–20 ng/mL (30–49 nmol/L), moderate vitamin deficiency: 5–12 ng/mL (12.5–29 nmol/L), and severe vitamin D deficiency: <5 ng/mL (12.5 nmol/L) (Nowson et al. 2012). Lastly according to the Institute of Medicine (IOM), Food and Nutrition Board (2011): vitamin D deficiency: <8–10 ng/mL (20–25 nmol/L) results in osteomalacia if untreated (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium et al. 2011).

54.1.2.4 Clinical Presentation

Initial symptoms can be subtle or asymptomatic until they become severe. Clinical presentation depends on the causes, e.g. adults with osteomalacia may experience chronic muscle aches and pains.

54.1.2.5 Screening

It has been recommended to screen for vitamin D deficiency in the following high-risk individuals (Holick et al. 2011):

- Osteoporosis
- Malabsorption syndrome
- Dark skinned individuals
- Obese persons (body mass index >30 kg/m^2)
- Disorders affecting the metabolism of vitamin D and phosphate (e.g. chronic kidney disease)

54.1.3 High-Risk Groups for Deficiency and Special Populations

54.1.3.1 Age >65 Years

Older people (age >65 years of age) are one of the high-risk groups for developing vitamin D deficiency, because they make vitamin D less efficiently due to less substrate (7-dehydrocholesterol in the skin) and reduced production rates of vitamin D from high levels of UV radiation exposure (Holick 2007). In addition, older people live in high-level residential care with chronic illness and have limited time outdoors. A study has shown that limited sun exposure in older people contributes to vitamin D deficiency (Durvasula et al. 2010).

54.1.3.2 Skin Colour

People with darker skin are also at higher risk of vitamin D deficiency due to the presence of thick layer of melanin pigment in skin and UVB does not penetrate well to the skin (Springbett et al. 2010). A study of healthy subjects illustrated vitamin D deficiency in 40% of black women (N = 1500) compared to only 4% of their white counterparts (Nesby-O'Dell et al. 2002). People with darker skin are likely to need 3–6 times longer sun exposure (Nowson et al. 2012).

54.1.3.3 Obesity

Obese people are likely to have vitamin D deficiency compared to those with normal weight. This is because vitamin D in adipose tissue may not be readily released, unless there is fat break-

down, so obesity results in lower vitamin D levels after receipt of oral or cutaneous synthesised vitamin D (Wortsman et al. 2000). Another study depicted that obese women with low 25(OH)D had suppression of PTH compared to the normal population. The lower average serum 25(OH)D level in the obese group may have a different physiologic significance compared to the normal population (Shapses et al. 2013).

54.1.3.4 Cultural/Religious Group

Research studies have found that UVB radiation doesn't penetrate through clothing. People with cultural norms/religions of wearing clothes covering most of their skin are also at high risk of vitamin D deficiency (Grover and Morley 2001; Kimlin et al. 2007). Some ethnic groups with fair skins use extreme sun protection which places them at risk of vitamin D deficiency Glass et al. 2009; van der Mei et al. 2007).

54.1.3.5 Limited Time Outdoor/ Environment

People with limited time outdoors such as office workers, factory or warehouse workers, taxi drivers, night-shift workers, those taking photosensitising medications (such as tetracyclines), and those who are sun avoidant (e.g. history of skin cancer) are also at risk of vitamin D deficiency due to decrease in sun exposure (Nowson et al. 2012). Sunscreen application affects vitamin D synthesis, with SPF 8 by 92.5% and SPF15 by 99% (Holick 2006).

54.1.3.6 Vitamin D Malabsorption Problems

People with the following conditions are at risk of vitamin D deficiency:

- Resection of the small intestine
- Coeliac disease, short bowel syndrome (Tangpricha et al. 2006)
- Cystic fibrosis (Hall et al. 2010)

54.1.3.7 Medications

Phenytoin and phenobarbital are associated with vitamin D deficiency since they can increase Vitamin D metabolism (Tangpricha 2016).

54.1.4 Dosing Options

In the USA, vitamin D supplementation is usually in the form of ergocalciferol (vitamin D_2) whereas in Australia, it is mainly cholecalciferol (vitamin D_3) orally (Nowson et al. 2012). Some evidence suggests that vitamin D_3 is more bioavailable than Vitamin D_2 (Holick 2007). Recommended doses based on the US Endocrine Society Guideline, the Canadian Society of Endocrinology and Metabolism, and the National Osteoporosis Foundation in 2011, for vitamin D deficiency are: 50,000 IU/week of vitamin D_2 or D_3 weekly for 8 weeks *or* 6000 IU of vitamin D_2 or D_3 daily for 8 weeks. If serum 25(OH)D level >30 ng/mL (74 nmol/L), maintenance treatment of 1500–2000 IU/day. For people who are obese, have malabsorption syndromes e.g. coeliac disease, or are taking medications that affect vitamin D metabolism, the recommendation is for 6000–10,000 IU/day of vitamin D and if serum 25(OH)D level >30 ng/mL (74 nmol/L), maintenance treatment of 3000–6000 IU/day. If the 25(OH)D concentration remains persistently low despite several attempts at correction with oral vitamin D, a trial of ultraviolet B light therapy (i.e. by tanning lamps) may be considered to improve vitamin D status.

54.1.4.1 Older Populations

Both vitamin D and calcium deficiencies are not uncommon in older people especially for those living in high-level residential care. The following suggestion is aimed at achieving optimal bone health and muscular function, to reduce the risk of falls and fractures in this group: vitamin D 1000 IU daily and calcium 1000–1300 mg daily preferably from diet (Table 54.2), or a combination of diet and supplementation (Avenell et al. 2009).

54.1.4.2 Toxicity

Vitamin D toxicity due to drug overdoses is uncommon. Most cases are due to accidental overdose. There is limited data in vitamin D supplementation and toxicity. One study showed that subjects using 10,000 IU of vitamin D daily for up to 5 months did not show toxicity (Vieth 1999,

Table 54.2 Foods high in calcium content (Osteoporosis Australia 2014)

Food	Calcium/serve (mg)	Standard serve	Grams/serve	K.J/serve
Milk, reduced fat, calcium fortified	520	Cup 250 ml	–	382
Skim milk	341	Cup 250 mL	–	382
Reduced fat milk	367	Cup 250 mL	–	551
Regular milk	304	Cup 250 mL	–	762
Reduced fat evaporated milk	713	Cup 250 mL	–	908
Regular soy milk	309	Cup 250 mL	–	660
Reduced fat soy milk	367	Cup 250 mL	–	702
Tofu firm	832	Cup 250 mL	260	1378
Regular natural yogurt	386	Tub	200	734
Low fat natural yogurt	488	Tub	200	498
Cheddar cheese	160	1 slice	21	349
Reduced fat cheddar cheese (15%)	209	1 slice	21	233
Shaved parmesan	204	–	21	355
Edam cheese	176	1 slice	21	312
Pecorino	156	1 slice	21	318
Reduced fat mozzarella	200	1 slice	21	258
Camembert	121	1 wedge	25	322
Sardines, canned in water, no added salt	486	Can	90	649
Sardines, canned in oil, drained	330	Can	90	824
Pink salmon, canned in water, no added salt	279	Small can	90	552
Pink salmon, canned in brine	183	Small can	90	575
Red salmon, canned in water, no added salt	203	Small can	90	734
Red salmon, canned in brine	175	Small can	90	688
Mussels, steamed or boiled	173	–	100	503
Snapper, grilled, with olive oil	163	1 fillet	100	635
Oysters, raw	132	–	100	303
Dried figs	160	6 figs	80	866
Cheesecake	163	1 slice	125	1786
Vanilla custard, reduced fat	130	1 tub	100	359
Soy beans, canned	106	Cup	200	844

2004). In clinical practice, the cut-off for vitamin D toxicity is a serum level >100 ng/mL (250 nmol/L) for a reasonable safety margin. When serum 25(OH)D level is >150 ng/mL (375 nmol/L), renal stones and hypercalcemia may occur due to intoxication.

Early symptoms of hypercalcemia include nausea, vomiting, and anorexia, followed by polyuria, polydipsia, weakness, fatigue, somnolence, headache, dry mouth, metallic taste, vertigo, tinnitus, and ataxia. Increased serum calcium levels are a constant finding when intoxication occurs and serum 25(OH)D levels may be normal in the early stage.

Prolonged sunlight exposure will not cause vitamin D toxicity because during sun exposure, isomerised vitamin D_3 is converted from previtamin D_3 (Fig. 54.1) and does not enter the circulation. Photoproducts are believed to have little effect on calcium metabolism (Holick 2004). Management of vitamin D toxicity includes ceasing vitamin D, stopping/decreasing the dietary intake of calcium foods, and restoring intravascular volume deficits; and for severe vitamin toxicity, corticosteroids or bisphosphonates (Vieth 1999).

54.1.5 Vitamin D Metabolites

The vitamin D metabolite, $1,25(OH)_2D$, has been well demonstrated in studies to have anti-proliferative, pro-differentiating, anti-inflammatory, and pro-apoptotic activities in cells and tissues. In addition, it has growth inhibitory effects on cancer cells in the breast, lung, liver,

prostate, colon, and pancreas, which express VDRs (Chiang et al. 2011).

54.1.5.1 Role of Vitamin D Binding Protein (DBP) in Vitamin D Metabolism

DBP is one of the specific serum carrier proteins for transportation of 25(OH)D and its active metabolite $1,25(OH)_2D$ to target tissues. About 90% of 25(OH)D binds to DBP in the circulation (Chun 2012). In vitro studies depict that DBP: protects 25(OH)D from degradation, prolongs its half-life, and protects against vitamin D deficiency (Safadi et al. 1999). Some animal studies illustrated that DBP is pivotal for total serum $1,25(OH)_2D_3$ levels but did not affect the amount of $1,25(OH)_2D_3$ entering into the cells or target tissues. If this is correct, the measurement of serum $1,25(OH)_2D_3$ may not truly reflect the biologically active $1,25(OH)_2D_3$ in the circulation (Bikle et al. 1986). Some studies show that DBP has potential direct action on bone resorption affecting bone density (Papiha et al. 1999).

54.1.5.2 24-Hydroxylase (24(OH)ase)

As noted previously, vitamin D has undergone liver and then kidney hydroxylation to form its active form (Fig. 54.1). 1,25-Dihydroxyvitamin D3 ($1,25(OH)_2D_3$) is the active metabolite of vitamin D and responsible for most of the biological actions after entering target organs (Fig. 54.2). In the kidney, apart from$1,25(OH)_2D_3$, 24, 25 dihydroxyvitamin D3 (24, $25(OH)_2D_3$) is also produced which is a relatively inactive metabolite as compared to $1,25(OH)_2D_3$. 24-Hydroxylase (24(OH)ase) is a mitochondrial enzyme that controls the amount of $1,25(OH)_2D_3$ in target tissues via 2 pathways (Fig. 54.2): increasing the catabolism of $1,25(OH)_2D_3$ to $1,24, 25(OH)_3D_3$, then leading to the product of calcitroic acid for excretion; and forming 24, $25(OH)_2D_3$ resulting in the reduction of 25(OH) D_3. Animal studies found that a reduction in 24(OH)ase causes an impairment of mineralisation in intramembranous bone suggesting that the main function of 24(OH)ase is vitamin D inactivation (Priemel et al. 2010).

54.1.5.3 Regulation of Renal Vitamin D Hydroxylases

54.1.5.3.1 Via Calcium, Phosphate, PTH, and 1,25(OH)2D3

Low serum calcium will increase serum PTH resulting in two outcomes: the production of $1,25(OH)_2D_3$ in the kidney and stimulation of the transcription of 1α(OH)ase. 1α(OH)ase is also negatively regulated by $1,25(OH)_2D_3$. 24(OH) ase is inhibited by low calcium and PTH, and is stimulated by $1,25(OH)_2D_3$ (Murayama et al. 1999).

54.1.5.3.2 Via FGF23

Fibroblast growth factor 23 (FGF23) is a phosphaturic factor that promotes renal phosphate excretion via decreasing phosphate reabsorption in the renal proximal tubules. FGF23 plays an important role in regulation of vitamin D metabolism in bone. The production of FGF23 in bone is stimulated by $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ binds to VDR. The ligand-bound VDR forms a heterodimer with nuclear retinoid X receptor (RXR) resulting in increased expression of FGF23 in osteocytes. Secreted FGF23 activates the FGF receptor bound by a transmembrane protein in renal tubular cells. FGF signalling suppresses expression of 1α(OH)ase and induces 24(OH) ase, thereby inhibiting synthesis and promoting catabolism of $1,25(OH)_2D_3$. Thus, FGF23—the transmembrane protein—results in decreased levels of $1,25(OH)_2D_3$ (Kuro-o 2008). It has been suggested that overactivity of FGF23 may cause phosphate wasting disorders such as hypophosphatemia, osteomalacia, and low serum 1,25(OH) D levels.

54.1.5.4 Extrarenal 1-Hydroxylase (1α(OH)ase)

54.1.5.4.1 Placenta

The trophoblast and maternal decidua in the placenta serves as a functional interface for exchange between mother and foetus. It has been reported that in early gestation, 1α(OH)ase is most abundant in decidua, and is expressed in foetal trophoblast and maternal decidual cells (Zehnder et al.

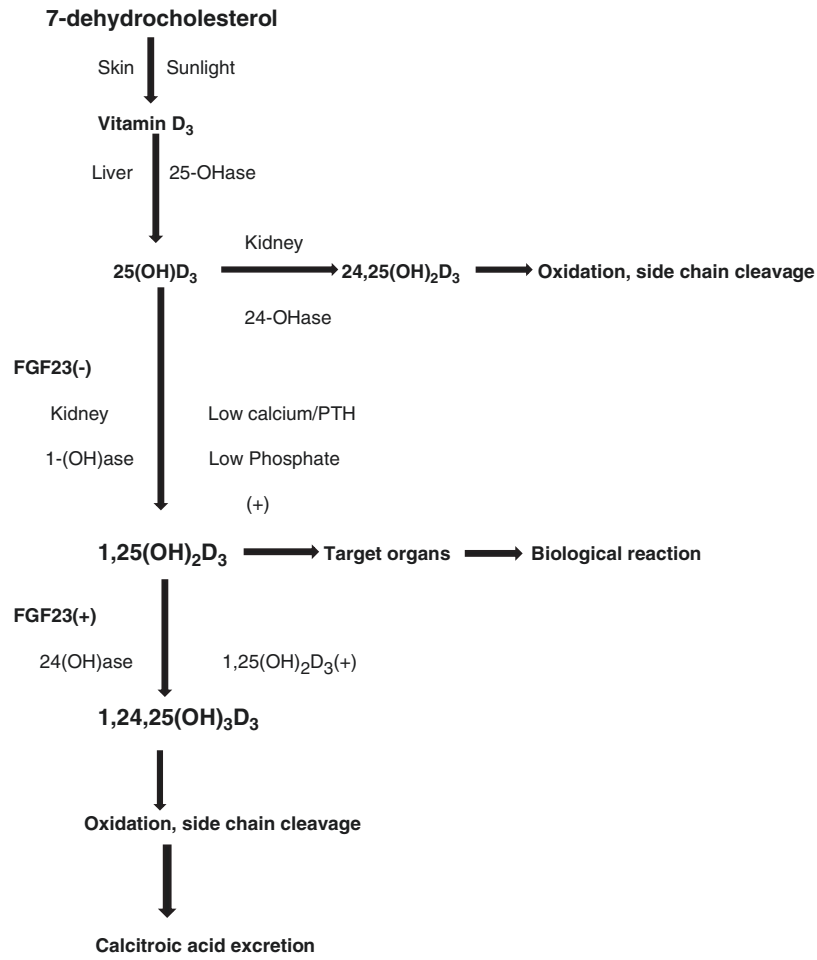


Fig. 54.2 Metabolic pathway for vitamin D (Christakos et al. 2010; Omdahl et al. 2002)

2002). The production of 1α(OH)ase is 8 times higher in the first trimester in decidual cells compared to the third trimester (Evans et al. 2006). $1,25(OH)_2D_3$ regulates the production of hormones during pregnancy and affects the trophoblast immunological, anti-inflammatory, and anti-microbial responses. In addition, trophoblasts produce $1,25(OH)_2D_3$ as well as respond to $1,25(OH)_2D_3$ (Ma et al. 2012).

54.1.5.4.2 Monocytes/Macrophages

It has been shown that 1α(OH)ase is expressed by macrophages and monocytes which also manufacture $1,25(OH)_2D_3$. However, it was observed that renal 1α(OH)ase has a different regulation compared to monocyte/macrophage 1α(OH)ase (Stoffels et al. 2007). From clinical evidence in patients with sarcoidosis, despite hypercalcemia, there is increased production of $1,25(OH)_2D_3$ by activated macrophages (Sharma 2000).

54.1.5.5 Vitamin D Metabolites and Chronic Kidney Disease (CKD) in the Elderly

With advancing age, there is a decline in the function of the conversion $25(OH)D_3$ to $1,25(OH)_2D_3$ in the kidney, and an increase in 24(OH)ase gene expression and clearance of $1,25(OH)_2D_3$. Age-related bone loss may be exacerbated by a decrease in kidney function and production of $1,25(OH)_2D_3$ and an increase in renal metabolism of $1,25(OH)_2D_3$.

For people with CKD, there is a decrease in vitamin D metabolism due to loss of renal mass and a decrease in the production of 1α(OH)ase

and an increase in FGF23 levels in early CKD as a result of decreased activity of 1α(OH)ase (Gutierrez et al. 2005).

Case Study: Osteomalacia

A 43-year-old woman presented with an unsteady gait. Her history included: childhood rickets, fractured right neck of femur, early menopause, and hypothyroidism (after hemithyroidectomy). She had an unsteady gait, bowing of the legs (Fig. 54.3), and scoliosis. She lived alone with social support from a carer.

Investigations

Serology showed a low calcium, phosphate and 25-hydroxyvitamin D, elevated alkaline phosphatase, and elevated PTH. 24-hour urine collection showed low calcium and low phosphate. X-ray of her lower limbs in Fig. 54.4 shows a fracture of the left proximal femur, with deformity and bowing of the legs which are typical features of osteomalacia (Holick 2007). X-ray of the spine showed an S-shaped spinal scoliosis with loss in vertebral body height and an extensive heterogeneous appearance of the bony skeleton. Bone biopsy with dynamic histomorphometry confirmed osteomalacia. She was treated with Calcitriol 3 capsules daily, phosphate tablet 1000 mg daily, and cinacalcet 30 mg daily.

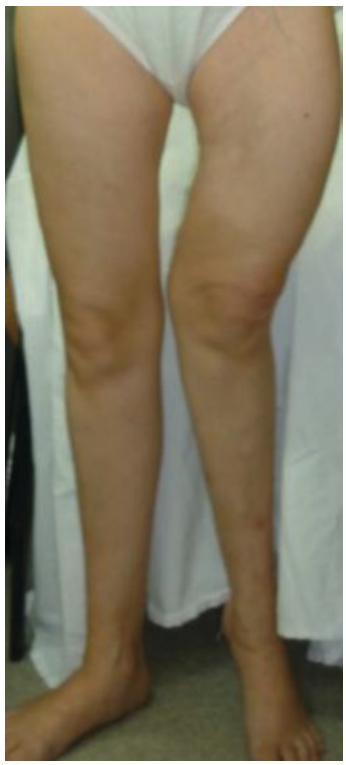


Fig. 54.3 Case study patient (Reproduced with permission)

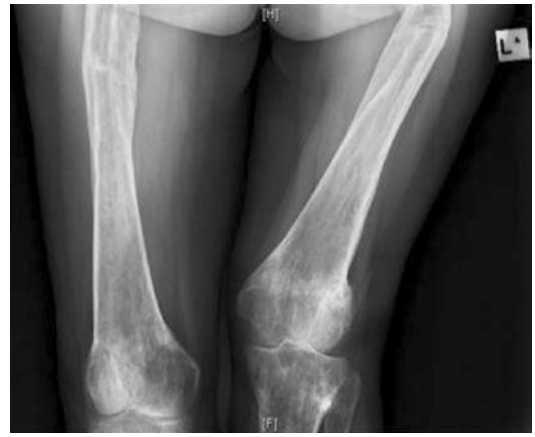


Fig. 54.4 Case study both femurs (Reproduced with permission)

The Role of the Endocrine Nurse

Vigilance in maintaining a normal vitamin D level via various measures is crucial to ensure adequate nutritional level for bone mineralisation. These measures include: adequate sun exposure (exposure of their arms and/or face in winter for about 15 min), compliance with vitamin D supplementation, foods high in vitamin D and calcium. If necessary, the patient and family members are referred to a dietitian for appropriate nutritional support to achieve optimal bone health.

Care of patients with osteomalacia involves multidisciplinary team members such as a nurse, endocrinologist, GP, physiotherapist, occupational therapist, dietician, and social worker. The endocrine nurse can provide edu-

cation and encourage compliance with vitamin D and calcium supplementation and education about correct use of tetracycline medications prior to a bone biopsy as errors in compliance render the test useless. The endocrine nurse can ensure regular follow-up of appointments and investigations with reminders and support for medical appointments and investigations including blood and/or urine tests (24-h collection) and BMD.

Appropriate referrals to other multidisciplinary team members are crucial and include occupational therapists for appropriate aids and equipment for daily living to prevent further fragility fractures. The physiotherapist provides ongoing assessment and exercises to strengthen muscles and improve physical function, with weight-bearing exercises to strengthen muscles and bones to maintain bone health and to reduce the risk of falls.

The vitamin D deficiency epidemic affects people of all ages, races, and religions worldwide. Vitamin D repletion has been found to be beneficial for both musculoskeletal and general health. The endocrine nurse plays an important role in maintaining the patient's bone and general health in hospital and community settings. Specific education is provided by the endocrine nurse in high vitamin D and calcium rich foods and appropriate sunlight exposure. Compliance with vitamin D supplements for a repletion regimen in the acute and maintenance phase with follow-up blood testing of serum 25(OH)D levels to maintain optimal musculoskeletal and general health is essential for treatment to be successful. Over the last decades, much research has emerged exploring Vitamin D metabolites, FGF23 and DBPs in relation to the benefits of vitamin D repletion for bone and extra-skeletal health. Endocrine nurses must keep up to date with the knowledge and skills to achieve optimal vitamin D levels in patients at risk of deficiency resulting in better health outcomes and quality of life.

54.2 Part B: Vitamin D Deficiency and Treatment in Children[1]

Key Points

- Vitamin D is essential for the absorption of calcium from the small intestine.
- Children need proportionately more calcium in relation to body size than adults; this is required for both longitudinal and appositional bone growth.
- Vitamin D deficiency in children is prevalent worldwide; the most severely affected present with hypocalcaemia or rickets. Many are asymptomatic.
- The endocrine nurse should play a key role in identifying children at risk, their assessment and treatment.
- Education of parents, patients, and other health care professionals is essential to improve concordance with treatment and prevent recurrence.

54.3 Bone Growth and Strength

Far from being an inert framework, bone is a dynamic structure, responding to factors including nutrition, hormones, and the stresses placed on it from physical activity. During childhood and adolescence, linear growth results from bone formation at the epiphyseal (growth) plates in the metaphysis of long bones. Chondrocytes divide by mitosis in the proliferative zone, mature, and then undergo apoptosis and calcification, finally being replaced by calcified bone by the action of osteoclasts and osteoblasts (Tortora and Derrickson 2011). This is referred to as bone modelling.

[1]Written by: Pauline Musson, Paediatric Clinical Nurse Specialist, Southampton Children's Hospital, Southampton, UK.

The mechanical load on the skeleton of physical activity leads to areas of micro stresses in the bone. At these sites, there is resorption of bone by osteoclasts and deposition of new bone by osteoblasts. This is known as remodelling and continues throughout life. In the long bones, bone resorption occurs in the medullary cavity and bone deposition beneath the periosteum, which increases bone thickness and strength and is referred to as appositional growth (Tortora and Derrickson 2011).

The rate of remodelling is influenced by the action of parathyroid hormone, 1,25 hydroxyvitamin D, Insulin like Growth factor (IGF-1), calcitonin, and local cytokines. During childhood, the rate of bone formation needs to exceed that of resorption in order to facilitate both longitudinal and appositional growth and ensure peak bone mass is achieved. Identification of and treatment of poor bone health/osteoporosis as early as possible is essential; a child's skeleton is able to reshape during remodelling, restoring mobility and function. This ability to reshape bones is not seen in adults (Ward et al. 2016).

An essential element of bone strength is conferred by the mineral content. Calcium and phosphate are deposited in the bone matrix throughout childhood, with approximately 50% of this being accrued during adolescence. The sex hormones (testosterone/oestrogen) and IGF-1 play an essential role in this process. Peak bone mass, or acquiring the maximum mineral content of bone, is achieved by around 25 years of age (Golden et al. 2014).

54.4 Calcium

In addition to being an essential component of healthy bone, calcium plays an important role in many other physiological processes in the human body. Calcium acts as a secondary messenger in cell signalling pathways, is needed for muscle fibre contraction, and is a co-factor in several processes including clotting.

In normal circumstances, the level of plasma calcium is tightly regulated to maintain it between 2.2 and 2.6 mmol/L, as levels outside this range have adverse effects. Hypocalcaemia gives rise to irritability, paresthesia (pins and needles type of tingling), muscle cramps and spasms, including tetany and convulsions. Clinical examination will elicit positive Chvostek and Trousseau signs. In infants, prolonged hypocalcaemia affects function of the cardiac muscle and can lead to left ventricular failure (Shaw and Mughal 2013).

Symptoms of hypercalcaemia include nausea, dizziness, and polyuria. In the longer term, this can also lead to renal calculi.

Plasma calcium levels are maintained by the actions of parathyroid hormone, vitamin D and calcitonin (Shaw and Mughal 2013).

Calcium is obtained from diet. The main food group containing calcium is dairy products such as milk and cheese. Other sources include green leafy vegetables, legumes, nuts, and fortified cereals. In clinical practice, the use of a tool such as proposed by Nordblad et al. (2016) can be helpful in assessing whether a child is having adequate calcium in their diet. Any child who is on a restricted diet or has malabsorption should be referred to a dietitian for a more in-depth assessment.

54.5 Vitamin D

Vitamin D is essential for the active absorption of calcium from the small intestine; without vitamin D, approximately only 10–15% of calcium intake is absorbed. This is not sufficient to meet physiological requirements at times of rapid growth such as infancy or adolescence and if not addressed can lead to symptomatic hypocalcaemia, osteomalacia, and rickets.

Muscle weakness is also seen in children with vitamin D deficiency and can give rise to non-specific muscle pains, proximal myopathy can lead to difficulty climbing stairs, delayed walking and in extreme cases, infants can present with life-threatening cardiomyopathy (Golden et al. 2014).

The main source of vitamin D in humans is from the action of ultraviolet B waves on the skin. UVB stimulates the manufacture of pre-vitamin D from 7-deoxycholesterol. Pre-vitamin D3 is isomerised into cholecalciferol (vitamin D3) and then

transported to the liver. Here the cholecalciferol undergoes hydroxylation into 25 OHD and this is then stored in the liver or adipose tissue.

Although most vitamin D is obtained from sun exposure, there are some dietary sources of vitamin D. However, there are only small amounts found in foods such as oily fish, egg yolks, some mushrooms, fortified spreads and cereals—so dietary intake alone would not be adequate.

54.6 Maintaining Serum Calcium

In response to a decrease in plasma calcium, parathyroid cells secrete Parathyroid Hormone (PTH). PTH directly stimulates osteoclast activity in bone, which releases calcium and phosphate into the circulation. PTH also stimulates further hydroxylation of 25OHD to 1,25 OHD in the kidney by 1α hydroxylase.

1,25 OHD increases the serum calcium levels by increasing both the absorption of calcium from the intestine and the resorption of calcium in the renal tubules. It also increases the renal excretion of phosphate to prevent hyperphosphataemia.

54.7 Rickets

Rickets only occurs in children who have not completed their linear growth, and is most commonly seen in younger children. The vitamin D deficiency will result in persistently elevated levels of PTH required to maintain serum calcium within the normal range. PTH also increases the renal excretion of phosphate and over time this results in serum phosphate levels falling to below normal. Bone formation at the growth plates is impaired, as phosphate levels within the normal range are required for apoptosis of the chondrocytes prior to mineralisation. New bone formed in these circumstances is inadequately mineralised osteoid. This is softer than healthy mineralised bone and deforms when under load—so as the child walks or crawls the long bones in the legs or arms become bowed. On X-ray, the osteoid bone is less dense and clearly undermineralised with splaying and cupping of the ends of the bones (Allgrove and Shaw 2015).

Vitamin D deficiency leading to persistently raised PTH in children and adults who have completed linear growth results in inadequate mineralisation during bone remodelling, this is known as osteomalacia.

54.8 Assessment of Vitamin D status

Assessment of vitamin D sufficiency is made by a blood test measuring the serum levels of 25OHD. Measurements of 1,25 OHD are not useful in this context—levels fluctuate in response to changes in plasma calcium and it has a very short half-life of 4 h (Allgrove and Shaw 2015).

In most areas of clinical practice, the currently accepted thresholds of 25OHD for assessment of vitamin D status are those agreed by the Institute of Medicine (2011).

- Deficiency <30 nmol/L
- Insufficiency 30–50 nmol/L
- Sufficiency >50 nmol/L

54.9 Factors Increasing Risk of Vitamin D Deficiency

Vitamin D deficiency is prevalent across the world in spite of public health awareness campaigns (Golden et al. 2014). Factors known to increase the risk of deficiency include:

- Area of residence: At latitudes below 37° there are sufficient UVB rays reaching the earth to enable vitamin D synthesis all year round. In the northern and southern hemispheres (latitudes above 37°), UVB rays are only sufficient for vitamin D synthesis during the middle of the day in the summer. There is insufficient UVB for any vitamin D synthesis during the winter.
- Increased use of sunscreen—In response to campaigns to raise awareness and reduce incidence of skin cancer, sunscreen use has significantly increased and is mandatory in many

schools and preschools. Sunscreen of factor 15 or above reduces the ability of the skin to produce vitamin D by approximately 95%.
- Skin colour—Because melanin absorbs UVB, people with darker pigmented skin need significantly longer sun exposure to generate enough vitamin D than those with fair skin.
- Wearing garments that cover the skin. This may be for cultural or religious reasons.
- Limited sun exposure—People with disabilities or those living in care institutions spend less time outside than their able-bodied peers.
- Obesity—factors that contribute to obesity, such as reduced time outside also increase risk of Vitamin D deficiency. 25OHD is also sequestered in body fat reducing the amount available.

54.10 Screening for Vitamin D Deficiency

Screening for vitamin D in the general population is not cost effective and historically advice has been to give supplements to all at risk groups. This has had only limited success, with poor implementation and uptake in many countries. Recognising this The Scientific Advisory Committee on Nutrition has now issued updated guidance advising universal supplementation should be given all year round in the UK (SACN 2016).

54.11 Vitamin D Supplementation

There is no universal agreement on the dose of daily supplements required to prevent vitamin D deficiency worldwide. The IOM (2011) recommends 400 IU daily for those under 1 year and 600 IU daily for those over 1 year. The guidance from the SACN (2016) for the UK is for lower amounts of 340–400 IU daily for infants under 1 year and 400 IU daily for everyone over this age.

Although this seems fairly straightforward, achieving concordance with these recommendations can be challenging with marked variations in clinical practice (Gupta and Warner 2011). Obtaining vitamin D supplementation on prescription from primary care is not possible in many areas and there are a small number of licensed products containing only vitamin D available. Multi-vitamin preparations available on prescription are often unpalatable and not all contain the recommended daily amount of vitamin D. The amount of a multi-vitamin preparation given should not be increased above the stated dose as these usually contain 100% of the recommended daily intake (RDA) of vitamin A; giving higher amounts can lead to vitamin A toxicity.

Vitamin D supplements are widely available as ‘over the counter’ (OTC) preparations from pharmacies and supermarkets. They are either as vitamin D3 known as cholecalciferol or vitamin D2 known as ergocalciferol. Cholecalciferol is formulated from animal product such as lanolin, whereas ergocalciferol is from plant sources. They are both effective at increasing 25OHD levels but cholecalciferol will not be acceptable for those following a strictly Halal or vegetarian diet. It is also important to be aware that many of the chewable pastilles contain gelatin, which would make them unacceptable to these groups.

The amount of vitamin D contained in available OTC preparations is variable. Further confusion is engendered by the dose being given in different units, with some labelled in IU and others in micrograms. 1 μg = 40 IU.

It is important to acknowledge that for some families the cost of the brand named chewable versions means they cannot afford to purchase these regularly. Products with added calcium are chalky and quite unpalatable for children. Additional calcium is not routinely required for children with vitamin D deficiency, but should be considered if the child has an inadequate dietary intake.

54.12 Treatment of Vitamin D Deficiency

The aim of treatment of vitamin D deficiency is to restore 25OHD levels to greater than 50 nmol/L in a safe manner without causing side effects.

This can be given as cholecalciferol or ergocalciferol in doses of 1550–10,000 units daily, depending on age, for 8–12 weeks (Cheung 2015). Care should be taken to ensure that 1,25 dihydroxyvitamin D is not prescribed in error as this will not replenish vitamin D stores and may cause hypercalcaemia and nephrocalcinosis (Gupta and Warner 2011).

Vitamin D is a fat-soluble vitamin and is best absorbed when taken with or after food. If daily administration is difficult then it can be given weekly as a larger dose, which some families find easier to manage. If gaining good concordance with daily or weekly dosing is not possible, then it can also be given as a large single dose (150,000–600,000 IU, depending on age) either by mouth or by intra-muscular injection; this is known as stoss therapy. In clinical practice, stoss therapy should be used cautiously, vitamin D toxicity is rare but has been seen in children given high dose treatment. Signs and symptoms include nausea, vomiting, constipation, and anorexia. It can also lead to hypercalcaemia and hypercalciuria (Cheung 2015).

Children being treated for rickets will need to be given additional calcium supplements to enable bone healing. They will have a high requirement for calcium and if not adequately supplemented are likely to experience symptomatic hypocalcaemia, which can be painful and distressing.

54.13 Excluding Other Causes of Rickets

Although hypophosphataemic rickets is rare, it is important that this is excluded as this requires specialist and long-term management to prevent severe deformity. This can be assessed following completion of treatment of the vitamin D deficiency by a blood test measuring inorganic phosphate. Once levels of 25OHD are within the normal range, the phosphate level should also be restored to normal; an ongoing low phosphate level should prompt further investigation.

54.14 Other Factors That Affect Bone Health

54.14.1 Nutrition

The child/young person needs nutrition that is adequate to achieve a healthy Body Mass Index (BMI). Adolescents with a very low BMI may have suppression of the hypothalamic-pituitary-gonadal axis resulting in sex hormone deficiency (Thornton and Gordon 2016).

In addition to calcium and vitamin D, the diet should also contain protein and elements including magnesium, copper, iron, zinc and vitamins A, C and K. Treatment/management of any condition that reduces the availability of nutrients is required to ensure there is no adverse impact on bone health. Conditions include: coeliac disease, cystic fibrosis, inflammatory bowel disease, anorexia nervosa, bulimia. Higher doses of Vitamin D than usual may be required to maintain sufficiency.

54.14.2 Physical Activity

As discussed, remodelling is essential for appositional growth of the bones. High impact physical activities that involve running or jumping are the most effective. It is also imperative to address this aspect of management in children whose mobility is limited, such as those with cerebral palsy or progressive diseases such as Duchenne's. Ensuring their mobility is preserved for as long as possible and using standing frames for periods of time has been shown to have a positive impact on bone health for those with Duchenne's (Buckner et al. 2015) but less effective for those with cerebral palsy (Fehlings et al. 2012).

54.14.3 Sex Steroids

Oestrogen and testosterone have a positive effect on bone health by increasing bone formation and inhibiting bone resorption. Lack of sex steroids during adolescence has a marked impact on the rate of bone deposition and if not replaced

reduces peak bone mass attained. Conditions that are likely to be associated with delayed puberty include Turner syndrome, anorexia nervosa, cerebral palsy, Duchenne Muscular Dystrophy, and others, requiring high dose glucocorticoid treatment (Golden et al. 2014).

54.14.4 Inflammatory Disorders

In conditions such as inflammatory bowel disease and juvenile idiopathic arthritis, the increased levels of cytokines have a direct effect on bone—causing increased resorption and affect absorption of the key nutrients required for healthy bone formation. Additionally, the treatments given for these conditions may also have a detrimental effect on bone turnover and health (Fehlings et al. 2012).

54.14.5 Liver and Renal Disease

Both of these conditions can impair the ability to synthesise vitamin D. In liver disease, there is reduced hydroxylation of vitamin D3 to 25OHD and in renal disease insufficient 1α hydroxylase to enable further hydroxylation to the active form 1,25 OHD.

54.14.6 Drug Treatment

Glucocorticoids have potent anti-inflammatory properties and are given in high doses as an essential part of treatment regimens for many conditions such as Duchenne Muscular Dystrophy, leukaemia, rheumatoid arthritis, kidney disease, and inflammatory bowel disease. However, treatment with high dose glucocorticoids for longer than 3 months has adverse effects on bone health and if this is not addressed results in osteoporosis (Högler and Ward 2015).

Glucocorticoids impair bone health by:

- Increasing the rate of bone absorption
- Reducing the rate of bone formation
- Inhibiting the absorption of calcium from the small intestine
- Suppression of gonadotrophins leading to sex hormone deficiency

The effect of glucocorticoids is most pronounced on trabecular bone resulting in vertebral collapse fractures, these can often be asymptomatic; adolescents at risk should be screened regularly by dual energy X-ray absorptiometry (Golden et al. 2014).

54.14.6.1 Drugs Increasing Levels of Cytochrome P450

Taking a complete drug history is an important part of assessment of this group of patients. Some herbal remedies such as St Johns Wort and some drugs including the older forms of anticonvulsants such as carbamazepine, phenobarbital, and phenytoin increase the levels of the liver enzyme cytochrome P450. This increases the metabolism of 25OHD. In clinical practice, this means that increased doses of vitamin D supplements are likely to be needed to maintain vitamin D sufficiency in children taking these drugs.

From the information above, it is clear that to maximise the potential of every child to attain peak bone mass requires attention to detail of all the factors that can affect this process. The two case studies below identify some of the issues seen in clinical practice and discuss ways of managing these.

Case Study 1

Jake was referred to the paediatric endocrine service at the age of 12 years for assessment of his bone health. Jake was diagnosed with Duchenne muscular dystrophy at the age of 8. Jake had no other health concerns and there was no significant family history of any medical conditions. Both parents were well and had experienced puberty at a 'normal' time.

At the time of his first appointment with the endocrine team, Jake was still fully ambulant and had been prescribed oral prednisolone for just over 4 years. A DEXA scan was arranged and Jake commenced on a multi-vitamin preparation to maintain vitamin D sufficiency. The results of

the DEXA showed that Jake's bone mineral density was −1 SDS below the mean (corrected for age & size). A lateral X-ray of his spine revealed asymptomatic vertebral fractures. Following discussion with the family, treatment with intravenous bisphosphonate was commenced.

Jake was reviewed in clinic at approximately 6 monthly intervals. Aged 14 years he remained prepubertal with Tanner staging of 1 for both pubic hair and genitalia and testicular volumes of 3–4 mL. Jake was commenced on treatment with testosterone at a dose of 50 mg by monthly intramuscular injection. Assessment of 25OHD revealed levels of 41 nmol/L, which is classified as insufficiency. In view of this Jake's prescription was changed to a combined product containing 400 IU of cholecalciferol and 500 mg calcium.

During this year Jake became wheelchair dependent, although still able to stand with aids. At the age of 15 years, there had been some pubertal progression to Tanner stage 3 for pubic hair and 2–3 for genitalia. A small increase in testicular volumes was noted to 4 mL on the left and 5 mL on the right. The treatment with testosterone was stopped to see if further progress was made without this. At this time 25OHD was measured and found to have improved to 70 nmol/L.

By the age of 16 years there had been no further progression through puberty and treatment with testosterone was recommenced at an increased dose of 100 mg monthly. This increased dose caused Jake to have persistent and frequent penile erections. This caused him some discomfort as well as embarrassment and difficulty in using the penile sheath system for collecting urine. The dose was reduced back to 50 mg for a further 6 months and then increased back to 100 mg with no further problems.

The effectiveness of the bisphosphonate treatment was assessed by serial DEXA scans showing continued improvement in bone density. At the age of 17 years, Jake opted to change his bisphosphonate treatment to oral risedronate. At this time Jake's 25OHD was again in the insufficient range at 44 nmol/L. He was then prescribed a treatment course of 10,000 IU daily for 12 weeks. This was inadvertently continued for approximately 9 months before changing back to the 400 IU daily preparation. A blood test at this time revealed a 25OHD of 162 nmol/L.

At the age of 18 years Jake's pubertal development was assessed at Tanner stage 4 for both pubic hair and genitalia. The dose of testosterone was increased to 250 mg monthly. At this time, the 25OHD was measured at 52 nmol/L.

54.15 Learning Points/Nursing Role

For Jake both the disease process (increased cytokines and immobility, increased likelihood of vitamin D deficiency) and treatment with glucocorticoids (increased bone resorption, reduced bone formation, reduced absorption of calcium and vitamin D, suppression of gonadotrophins) contributed to his reduced bone health. The role of the nurse is important in supporting and educating Jake and his family about the treatment options and the importance of good concordance with these.

The variations in 25OHD results mirror variable concordance with supplements, as there were no other changes in treatment that would account for this. Additionally, if he had taken the 10,000 units daily consistently for the 9 months incorrectly prescribed then a 25OHD greater than 162 nmol/L would have been expected. It may have been helpful for the endocrine nurse to have discussed this in more detail with the family going through the available products and dosing schedules that would have been suitable. However at this time there were only a few licensed products available and most of these were combinations of cholecalciferol and calcium, so the choice was limited. There were suitable OTC products available and perhaps a discussion with parents to see if they would be willing to purchase these instead of having a less palatable one on prescription would have been beneficial. Improving concordance may have eliminated the need for the period of high dose treatment and reduced the risk of prescription errors. If there is no improvement in vitamin D levels following treatment, poor compliance with the prescribed treatment is the most likely cause. It is however

important to ensure that there is no evidence of malabsorption.

From the history above, it is clear that Jake also had delayed puberty and if not addressed then this would also negatively impact on his bone health by reducing the peak bone mass attained. It is also clear that induction of puberty seems to have been managed more slowly than would be usual given that Jake did not commence on adult doses of testosterone until he was 18 years of age. In common with many other children with a chronic and disabling condition, Jake's parents were involved in his personal care, hygiene, and toileting, and Jake did not have any independence or privacy. The effects of testosterone were evident to all and made some aspects of his care harder to complete and increased both his and his parents' embarrassment. Additionally, his parents found it difficult to accept the changes in behaviour that occur during teenage years—the attempts at rebellion, temper outbursts, and moodiness. It was difficult for them to accept that the testosterone was vital to maximise his bone health and that going through puberty could not be avoided. This is a common issue faced by parents of children with disabilities and the input of the endocrine nurse in supporting these families and ensuring they understand the issues and choices around treatments is essential.

Case Study 2

Jayesh is the second son born to parents of Indian origin now living in the UK.

On a visit to their extended family in India he was taken to a doctor with concerns about bowing of his lower legs. The doctor told the family he did not have rickets but needed treatment with vitamin D. The dose prescribed is not known but this was administered, as directed, by his parents for approximately 4 months.

After returning to the UK he was seen at a local hospital for further assessment including blood tests. At this time his PTH and bone profile were in the normal range and the 25OHD was 87.3 nmol/L. Parents were told this level was high and to stop giving Jayesh cholecalciferol.

Four months later Jayesh was seen by the paediatric orthopaedic team for assessment of genu varum. Following clinical and X-ray assessment it was confirmed that there was no evidence of rickets; however, blood tests confirmed vitamin D deficiency with a 25OHD of 24 nmol/L. PTH was normal at 4.2 pmol/L and bone profile was also within the normal range.

These results prompted a referral to the paediatric endocrine clinic with concerns that vitamin D deficiency had recurred so quickly following very robust level 4 months previously.

By the time of the appointment with the endocrine nurse Jayesh was 23 months old. He was otherwise well with no underlying chronic illness or signs/symptoms to suggest malabsorption. His height and weight were on the 25th centile. Jayesh was active and moving around normally during the consultation and had no joint swelling or tenderness. Jayesh ate a vegetarian diet and was still breastfed. He did not drink milk or like dairy products and ate very little of these.

The drop in 25OHD levels from 87.3 to 24 nmol/L in a period of 4 months was an unexpected finding and parents were concerned this meant there was something more serious causing this and that the vitamin D deficiency was causing harm. From the history it was clear that Jayesh's intake of calcium was extremely low and this was most likely to be contributing significantly to the persistent and severe vitamin D deficiency.

This was explained to parents and Jayesh was prescribed cholecalciferol 3000 IU daily for 12 weeks and calcium supplements. It was also recommended to parents that Jayesh should continue on supplementation of cholecalciferol at a dose of 400 IU daily throughout his childhood while resident in the UK. Three months later the genu varum had completely resolved and Jayesh was discharged from the orthopaedic service. A referral was made to the local dietician for ongoing follow-up and managing his calcium supplementation until such time as this is no longer required.

54.16 Learning Points/Nursing Role

Jayesh had previously been prescribed cholecalciferol daily, which had increased his 25OHD levels to within the normal range; this indicates

that absorption is not an issue. The decision to stop any supplements and his parents being told that the level of 87.3 nmol/L was too high reflects the poor understanding of some health care professionals regarding normal levels and national recommendations regarding universal supplementation of children under 4 and 'at risk' groups.

In physiological terms Jayesh's calcium deficiency would lead to persistent secretion of PTH to prevent hypocalcaemia. PTH increases serum calcium in two ways, by stimulating osteoclast activity releasing calcium and phosphate into the circulation and increasing the amount of calcium absorbed from the small intestine by stimulating the hydroxylation of 25OHD to the active form 1,25OHD by 1α hydroxylase.

As there was so little calcium in Jayesh's diet, increased amounts of 1,25 OHD were necessary to maximise the absorption. In simple terms, this would mean that Jayesh's stores of 25OHD would be hydroxylated at a much faster rate than is usual resulting in the marked fall in levels seen prior to referral. Rickets has been reported in children with normal vitamin D levels but with inadequate calcium intake—both of these should be considered during patient assessment.

54.17 Conclusions

Vitamin D deficiency in children is entirely preventable and there are policies or guidelines in place in most of the world regarding supplementation for those groups known to be at risk. Unfortunately the lack of knowledge and understanding by both the public and health care professionals contributes to the poor uptake of supplementation. This results in Vitamin D deficiency remaining prevalent worldwide with children continuing to present to secondary care with vitamin D deficiency, hypocalcaemia, and rickets. As well as the short-term effects there are concerns about the impact this may have on bone health in adulthood.

By demonstrating a thorough understanding of the physiology of calcium homeostasis, bone formation, and factors that may impact on bone health, the endocrine nurse will be able to identify children at risk and provide education and advice on the most appropriate treatment or supplement for their patient group.

References

Adams JS, Kantorovich V, Wu C, Javanbakht M, Hollis BW. Resolution of vitamin D insufficiency in osteopenic patients results in rapid recovery of bone mineral density. J Clin Endocrinol Metab. 1999;84(8):2729–30.

Alam U, Najam O, Al-Himdani S, Benoliel S, Jinadev P, Berry JL, et al. Marked vitamin D deficiency in patients with diabetes in the UK: ethnic and seasonal differences and an association with dyslipidaemia. Diabet Med. 2012;29(10):1343–5.

Alam U, Amjad Y, Chan AW, Asghar O, Petropoulos IN, Malik RA. Vitamin D deficiency is not associated with diabetic retinopathy or maculopathy. J Diabetes Res. 2016;2016:6156217.

Allgrove J, Shaw NJ, editors. A practical approach to vitamin D deficiency and rickets in calcium and bone disorders in children and adolescents. 2nd ed. Basel: Karger; 2015.

Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167(16):1730–7.

Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. Cochrane Database Syst Rev. 2009;(2):CD000227.

Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014;99(11):4336–45.

Biancuzzo RM, Clarke N, Reitz RE, Travison TG, Holick MF. Serum concentrations of 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 in response to vitamin D2 and vitamin D3 supplementation. J Clin Endocrinol Metab. 2013;98(3):973–9.

Bikle DD, Gee E, Halloran B, Kowalski MA, Ryzen E, Haddad JG. Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein. J Clin Endocrinol Metab. 1986;63(4):954–9.

Bischoff-Ferrari HA. Vitamin D and fracture prevention. Rheum Dis Clin North Am. 2012;38(1):107–13.

Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med. 2004;116(9):634–9.

Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum

concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84(1):18–28.
Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169(6):551–61.
Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2011;7:CD007470.
Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007;92(4):1415–23.
Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. J Am Geriatr Soc. 2007;55(2):234–9.
Buckner JL, Bowden SA, Mahan JD. Optimizing bone health in duchenne muscular dystrophy. Int J Endocrinol. 2015; https://doi.org/10.1155/2015/928385.
Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992;327(23):1637–42.
Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. Endocrinol Metab Clin North Am. 2010;39(2):243–53.
Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat. 2010;121(2):469–77.
Cheung MS. Drugs used in paediatric bone and calcium disorders in calcium and bone disorders in children and adolescents. 2nd ed. Basel: Karger; 2015.
Chiang KC, Yeh CN, Chen MF, Chen TC. Hepatocellular carcinoma and vitamin D: a review. J Gastroenterol Hepatol. 2011;26(11):1597–603.
Chun RF. New perspectives on the vitamin D binding protein. Cell Biochem Funct. 2012;30(6):445–56.
Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(12):827–38.
Correia LC, Sodre F, Garcia G, Sabino M, Brito M, Kalil F, et al. Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. Am J Cardiol. 2013;111(3):324–7.
Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21(7):1151–4.
Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr. 2004;80(1):108–13.
Durvasula S, Kok C, Sambrook PN, Cumming RG, Lord SR, March LM, et al. Sunlight and health: attitudes of older people living in intermediate care facilities in southern Australia. Arch Gerontol Geriatr. 2010;51(3):e94–9.
Evans KN, Nguyen L, Chan J, Innes BA, Bulmer JN, Kilby MD, et al. Effects of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 on cytokine production by human decidual cells. Biol Reprod. 2006;75(6):816–22.
Fehlings D, Swtzer L, Argawal P, Wong C, Sochett E, Stevenson R, Sonnenberg L, Smile S, Young E, Huber J, Milo-Manson G, Kuwaik G, Gaebler D. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: a systematic review. Dev Med Child Neurol. 2012;54:106–16.
Glass D, Lens M, Swaminathan R, Spector TD, Bataille V. Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK. PLoS One. 2009;4(8):e6477.
Golden NH, Abrams SA, the Committee on Nutrition. Optimizing bone health in children and adolescents. Pediatrics. 2014;134(4):e1229–43.
Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, Sarafin K, et al. 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. Osteoporos Int. 2011;22(5):1389–99.
Grover SR, Morley R. Vitamin D deficiency in veiled or dark-skinned pregnant women. Med J Aust. 2001;175(5):251–2.
Gupta K, Warner J. Inappropriate and inconsistent modalities of treatment of vitamin D deficiency in children. Arch Dis Child. 2011;96(8):787.
Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005;16(7):2205–15.
Hall WB, Sparks AA, Aris RM. Vitamin d deficiency in cystic fibrosis. Int J Endocrinol. 2010;2010:218691.
Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol Biol. 2005;97(1–2):13–9.
Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77(1):204–10.
Högler W, Ward L. Osteoporosis in children with chronic disease in calcium and bone disorders in children and adolescents. 2nd ed. Basel: Karger; 2015.
Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80(6 Suppl):1678S–88S.
Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006;116(8):2062–72.
Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81.
Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2008;93(3):677–81.

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.

Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: an epigenetic perspective. Curr Opin Clin Nutr Metab Care. 2012;15(6):567–79.

Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary reference intakes for calcium and vitamin D. Washington DC: National Academies Press; 2011.

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med. 2008;264(6):599–609.

Kantorovich V, Gacad MA, Seeger LL, Adams JS. Bone mineral density increases with vitamin D repletion in patients with coexistent vitamin D insufficiency and primary hyperparathyroidism. J Clin Endocrinol Metab. 2000;85(10):3541–3.

Kimlin M, Harrison S, Nowak M, Moore M, Brodie A, Lang C. Does a high UV environment ensure adequate vitamin D status? J Photochem Photobiol B. 2007;89(2–3):139–47.

Krall EA, Wehler C, Garcia RI, Harris SS, Dawson-Hughes B. Calcium and vitamin D supplements reduce tooth loss in the elderly. Am J Med. 2001;111(6):452–6.

Kuro-o M. Endocrine FGFs and Klothos: emerging concepts. Trends Endocrinol Metab. 2008;19(7):239–45.

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85(6):1586–91.

Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. NCHS Data Brief. 2011;(59):1–8.

Ma R, Gu Y, Zhao S, Sun J, Groome LJ, Wang Y. Expressions of vitamin D metabolic components VDBP, CYP2R1, CYP27B1, CYP24A1, and VDR in placentas from normal and preeclamptic pregnancies. Am J Physiol Endocrinol Metab. 2012;303(7):E928–35.

Maddock J, Berry DJ, Geoffroy MC, Power C, Hypponen E. Vitamin D and common mental disorders in mid-life: cross-sectional and prospective findings. Clin Nutr. 2013;32(5):758–64.

Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. Diabetologia. 2005;48(7):1247–57.

Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008;8(9):685–98.

Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011;59(12):2291–300.

Murayama A, Takeyama K, Kitanaka S, Kodera Y, Kawaguchi Y, Hosoya T, et al. Positive and negative regulations of the renal 25-hydroxyvitamin D3 1alpha-hydroxylase gene by parathyroid hormone, calcitonin, and 1alpha,25(OH)2D3 in intact animals. Endocrinology. 1999;140(5):2224–31.

Nair R, Maseeh A. Vitamin D: the "sunshine" vitamin. J Pharmacol Pharmacother. 2012;3(2):118–26.

Negri AL. Proximal tubule endocytic apparatus as the specific renal uptake mechanism for vitamin D-binding protein/25-(OH)D3 complex. Nephrology (Carlton). 2006;11(6):510–5.

Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr. 2002;76(1):187–92.

Nielsen NO, Bjerregaard P, Ronn PF, Friis H, Andersen S, Melbye M, et al. Associations between vitamin D status and type 2 diabetes measures among inuit in Greenland may be affected by other factors. PLoS One. 2016;11(4):e0152763.

Nordblad M, Graham F, Mughal MZ, et al. Rapid assessment of dietary calcium intake. Arch Dis Child. 2016;101:634–6.

Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012;196(11):686–7.

Omdahl JL, Morris HA, May BK. Hydroxylase enzymes of the vitamin D pathway: expression, function, and regulation. Annu Rev Nutr. 2002;22:139–66.

Papiha SS, Allcroft LC, Kanan RM, Francis RM, Datta HK. Vitamin D binding protein gene in male osteoporosis: association of plasma DBP and bone mineral density with (TAAA)(n)-Alu polymorphism in DBP. Calcif Tissue Int. 1999;65(4):262–6.

Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care. 2006;29(3):650–6.

Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov. 2010;9(12):941–55.

Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res. 2010;25(2):305–12.

Ritu G, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. Nutrients. 2014;6(2):729–75.

Safadi FF, Thornton P, Magiera H, Hollis BW, Gentile M, Haddad JG, et al. Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein. J Clin Invest. 1999;103(2):239–51.

Scientific Advisory Committee on Nutrition (SACN) recommendations on vitamin D. 2016. www.gov.uk/government/publications/sacn-vitamin-d-and-health-report

Shapses SA, Lee EJ, Sukumar D, Durazo-Arvizu R, Schneider SH. The effect of obesity on the relationship between serum parathyroid hormone and 25-hydroxyvitamin D in women. J Clin Endocrinol Metab. 2013;98(5):E886–90.

Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med. 2000;6(5):442–7.
Shaw N, Mughal M. Vitamin D and child health. Part 1 (skeletal aspects). Arch Dis Childhood. 2013. Published online first: 2 January 2013. https://doi.org/10.1136/archdischild-2011-301264.
Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113(4):561–8.
Simha V, Mahmood M, Ansari M, Spellman CW, Shah P. Effect of vitamin D replacement on insulin sensitivity in subjects with vitamin D deficiency. J Invest Med. 2012;60(8):1214–8.
Springbett P, Buglass S, Young AR. Photoprotection and vitamin D status. J Photochem Photobiol B. 2010;101(2):160–8.
Stoffels K, Overbergh L, Bouillon R, Mathieu C. Immune regulation of 1alpha-hydroxylase in murine peritoneal macrophages: unravelling the IFNgamma pathway. J Steroid Biochem Mol Biol. 2007;103(3–5):567–71.
Szekely JI, Pataki A. Effects of vitamin D on immune disorders with special regard to asthma, COPD and autoimmune diseases: a short review. Expert Rev Respir Med. 2012;6(6):683–704.
Tangpricha V. Vitamin D deficiency and related disorders; 2016.
Tangpricha V, Luo M, Fernandez-Estivariz C, Gu LH, Bazargan N, Klapproth JM, et al. Growth hormone favorably affects bone turnover and bone mineral density in patients with short bowel syndrome undergoing intestinal rehabilitation. JPEN J Parenter Enteral Nutr. 2006;30(6):480–6.
The Royal College of Pathologists of Australasia. Position statement: use and interpretation of vitamin D testing; 2013.
Thornton D, Gordon CM. Restrictive eating disorders and skeletal health in adolescent girls and young women. Calcif Tissue Int. 2016;100(5):449–60.
Tortora G, Derrickson B. Bone's role in calcium homeostasis in principles of anatomy & physiology. 13th ed. New York: Wiley; 2011.
Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326(7387):469.
Upala S, Sanguankeo A, Permpalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2015;15:84.
van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, et al. The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect. 2007;115(8):1132–9.
van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab. 2011;25(4):671–80.
Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999;69(5):842–56.
Vieth R. Why the optimal requirement for vitamin D3 is probably much higher than what is officially recommended for adults. J Steroid Biochem Mol Biol. 2004;89–90(1–5):575–9.
Ward LM, Konj VN, Ma J. The management of osteoporosis in children. Osteoporos Int. 2016;27(7):2147–79.
Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72(3):690–3.
Yu J, Gattoni-Celli M, Zhu H, Bhat NR, Sambamurti K, Gattoni-Celli S, et al. Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AbetaPP transgenic mice. J Alzheimers Dis. 2011;25(2):295–307.
Yu S, Fang H, Han J, Cheng X, Xia L, Li S, et al. The high prevalence of hypovitaminosis D in China: a multicenter vitamin D status survey. Medicine (Baltimore). 2015;94(8):e585.
Zehnder D, Bland R, Chana RS, Wheeler DC, Howie AJ, Williams MC, et al. Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. J Am Soc Nephrol. 2002;13(3):621–9.

Key Reading

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Hassan Murad M, Weaver GM, The Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical practices Guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
2. Nowson CA, McGrath JJ, Ebeling PR, Haikerwal A, Daly RM, Sanders KM, Seibel MJ, Mason RS. Vitamin D and health in adults in Australia and New Zealand a position statement. Med J Aust. 2012;196(11):686–7.
3. Holick MF, Hossein-nezhad A. Vitamin D global perspective. Mayo Clin Proc. 2013;88(7):720–55.
4. Haroon M, Fitzgerald O. Vitamin D deficiency and its repletion: a review of current knowledge and consensus recommendations. J Arthritis. 2012;1:105. https://doi.org/10.4172/2167-7921.1000105.
5. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81.

Part IX

Obesity and Disorders of Lipid Metabolism

Cecilia Follin

55 Dietary and Behavioural Interventions in the Management of Obesity

Clare Grace and Adrian Brown

Contents

55.1 **Aims of Dietary and Behavioural Treatment** 1067

55.2 **Dietary and Behavioural Assessment** 1067
55.2.1 Negative Attitudes to Obesity 1067
55.2.2 Raising the Issue of Weight 1068
55.2.3 What to Assess 1068

55.3 **Dietary Approaches** 1070
55.3.1 Low Fat Diet 1071
55.3.2 The 600 kcal Deficit Approach 1071
55.3.3 The Mediterranean Diet 1072
55.3.4 Low Glycaemic Index Diets 1073
55.3.5 Low Carbohydrate Diets 1073
55.3.6 Formula Diets 1074
55.3.7 Intermittent Energy Restriction 1076
55.3.8 Fad Diets 1076

55.4 **Behaviour Modification** 1077
55.4.1 Motivational Approaches 1077
55.4.2 Behavioural and Cognitive Approaches 1077
55.4.3 Core Strategies 1077

55.5 **Conclusions** 1079

References 1080

Abstract

Obesity is a chronic, often progressive disease, with a complex web of psychological, social, and biological factors underpinning why people overeat, struggle to be active, and gain excess body weight and adiposity. As such its management is not simply about eating less and exercising more, rather there is a need to understand the drivers to excess weight gain with comprehensive assessment identifying modifiable factors. Multicomponent programmes including dietary treatment, physical activity, and behaviour modification are more effective than interventions focusing on one aspect alone (Avenell et al. 2004). Rather than one superior dietary intervention

C. Grace
Relish Nutrition Consultancy, North Yorkshire, UK

A. Brown (✉)
University College London, London, UK
e-mail: a.c.brown@ucl.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_55

there are a range of effective evidence-based treatments that can be matched to patient preferences and the presence and/or severity of comorbid disease. Behavioural modification focuses on patient-centred care, incorporating motivational, behavioural, and cognitive elements and recognizes that nurse's attitudes and skills can have a profound effect on patient outcomes.

Nurses are on the frontline of obesity management raising the issue of weight where appropriate, undertaking assessment of patient's complex needs, signposting to services and providing education and support for weight loss and maintenance. Given the escalating prevalence of obesity, it is essential that nurses have a comprehensive understanding of how best to treat this condition. Obesity management is particularly relevant in the endocrine setting given the range of conditions closely linked with excess weight, such as type 2 diabetes mellitus (T2D) or polycystic ovarian syndrome, and in which comprehensive management may improve associated symptoms and risks.

Qualitative research exploring nursing beliefs about their role in managing obesity identify its assigned importance but highlight the desire for more obesity training, an infrastructure which supports high quality care, a greater understanding of evidence-based treatments, and improved access to resources (Nolan et al. 2012).

This chapter addresses some of these concerns, presenting an overview of the evidence base related to dietary and behavioural modification in obesity management, considers the assessment process, and highlights training opportunities and educational resources where appropriate.

Keywords

Weight bias · Multicomponent Comprehensive assessment · Dietary interventions · Self-monitoring · Motivation Expectations

Abbreviations

BMI	Body mass index
CBT	Cognitive behavioural therapy
CVD	Cardiovascular disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
GI	Glycaemic index
GL	Glycaemic load
HbA1c	Glycated haemoglobin
IER	Intermittent energy restriction
LC	Low carbohydrate
LDL	Low density lipoprotein
LED	Low energy diet
MI	Motivational interviewing
MR	Meal replacements
NICE	National Institute for Health and Clinical Excellence
PAL	Physical activity level
T2D	Type 2 diabetes
TDR	Total diet replacement
VLED	Very low energy diet

Key Terms

- **Behavioural therapy**: uses techniques derived from behaviourism to modify learned behaviours.
- **Binge eating disorder**: Eating abnormally large amount of food, feeling loss of control during eating.
- **Cognitive restructuring**: learning to identify and change patterns of thinking.
- **Formula diets**: Liquid shakes, soups, bars replace food for a specific period.
- **Glycaemic Index (GI)**: Relative ranking of carbohydrate in foods according to how they affect blood glucose levels. Carbohydrates with a low GI value (55 or less) are more slowly digested, absorbed and metabolised and cause a lower and slower rise in blood glucose.
- **Low carbohydrate diets**: Less than 130 g/day.

- **Severe obesity**: BMI (body mass index) >35 kg/m^2.
- **The Mediterranean diet**: High intake of fruits, vegetables, nuts, seeds, olive oil.

Key Points

- The nurse's experience of obesity treatment and the associated treatment outcomes.
- Previous weight bias may impact on the patient's response to assessment and treatment.
- Comprehensive assessment is the foundation of tailored weight management support.
- Multicomponent programmes, including dietary change, physical activity, and behaviour modification are more effective than isolated interventions.
- There are a range of evidence-based dietary interventions rather than one superior dietary treatment.

55.1 Aims of Dietary and Behavioural Treatment

The aims of dietary and behavioural treatment are to

- Make and sustain changes to eating behaviour
- Consider needs and expectations
- Make acceptable long-term changes
- Improve health and quality of life
- Modify weight, where possible

Encouraging patients to strive for their ideal body weight can be unhelpful, particularly for those with severe and complex obesity. Modest weight change of 5–10% has been associated with improvements in metabolic health and reduced risk of obesity-related diseases (The Look Ahead Research Group 2014). However, once comorbidities are present modest weight loss is unlikely to provide sustained benefit.

For patients with a BMI <35 kg/m^2 with no medical, functional, or psychological consequences of obesity, modest weight loss of 5–10%, and/or prevention of further weight gain may be appropriate. In instances of severe and complex obesity, often BMI >35 kg/m^2, although this may occur at lower BMI in certain ethnic groups, a 15–20% weight loss may be needed to see metabolic benefit (Scottish Intercollegiate Guidelines Network 2010) and reverse intractable complications and this often requires intensive dietary treatment.

55.2 Dietary and Behavioural Assessment

55.2.1 Negative Attitudes to Obesity

Reflecting on patient's experiences of weight bias, the nurse's attitudes to obesity and how this may influence the patient's response to assessment and management can be helpful.

Many obese patients will have experienced negative attitudes with widespread stereotypes suggesting they are lazy, weak-willed, and lacking in self-discipline (Brown 2006). Indeed obesity is often portrayed as self-inflicted with many patients experiencing high levels of shame and self-blame (Puhl and Brownell 2003). Research suggests health professionals draw on these negative beliefs to justify inaction in treating obesity, and this may be linked with negative clinical practices (Frank 1993). It is important to reflect on how past experiences of weight bias may detrimentally impact the patient's confidence and willingness to, for example, discuss eating habits or attend appointments following treatment relapse.

Online training: Preventing weight bias: helping without harming in clinical practice www.uconruddcenter.org.

Explore your own attitudes: http://biastoolkit.uconruddcenter.org/module1.html.

55.2.2 Raising the Issue of Weight

Broaching the topic of body weight with a patient can be challenging. A number of barriers have been identified including a lack of time, uncertainty over treatment effectiveness and concern over offending people (Michie 2007). However, starting the conversation is essential if appropriate care is to be provided. Reassuringly, research suggests most people find brief conversations about weight instigated by health professionals very helpful particularly if they are provided with assistance and support (Aveyard et al. 2016).

Refer to "Let's talk about weight: a step by step guide to brief interventions with adults for health and care professionals" 2017 www.gov.uk.

If signposting to treatment rather than managing "in house", knowledge of local services and their referral criteria and processes is essential. See publichealthmatters.blog.gov.uk for further advice on identifying local services and local obesity care pathways.

55.2.3 What to Assess

The aim of assessment is to identify behaviours or conditions that may hinder management and specific modifiable factors that can form the basis of tailored advice. Dietary assessment usually forms part of a broader clinical assessment exploring the impact of excess weight on the presence and/or severity of medical, functional, and/or psychological comorbidities. Some medical symptoms or conditions may need treatment prior to commencing lifestyle modification in order to increase the likelihood of success. For example, extreme sleepiness linked with obstructive sleep apnoea may benefit from initial symptom control before implementing lifestyle changes.

55.2.3.1 Exploring Importance and Motivation

Not all patients want to treat their obesity or commit to treatment so exploring the importance of change and the reasons for addressing their weight is critical (Miller and Rollnick 2002). Discussing these reasons will strengthen and build motivation and help facilitate change.

Some common examples of specific, quality of life-related reasons

- To feel healthier
- To reduce joint pain and improve my ability to move about
- To be a better role model to my children
- To have a healthier relationship with food

Motivation or "willpower" is at times perceived as something you either have or you don't. However in reality, it is far more complex and influenced by the importance attached to a change and the confidence to implement it. This will help identify whether there needs to be a focus on increasing importance, improving confidence, or both.

Scoring systems can be used to assess the importance and confidence a patient may feel towards changing a particular behaviour although these need to be integrated into the broader conversation about weight and used by skilled practitioners with the associated behavioural skills. (on a scale of 0–10, where 0 is not important/not confident at all and 10 is extremely important/confident, where would you place yourself? (Rollnick et al. 1999)).

55.2.3.2 Expectations of Treatment

There is often a mismatch between the practitioner and the patient's expectations of what can be achieved with obesity treatment (Linne et al. 2002). This may relate to the extent of weight loss, the associated benefits (health, social, psychological), and the level of support available. Identifying and discussing these discrepancies particularly those relating to expected weight loss is one of the most challenging aspects of obesity management and needs to be considered at initial assessment.

With uncomplicated obesity, weight losses of 5–10% over 6–12 months are defined as success; however, research suggests patients want considerably greater losses with a recent study reporting over 90% of participants selected a goal ≥10% (Lent et al. 2016), with these disparities increasing with BMI (Foster et al. 2001; White et al. 2007). Although this magnitude of change is possible with intensive dietary treatments, very few achieve it using standard interventions. Research remains unclear about the most effective way of addressing these disparities, so practitioners are encouraged to provide information on the usual weight loss outcomes achieved with treatment.

It may also be helpful to explore broader expectations such as the hope weight loss will automatically improve self-esteem, body image, or psycho-social outcomes. Although these may be positively affected, they are influenced by a broad spectrum of factors unrelated to weight and discussing this at the start of treatment and linking with treatment goals is important.

55.2.3.3 Weight History

Weight history may identify contributing factors to obesity and give an indication of genetic predisposition. There are individuals strongly predisposed to excessive weight gain and discussing this can help convey understanding, empathy, and help address self-blame or shame about size.

Early onset childhood obesity and a strong family history suggest genetics may be making a significant contribution to weight control (Whitaker et al. 1997). Concern has been expressed that discussing differences in genetic risk may lead to fatalism and reduced motivation to address lifestyle. However, research suggests conveying genetic information to participants actually enhances motivation to alter lifestyles (Meisel and Wardle 2014). Balancing this message is challenging but focuses on acknowledging weight control is harder for some people than others but lifestyle change and successful weight management remains possible.

55.2.3.4 Dieting History

Discussing previous dieting attempts allows the time, effort, and frustration patients may have experienced to be acknowledged. Exploring triggers to previous attempts, the quantity and speed of weight loss and the helpful (e.g. group environment, regular weighing) and unhelpful elements of previous approaches are important and may help guide advice.

55.2.3.5 Eating Patterns

There are various maladaptive eating behaviours commonly found in this group (Peneau et al. 2013) including:

- Skipping meals
- Chaotic, disorganized eating
- Mindless eating
- Emotional eating
- Grazing
- Stress-related eating
- Night eating

To help identify relevant eating patterns consider exploring

- Time of day/context of eating/what else doing
- Frequency of eating meals/snacks
- Physical hunger, food cravings
- Fullness, satiety before and after food
- Speed of eating
- Physical state—e.g. daytime sleepiness, stress
- Feelings before, during, and after eating

Observational studies suggest regular eating improves dietary quality and weight control (Kirk and Hill 1997). Breakfast eating is a common habit recorded in the US National Weight Control Registry, a database of individuals successful at sustaining significant weight loss (Wyatt et al. 2002). However, randomized controlled trials examining breakfast eating and weight change do not show a clear effect (Schlundt et al. 1992; Dhurandhar et al. 2014). Given there is no consensus on optimal eating frequency, a flexible approach is needed during management. However, some opportunistic and emotional eating often occurs against a backdrop of excessive physical hunger from extended fasting, so here structure may be needed.

Binge eating disorder is present in up to 30% of obese people (Bruce and Wilfley 1996; Spitzer et al. 1993), so vigilance for possible symptoms is important. If concerned, a referral to psychological services may be appropriate and the use of assessment questionnaires can be helpful.

Binge cessation is the primary goal in managing this disorder, so deferring weight loss treatments until eating behaviours are stable is generally recommended. National Institute for Health and Clinical Excellence (NICE) eating disorder guidance outlines a stepped approach to treatment with self-help cognitive behavioural therapy (CBT) the first step (National Institute for Clinical Excellence 2017). If ineffective after 4 weeks, referral to a group or an individual CBT programme should be considered. Be aware that local eating disorder services may not accept referrals for binge eating disorder, and therefore specialist funding might need to be accessed.

Binge eating disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) but be vigilant for the symptoms given below:

- Eating an abnormally large amount of food in a discrete time period
- Feeling a loss of control during eating
- Eating quickly
- Eating until uncomfortably full
- Eating when not physically hungry
- Secret eating
- Feeling guilty and distressed after eating
- No compensatory behaviours, e.g. self-induced vomiting, excessive exercise, or laxative abuse

Given individuals with obesity often have disordered eating, it is important to distinguish between this and a clinical diagnosis of binge eating to avoid unnecessary referral. If unsure, refer to appropriately trained colleagues.

55.2.3.6 Current Dietary Intake

It is important to assess what and how much is eaten while acknowledging this may be difficult for some patients, particularly those experiencing shame about their eating.

Dietary assessment relies on self-report and can only provide an overall impression of eating habits and nutritional intake. Studies have shown obese subjects can under-report energy intakes by 30 and 70% compared with lean controls; therefore, trying to achieve greater accuracy through intensive questioning can be counter-productive and risks increasing patient resistance.

Diet histories or 24-h recalls have traditionally been used to evaluate dietary intake although the questioning style is important. The aim is to gather an overview of eating habits, exploring timings of meals, where food is eaten, hunger levels and associated thoughts and feelings. Discussing these issues before the types and quantities of foods may prove helpful and self-monitoring may provide further quantitative information.

Consider exploring the frequency of:

- Sugary drinks
- Take away meals
- Fruit and vegetable intake
- Alcohol intake
- High calorie snack foods

Questionnaires are another possible assessment method although the time taken to complete, analyse, and interpret findings should be considered.

- Check out this summary of brief assessment tools for use in clinical practice (England et al. 2015)
- Patient self-assessment—How Are You Quiz www.nhs.uk
- Rapid eating assessment questionnaire [REAP] (Gans et al. 2003)—designed for use in primary care by nursing staff

55.3 Dietary Approaches

There is no one superior dietary treatment for obesity management (Johnston et al. 2014) rather a range of evidence-based diets that can be matched to patient preferences, past experiences, and the presence of comorbidities. The focus of

treatment needs to be broadened beyond simply considering *what* and *how much* is eaten, towards helping patients consider *why* and *how* they are eating, so treatment can address these underlying issues (Grace 2011).

55.3.1 Low Fat Diet

Low fat diets remain the most researched treatment choice for obesity, with various theories linking high fat foods with weight gain including its high energy density, hedonic (reward) properties, and preferential storage (Blundell and Stubbs 1999; Drewnowski 1997; Flatt 1995).

Several large systematic reviews comparing lower with usual fat intake have shown consistent but small effects when reducing dietary fat (Hooper et al. 2012, 2015). The Look AHEAD (Action for Health in Diabetes) trial, a study exploring the impact of intensive lifestyle intervention on the development of cardiovascular disease (CVD) used a low fat diet (<30% energy from fat, <10% energy from saturated fat) as part of treatment in the intervention group with clinically meaningful weight loss of 8.6% at 12 months and 4.7% at year 8 observed (The Look Ahead Research Group 2014) A number of other large studies such as the Diabetes Prevention Trial (The Diabetes Prevention Program Research Group 2002) and the Finnish Diabetes Prevention study (Tuomilehto et al. 2001) have also observed weight losses with low fat approaches although these were all used as part of multicomponent programmes.

Most research exploring dietary fat and weight have considered different types of fat as equivalent in energy regulation. Limited research suggests possible differences in how saturated, unsaturated and trans-fats effect fatty acid oxidation rates, adipose tissue deposition, and other mechanisms involved in weight regulation with unsaturated fats associated with the most benefit (Piers et al. 2002, 2003; Soares et al. 2004).

The effect of modifying dietary fat on CVD risk reduction is also important. Despite ongoing controversy, a recent review concluded lowering saturated fats and partial replacement with polyunsaturates reduced CVD by ~30% although replacement with refined carbohydrates did not lower risk (Sacks et al. 2017). This recommendation on modifying fat intake should occur alongside the broader promotion of a healthy dietary pattern.

Although evidence supports modest weight loss with low fat diets, there is interest in whether other dietary treatments produce better results. In 2015, a systematic review comparing low fat with low carbohydrate diets found greater weight loss, albeit a modest 1.15 kg in the low carbohydrate group (Tobias et al. 2015). Although some concluded "low fat diets don't work", this review also noted those adopting low fat diets in place of usual eating lost 5.4 kg. Careful interpretation of this review is needed given the variation in sample populations and the diverse intervention and control diets.

55.3.2 The 600 kcal Deficit Approach

Basing dietary advice on reported food intake can be challenging when severe under-reporting of energy intake occurs (Lichtman et al. 1992; Prentice et al. 1986). This 600 kcal deficit approach bases agreed changes on an estimate of the energy requirements for weight loss rather than on reported intake. This requires the prediction of resting metabolic rate and an estimate of energy expended through physical activity as described below (Lean and James, 1986; Frost et al. 1991). A review of the effectiveness of this approach found weight losses of 5.31 kg at 12 months (Avenell et al. 2004).

55.3.2.1 How the 600 kcal Deficit Diet Is Calculated

- Calculate resting metabolic rate using Mifflin St. Joer predictive equation (Mifflin et al. 1990) (Table 55.1).
- Multiple results by a factor for physical activity called a PAL (Physical Activity Level) value.
- Subtract 600 kcal to give an estimate of energy needs for weight loss.
- Food group portion control charts can be used to help patients develop a meal plan based on this information.

Table 55.1 Mifflin St. Joer equations for predicting resting metabolic rate (Mifflin et al. 1990)

Men:	RMR = [10 × weight] + [6.25 × height] − [5 × age] + 5
Women:	RMR = [10 × weight] + [6.25 × height] − [5 × age] − 161

Equations use weight in kg, height in cm

Table 55.2 Physical activity level [PAL] descriptions (Scientific Advisory Committee on Nutrition 2009)

Typical activity = 1.63
Less active = 1.49
More active = 1.78

The PAL value is a numerical number given to describe levels of activity and is derived from studies where measures of resting metabolic rate are combined with total energy expenditure from doubly labelled water (Table 55.2).

Theoretically, this can produce 0.5 kg weight loss per week, given the weekly deficit of 3500 kcal is equivalent to 0.5 kg of fat. This is however an oversimplified model and has been shown to not reflect the weight losses seen in reality (Hall 2008). Over 6 months, losses of 10–12 kg should occur but in practice only half this predicted value is observed (Heymsfield et al. 2007) highlighting the compensatory mechanisms activated by weight loss, difficulties in compliance, and the complexity of obesity management.

This approach suits individuals seeking detailed guidance on portion sizes, or who find counting and exchange systems helpful. It should be noted that this approach only provides an estimate of energy needed for weight loss and the skill of the practitioner is required in tailoring the calculated energy prescription to the needs of the individual.

55.3.3 The Mediterranean Diet

The Mediterranean diet is an amalgamation of dietary practices from across a range of European countries including Crete, Greece, and Southern Italy and features a high intake of fruits and vegetables, legumes, nuts and seeds, olive oil, moderate consumption of wine, and low intakes of red and processed meats and refined sugars (Keys and Keys 1975). Nutritionally, this translates into increased consumption of fibre and whole grains, unsaturated fats, and anti-oxidants. The association of these dietary patterns with longevity and lower rates of cancer and CVD is well recognized (Sofi et al. 2008; Trichopoulou et al. 2003).

A pivotal trial, the Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) study randomized participants at high risk of CVD to either a Mediterranean diet supplemented with olive oil or nuts or a low fat diet. After 4.8 years, the results showed both Mediterranean diets were comparable, achieving a 30% risk reduction in myocardial infarction, stroke, or death and were superior to the low fat diet in the primary prevention of CVD (Martinez-Gonzalez et al. 2015). Despite benefiting CVD risk, further analysis of the PREDIMED cohort found there was no clinically significant beneficial effect on weight loss found within this cohort, with adjusted 5-year change between −0.08 and −0.43 kg (Estruch et al. 2016).

Given the higher fat content of the Mediterranean diet (ranges from <25 to >35%) (Willett et al. 1995), there has been some uncertainty about its role in weight management. There have been inconsistent findings in research exploring whether the Mediterranean diet promotes weight gain or leads to weight loss (Buckland et al. 2008). However, a recent systematic review which included people with obesity and a follow-up beyond 12 months found modest weight loss in the Mediterranean diet group (mean changes ranged from −3.8 to −10.1 kg) and in three of the trials produced greater weight loss than the low fat diet (Mancini et al. 2016). The review concluded the Mediterranean diet was an effective intervention but was not superior to other dietary treatments.

This is an important treatment approach to consider in obesity management particularly given its known CVD benefits. Further clarity on its relationship with weight is needed and whether

in practice energy restricted or ad libitum Mediterranean diets are more appropriate.

55.3.4 Low Glycaemic Index Diets

Glycaemic index (GI) is a method of ranking carbohydrate-containing foods according to their capacity to raise blood glucose levels after a meal and glycaemic load (GL) is the amount of carbohydrate in a portion of food and the speed with which it will raise blood glucose levels (Jenkins et al. 1980, 1981).

Whether low GI or low GL diets are helpful, dietary treatments in obesity management remain controversial (Brand-Millar 2005; Sloth et al. 2005). In theory, high GI diets increase postprandial hyperglycaemia and hyperinsulinaemia leading to altered fuel partitioning and increased body fat storage (Brand-Miller et al. 2002). Conversely, low GI diets may support weight loss through effects on increasing satiety and reducing hyperinsulinaemia after meals (McMillan-Price and Brand-Miller 2006). Although these theories are supported by animal research in humans findings are mixed (Sloth and Astrup 2006), with appetite influenced only in the short term (Ford and Frost 2010). There have been two reviews of low GI diets in obesity management. A Cochrane review in 2007 concluded a 1.09 kg greater difference in weight loss between the low GI and high GI group although the clinical relevance of this has been questioned (Thomas et al. 2007). However, treatment was short term with brief follow-up and less than half of the studies included those with obesity (Thomas et al. 2007). More recently, a systematic review considering only research in obese participants found no effect of the low GI intervention on weight change compared to control treatments (Braunstein et al. 2016).

It is also important to consider the impact of low GI diets on cardiovascular risk reduction and glycaemic control given the risk profile of this population. Three recent Cochrane reviews contrasting low and high GI diets in the prevention of CVD, dietary fibre for primary prevention of CVD, and whole grain cereals in primary and secondary CVD all concluded that there was insufficient evidence to recommend low GI or fibre diets (Clar et al. 2017; Hartley et al. 2016; Kelly et al. 2017). In terms of glycaemic control, using low GI diet has been shown to reduce HbA1c by 0.5% and also reduce hypoglycaemic episodes (Thomas and Elliott 2009).

As such it seems premature to routinely recommend this strategy as an evidence-based obesity management approach until further findings from large scale, high quality, long term randomized controlled trials are available.

55.3.5 Low Carbohydrate Diets

Low carbohydrate (LC) diets, officially defined as less than 130 g/day, are a popular approach for managing weight. Diets providing less than 50 g/day are termed very low carbohydrate ketogenic diets (Feinman et al. 2015).

Although there have been numerous reviews comparing LC diets with control interventions, the variations in study design, duration, the composition of intervention, and control diets have limited the interpretations drawn. In most of the reviews, greater short-term weight loss is found in the LC versus comparison diet although the clinical relevance is questionable given the differences range from 0.1 to 2.2 kg (Tobias et al. 2015; Sackner-Bernstein et al. 2015; Hashimoto et al. 2016; Bueno et al. 2013; Clifton et al. 2014).

There are conflicting findings on the impact of LC diets on CVD risk reduction. One review suggested greater reductions in triglycerides and high density lipoprotein concentrations but less favourable effects on total and low density lipoprotein (LDL) cholesterol compared to control diets (Nordmann et al. 2006). This may relate to the higher total and saturated fat content of LC diets compared to low fat approaches.

Several reviews exploring LC diets in overweight people with T2D have found comparable reductions in weight and glycaemic control regardless of the dietary intervention used. In one review although the low carbohydrate diet led to greater improvements in glycaemic control, the

clinical relevance was questionable with a mean difference in HbA1c of 0.14% (Ajala et al. 2013).

Concerns have been raised about possible adverse effects of LC diets including inadequate micronutrient intake, lack of dietary fibre, negative effects on renal function, and increased risk of CVD. Although dietary adequacy may be compromised with lower fibre and higher amounts of red meat (Elidottir et al. 2016), there is little supporting evidence that using LC diets has detrimental effects although long-term outcome data is needed.

At present, there is no compelling evidence to recommend LC diets as first-line therapy although individuals who choose to adopt a very low or low carbohydrate diet should be supported in their decision with suggested referral to a qualified nutrition professional (Dyson 2016).

55.3.6 Formula Diets

Formula diets are liquid shakes, soups, or bars fortified with vitamins and minerals, which either partially or completely replace food in the diet for a specified period. With total diet replacement, the formula diet can provide either a low energy (800–1200 kcal/day) or a very low energy diet (less than 800 kcal/day).

55.3.6.1 Partial Meal Replacements

Partial meal replacements (MR) provide 1200–1600 kcal/day by replacing two meals per day during the weight loss phase with the remaining meal made up of healthy foods. They may help due to their pre-defined portion size and convenience.

A review comparing MR with control dietary treatments found a 2.4 kg greater reduction at 1 year (Heymsfield et al. 2003). Meal replacements were also used in the intensive multicomponent treatment and maintenance intervention in the Look AHEAD study. The intensive lifestyle group lost 8.6% of their weight at 1 year compared to 0.7% in the control group and those regularly using MR lost the most weight over this time (Wadden et al. 2009). Research in type 2 diabetes has also found MR produce greater reductions in HbA1c, fasting glucose and fasting insulin, although there have been calls for better quality research to improve confidence in the conclusions drawn (Noronha et al. 2016).

A review of evidence by the Dietitians Association of Australia in 2012 concluded "achieving a reduction in energy intake by incorporating MR, monitored by health professionals, provides greater weight loss in overweight and obese adults than general dietary advice for periods of 1–12 months" (Dietitians Association of Australia 2012). Indeed the majority of reviews on MR suggest when used as part of multicomponent programmes with health professional support they are just as effective, if not more so than other dietary treatments. There is a need for future research to incorporate longer term follow-up and explore who does best with this type of approach. Little is known about the effectiveness of MR purchased over the counter where there is no professional support, structured education, or close monitoring.

55.3.6.2 Total Diet Replacements

With a total diet replacement (TDR) all conventional foods are replaced with formula products and daily energy intake can be varied depending on the number of products advised. Traditionally, TDR provided ≤800 kcal/day and were referred to as very low energy diets (VLED). However, recent evidence has found comparable weight losses with low energy diets (LED) (800–850 kcal/day) and comparably fewer side effects (Christensen et al. 2011); therefore, focus has shifted towards using LED with intakes between 800 and 1200 kcal/day.

Interest in total diet replacements has also been sparked by the realization that conventional diets that create modest energy deficits and weight losses may lead to metabolic improvements and prevent development of disease but rarely cause remission disease once it is present. As such those with complex obesity may need to lose 15–20% weight to experience improvement or remission of comorbid disease (Scottish Intercollegiate Guidelines Network 1996). This necessitates intensive management with approaches such as TDR. Recent evidence also

suggests those losing the most weight early in treatment do better long-term running counter to the slow steady weight loss recommendation (Nackers et al. 2010; Unick et al. 2015; Wadden et al. 2011).

55.3.6.2.1 Very Low Energy Formula Diet

Very low energy diets (VLED, 600–800 kcal/day) have traditionally been the most controversial dietary treatment due to questions over long-term efficacy and historical safety concerns related to nutritional inadequacy in the early formulations that have now been resolved (Brown et al. 2015).

VLED have been shown to produce signficant short term weight losses and improvements in comorbidities although, several reviews suggest no difference in weight loss between VLED and LED over the long term (12 months) (Tsai and Wadden 2006). However, given many of these studies failed to address weight maintenance this is perhaps unsurprising. More is now known about strategies to minimize weight regain after VLED including behaviour modification, ongoing use of formula products, weight loss medication, and a longer food reintroduction phase (Johansson et al. 2014; Christensen et al. 2017).

Common side effects (diarrhoea, constipation, headaches, nausea, dizziness, poor cold tolerance, dry skin, and thinning hair) tend to be fairly mild and transient often occurring during the weight loss phase (Christensen et al. 2011; Lean et al. 2018). More serious but less common side effects include acute gout and gallstones. Clinical supervision and medical monitoring are important particularly for those with comorbid disease where medication adjustment will be needed as requirements change in response to energy restriction, metabolic changes, and rapid weight loss. The Counterweight-Plus feasibility study explored the outcome of a 12-week TDR in 91 obese participants (mean BMI 48) treated in primary care and found a mean weight loss of 12.4 kg at 12 months in those completing the study, with 33% of study participants maintaining more than 15 kg (Lean et al. 2013). This suggested such a dietary method was possible in a clinical setting given the right support.

55.3.6.2.2 VLED in Type 2 Diabetes

In 2011, a pivotal study examined the possibility of reversing beta cell failure and insulin resistance and producing T2D remission using a VLED (Lim et al. 2011). After the first week fasting glucose had normalized, hepatic insulin sensitivity improved and by week eight, beta cell function was nearly normal and pancreatic fat content had fallen (Lim et al. 2011). Excess fat (ectopic fat) in the pancreas and liver is now understood as central to T2D development and acute energy restriction key to its management (Taylor and Barnes 2018).

A number of small studies using VLED in those with T2D treated with insulin have found encouraging effects on weight loss, glycaemic control, and CVD risk although there is a need for improved study design and longer term studies (Snel et al. 2012; Paisey et al. 2002; Hammer et al. 2008; Pedersen et al. 2015).

55.3.6.2.3 Formula Low Energy Diet

Low energy diets (LED) are between 800 and 1200 kcal/day although most recent research has used formula LED diets providing 800–850 kcal/day (Brown et al. 2015).

The recent Diabetes in Remission (DiRECT) trial has shed light on the use of formula LED with a specialist weight maintenance programme in the management of early onset T2D (≤6 years) and more specifically the feasibility of inducing T2D remission (Lean et al. 2018). The study a randomized trial undertaken in 49 primary care practices, included individuals (BMI 27–45 kg/m^2) diagnosed with T2D within the previous 6 years. The intervention group followed the formula LED for 12 week, with the option to increase to 20 weeks if insufficient weight loss was achieved. A stepped food reintroduction followed with structured long-term support. The control group followed current clinical practice care of 3 monthly contacts. At 12 months, 24% of those in the intervention group had lost ≥15 kg compared to none in the control group (Lean et al. 2018). Diabetes remission, defined as HbA1c <6.5% (48 mmol/mol) after at least 2 months of all antidiabetic medication from baseline to 12 months, had occurred in nearly half of those (46%) in the

intervention group compared to 4% in the control group. Mean body weight fell by 10 kg in the intervention group and 1 kg in the control group. Although some weight regain was observed during food reintroduction and maintenance phases this was not the rapid regain reported to occur with formula TDR. This study clearly demonstrated the capacity of intensive formula low energy TDR with the additional of a long-term weight maintenance programme to produce T2D remission. The long-term follow-up of this cohort is awaited with interest and seems likely to provide further guidance on how best to optimize weight maintenance.

The NICE obesity guidance (National Institute for Clinical Excellence 2014) suggests LED can be considered in obesity management but highlighted possible nutritional inadequacy of food-based approaches. Formula low energy diets overcome this concern due to their nutritional completeness for vitamin and minerals and given the latest evidence on their efficacy it is important to consider this as an evidenced-based treatment option.

NICE recommendations on VLED state that they should not be used as a routine treatment but reserved for use in those with a clinical need for rapid weight loss (National Institute for Clinical Excellence 2014). They further recommend VLED are used as part of multicomponent programmes, require comprehensive assessment and counselling on the risks and benefits particularly the potential of weight regain.

55.3.7 Intermittent Energy Restriction

Most dietary approaches use continuous energy restriction where energy deficits are adopted daily but an alternative is to markedly restrict (60–85% lower than typical intake; or approximately 600 kcal) on only a few days and return to usual intake on the remainder. This approach has become increasingly popular and is referred to as intermittent fasting/energy restriction (IER) or colloquially as the 5:2 diet.

Findings from systematic reviews suggest IER can produce similar but not superior weight losses and metabolic improvements compared to other dietary interventions and may offer an alternative approach for some individuals (Harvie and Howell 2017; Harris et al. 2018). However, research is limited by small sample sizes and short-term duration.

Comparable metabolic improvements have been observed in total cholesterol, LDL-cholesterol, triglycerides, and/or blood pressure although in healthy overweight or obese populations greater reductions in insulin resistance have been found in those using IER (Harvie et al. 2011, 2013). No differences in body composition changes with weight loss or resting metabolism have been observed. Despite the commercial popularity of the 5:2 diet to date very few studies of a quality that could guide best practice have been published.

Although there have been some concerns this approach may trigger erratic eating patterns, eating disorders, compensatory hyperphagia on "normal" eating days or low mood, there is no supporting evidence although longer term studies are needed.

55.3.8 Fad Diets

Fad diets are those unsupported by scientific evidence, promise quick effortless weight loss, and are often accompanied by enticing marketing messages. Examples of fad diets include detox programmes, food combining, blood group diet, and the grapefruit diet.

To help patients recognize fad diets and resist their non-evidence-based solutions, the American Heart Association [www.american-heart.org] suggests being aware of the following claims:

- **Magic or miracle foods** that burn fat
- **Bizarre quantities** of only one food or type of food
- **Rigid menus**
- **Specific food combinations**
- **No warning** to those with medical conditions to seek their doctor's advice
- **No increased physical activity**

55.4 Behaviour Modification

Behavioural modification focuses on patient-centred care and incorporates motivational, behavioural, and cognitive elements while acknowledging the nurses attitudes and skills have a profound effect on outcomes. It is different from traditional advice giving where the professional is the expert and the patient a passive recipient.

55.4.1 Motivational Approaches

Motivational interviewing (MI) is "a collaborative conversation style for strengthening a person's own motivation and commitment to change" (Miller and Rollnick 2013) and involves expressing empathy, acknowledging past efforts, and helping identify patient's goals and values. Traditionally, ambivalence has been viewed as non-compliance rather than a normal part of changing that requires compassion and a problem-solving approach.

Comprehensive training is important to develop the required skills such as reflective listening, affirmations, and providing information in a helpful way. For further guidance, refer to www.motivationalinterviewing.org. Importance and confidence are key determinants of motivation. Patient's values and beliefs about change affect the importance of that change and influence motivation accordingly. If a change aligns with the individual's values, is believed important and effective, motivation will probably increase and implementation is more likely. Likewise, beliefs about one's abilities to change affect confidence that in turn can influence motivation.

55.4.2 Behavioural and Cognitive Approaches

Using cognitive behavioural approaches improves outcomes in managing obesity with a 3.1 kg greater weight loss using this approach compared to usual care (National Institute for Clinical Excellence 2014). There are a number of core strategies that form the foundation of this approach and require comprehensive training to maximize outcomes achieved.

55.4.3 Core Strategies

55.4.3.1 Self-Monitoring

Self-monitoring is a time-consuming and challenging skill but is the cornerstone of most behavioural treatments in obesity, with those regularly self-monitoring their behaviour achieving superior weight loss. Participants in the National Weight Control Registry, a database of individuals successfully maintaining greater than 10 kg weight loss, report frequent monitoring of eating habits and weight (Hill and Wing 2003).

The purpose of self-monitoring is to increase patient's awareness of their own behaviours and how they relate to weight. Monitoring can focus on eating habits, physical activity, and/or weight although in reality all of these need to be considered. This strategy can be used throughout treatment although some may become fatigued and choose to use intermittently particularly during challenging times.

Self-monitoring helps identify behaviours to address in treatment but may also independently lead to change as self-awareness enhances. Identifying the "problem" is the first step in problem solving, another important behavioural strategy. Practitioners need to accept and understand the extent of under-reporting of food intake, evident in many diaries, and not be distracted from the true purpose of self-monitoring [self-awareness and problem identification] by pursuing the quest for accurate nutrient quantification.

Paper diaries are often used to monitor food intake however phone apps, e.g. Carbs & Cals, My Fitness Pal use food photographs to guide portion size estimation and provide instant feedback and have higher rates of acceptability and satisfaction.

It is essential that self-monitoring is used sensitively given some patients may be fearful of being judged about their eating. As such it is best to reserve this strategy until trust has been

established and patients understand that the purpose of diaries is to increase awareness of their own behaviours rather than a record to be inspected and commented on by the health professional.

Self-monitoring body weight is also important with research suggesting frequent weight checks are associated with improved weight management. Although there is no agreement on the optimal frequency of weighing a number of studies suggest higher frequency, sometimes daily weighing, is more effective for weight loss and maintenance than the commonly recommended once a week checks. This higher frequency monitoring facilitates earlier identification of lapses, triggering earlier self-correction. Some patients may need guidance on how to respond to the number on the scale so the reading is treated simply as information rather than for self-criticism. In clinical practice, the frequency of weighing needs careful exploration with individuals to agree on a helpful monitoring frequency. Daily weighing is not recommended for those diagnosed with an eating disorder or in children and adolescents (Grace 2011).

55.4.3.2 Stimulus Control

The environment can have a substantial negative or positive impact on eating. This strategy involves working with patients to identify, and then develop ways of modifying, the cues or the barriers linked with overeating. A helpful time to use stimulus control is following a lapse when concrete examples of unhelpful habits can often be traced back to cue exposure. A cue can be external (situations relating to shopping, cooking, or eating) or internal (boredom, sadness, anger, hunger, cravings).

Examples of changes to external cues may include

- When shopping
  - Limiting high calorie snacks
  - Buying plenty of fruits and vegetables
- When cooking
  - Preparing only the amount needed
  - Altering portions served
  - Reducing plate size
- When eating
  - Avoiding watching TV, reading, or driving while eating
  - Prioritizing eating at the table

Eating mindlessly while preoccupied with another activity (e.g. watching TV) is an increasingly common behaviour linked with weight gain (Wansink 2011). Distracted eating reduces awareness of foods consumed and lowers satisfaction from eating. Sitting in front of the TV at other times of the day may subsequently trigger cravings and breaking this pattern by removing the stimulus and changing the location of meals may prove useful.

Eating in response to internal triggers (e.g. cravings, emotions) is common and can be challenging to manage. The first step is to make the distinction between physical hunger and food cravings. Talking through the sensations of physical hunger (gnawing in stomach, light headed, irritability, shakiness) and comparing with those associated with cravings (urges in the head or mouth, linked with emotions, often for a specific food) can be helpful.

There are then three options in managing food cravings:

- Use distraction until the food craving has passed—waiting 15–20 min and asking is this really physical hunger?
- Try to identify and address body's real needs, e.g. sleep or relaxation.
- Eat anyway—Take time, savour the taste, pick a fixed portion, and avoid feeling guilty. Recognize if this occurs too frequently; it will hinder weight loss.

55.4.3.3 Goal Setting

Planning and goal setting are essential to developing a successful action plan. It is often more meaningful to talk about the what, how, and when of change rather than SMART goals which may have limited meaning to patients. It is important not to confuse goal setting with targets such "eat less sugar" or "include breakfast" which are too vague to be helpful. Patients need to provide as much detail as possible and consider whether this is realistic.

Detailed food change plan	
What to change:	Have breakfast every day
How to change:	Set alarm 20 min earlier Leave cereal packet on table Add healthy cereal to shopping list
What might get in the way?	Press the snooze button
How might I overcome this?	Move the alarm out of reach
When will I start?	Tomorrow

55.4.3.4 Problem Solving

Problem solving is a core patient skill particularly given its value in overcoming challenging situations that can derail new behaviours. It helps patients develop a positive mindset towards overcoming difficulties rather than their avoidance. A step-by-step approach is used to identify the problem and develop various options to overcome challenges. If patients struggle to make suggestions, the practitioner can draw on other patient's experiences but asking permission before doing this may reduce resistance. The patient chooses the preferred option and a detailed plan is developed. Patients should be encouraged to think of their plan as a work in progress that can be adjusted depending on how it works in reality.

55.4.3.5 Cognitive Restructuring

Understandably, people who struggle with weight may have negative self-defeating thoughts about their size, their difficulties managing it, and the likelihood of succeeding long term. Negative thoughts tend to be automatic, distorted, unhelpful, and often accepted as true. Helping patients to identify and then challenge negative thinking requires a confident and skilled practitioner but it can be helpful for patients to consider "What evidence is there that this thought is true or false?" "What would you say to a friend who had these thoughts?" Over time, patients can learn to reframe negative thoughts in a more helpful way.

55.4.3.6 Social Support

People with higher levels of social support tend to do better in weight management compared to those with little. The forms of support can vary from family members, friends, peers, group programmes, or other social activities. Social support probably helps through its influence on motivation, self-efficacy, and self-acceptance. Helping the patients recognize the value of social support and build a network of helpful support is an important aspect of behavioural modification.

55.4.3.7 Self-Rewards

Using self-rewards or positive reinforcement after achieving a behavioural goal increases the chance of the behaviour continuing. Indeed using self-rewards increases weight loss maintenance at 12 months (Kramer et al. 1986; Brownell 1989). This can be a challenging strategy to implement as patients may struggle to identify rewards unrelated to eating or feel undeserving of a reward but perseverance is important as this strategy will support long-term behaviour change.

55.4.3.8 Relapse Prevention

Lapses are a normal part of changing and often occur in response to high-risk situations such as social events or emotional challenges. The inevitability of lapses and the need to learn management skills should be discussed at the start of treatment to ensure patients understand how to prevent lapses becoming relapse. Lapses are an opportunity for identifying high-risk situations, using problem solving to achieve different outcomes and cognitive restructuring to reframe associated negative thoughts.

55.5 Conclusions

Given the interpersonal skills of the nurse have a substantial impact on the likely outcome of obesity management, it is essential for individuals to reflect on their attitudes to obesity and invest in training to facilitate the skilled application of behaviour modification. The nurse's role may focus on raising the issue of weight sensitively and signposting to appropriate local services. When nurses are providing lifestyle treatments, comprehensive assessment is crucial to facilitate appropriate treatment choices that take account

of the complexity of obesity. A key component of the nursing role is the provision of patient education and skills development crucial to the long-term management of obesity.

References

Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr. 2013;97(3):505–16.

American Psychiatric Association. Binge-eating disorder. Diagnostic & statistical manual of mental disorders. Arlington: American Psychiatric Association; 2013. p. 350–3.

Avenell A, Broom J, Brown J, Poobalan A, Ancott L, Stearns S. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvements. Health Technol Assess. 2004;8(21):iii–iv, 1–182.

Aveyard P, Lewis A, Tearne S, et al. Screening and brief intervention for obesity in primary care: a parallel, two arm randomised trial. Lancet. 2016;388(10059):2492–500.

Blundell JE, Stubbs RJ. High and low carbohydrate and fat intakes: limits imposed by appetite and palatability and their implications for energy balance. Eur J Clin Nutr. 1999;53(Suppl 1):S148–65.

Brand-Millar J. Glycaemic index and body weight. Am J Clin Nutr. 2005;81:722–3.

Brand-Miller JC, Holt SH, Pawlak D, Mcmillan J. Glycemic index and obesity. Am J Clin Nutr. 2002;76(1):281S–5S.

Braunstein CR, Mejia SB, Stoiko E, et al. Effect of low-glycemic index/load diets on body weight: a systematic review and meta-analysis. FASEB J. 2016;30(1 Suppl):906.9.

Brown I. Nurses' attitudes towards adult patients who are obese: literature review. J Adv Nurs. 2006;53(2):221–32.

Brown A, Frost G, Taheri S. Is there a place for low-energy formula diets in weight management. Br J Obes. 2015;1(3):84–119.

Brownell KD. Weight cycling. Am J Clin Nutr. 1989;49(5 Suppl):937.

Bruce B, Wilfley D. Binge eating among the overweight population: a serious and prevalent problem. J Am Diet Assoc. 1996;96(1):58–61.

Buckland G, Bach A, Serra-Majem L. Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. Obes Rev. 2008;9(6):582–93.

Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110(7):1178–87.

Christensen P, Bliddal H, Riecke BF, Leeds AR, Astrup A, Christensen R. Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial. Clin Obes. 2011;1(1):31–40.

Christensen P, Henriksen M, Bartels EM, et al. Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial. Am J Clin Nutr. 2017;106(3):755–63.

Clar C, Al-Khudairy L, Loveman E, et al. Low glycaemic index diets for the prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;7:CD004467.

Clifton PM, Condo D, Keogh JB. Long term weight maintenance after advice to consume low carbohydrate, higher protein diets—a systematic review and meta analysis. Nutr Metab Cardiovasc Dis. 2014;24(3):224–35.

Cooper Z, Fairburn C, Hawker D. Cognitive-behavioral treatment of obesity: a clinician's guide. New York: Guildford Press; 2004.

Dhurandhar EJ, Dawson J, Alcorn A, et al. The effectiveness of breakfast recommendations on weight loss: a randomized controlled trial. Am J Clin Nutr. 2014;100(2):507–13.

Dietitians Association of Australia. DAA Best practice guideliens for the treatment of overweight and obesity in adults DAA; 2012.

Drewnowski A. Taste preferences and food intake. Annu Rev Nutr. 1997;17:237–53.

Dyson P. Evidence based summary of the research into low carbohydrate diets for weight loss. www.bda.uk.com. British Dietetic Association; 2016.

Elidottir A, Halldorsson T, Gunnarsdottir I, Ramel A. Dietary intake and cardiovascular risk factors in Icelanders following voluntarily a low carbohydrate diet. PLoS One. 2016;11(8):e0156655.

England CY, Andrews RC, Jago R, Thompson JL. A systematic review of brief dietary questionnaires suitable for clinical use in the prevention and management of obesity, cardiovascular disease and type 2 diabetes. Eur J Clin Nutr. 2015;69(9):977–1003.

Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. Lancet Diabetes Endocrinol. 2016;4(8):666–76.

Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31(1):1–13.

Flatt JP. Use and storage of carbohydrate and fat. Am J Clin Nutr. 1995;61(4 Suppl):952S–9S.

Ford H, Frost G. Glycaemic index, appetite and body weight. Proc Nutr Soc. 2010;69(2):199–203.

Foster GD, Wadden TA, Phelan S, Sarwer DB, Sanderson RS. Obese patients' perceptions of treatment outcomes and the factors that influence them. Arch Intern Med. 2001;161(17):2133–9.

Frank A. Futility and avoidance. Medical professionals in the treatment of obesity. JAMA. 1993;269(16): 2132–3.

Frost G, Masters K, King C, et al. A new method of energy prescription to improve weight loss. J Hum Nutr Diet. 1991;4(6):369–73.

Gans KM, Ross E, Barner CW, Wylie-Rosett J, McMurray J, Eaton C. REAP and WAVE: new tools to rapidly assess/discuss nutrition with patients. J Nutr. 2003;133(2):556S–62S.

Grace C. A review of one-to-one dietetic obesity management in adults. J Hum Nutr Diet. 2011;24(1):13–22.

Hall KD. What is the required energy deficit per unit weight loss? Int J Obes. 2008;32(3):573–6.

Hammer S, Snel M, Lamb HJ, et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. J Am Coll Cardiol. 2008;52(12):1006–12.

Harris L, McGarty A, Hutchison L, Ells L, Hankey C. Short-term intermittent energy restriction interventions for weight management: a systematic review and meta-analysis. Obes Rev. 2018;19(1):1–13.

Hartley L, May MD, Loveman E, Colquitt JL, Rees K. Dietary fibre for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2016;(1):Cd011472.

Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight and normal weight subjects—a narrative review of human and animal evidence. Behav Sci (Basel). 2017; 7(1).

Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes. 2011;35(5):714–27.

Harvie M, Wright C, Pegington M, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. Br J Nutr. 2013;110(8):1534–47.

Hashimoto Y, Fukuda T, Oyabu C, et al. Impact of low-carbohydrate diet on body composition: meta-analysis of randomized controlled studies. Obes Rev. 2016;17(6):499–509.

Heymsfield SB, van Mierlo CA, van der Knaap HC, Heo M, Frier HI. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. Int J Obes Relat Metab Disord. 2003;27(5):537–49.

Heymsfield SB, Harp JB, Reitman ML, et al. Why do obese patients not lose more weight when treated with low-calorie diets? A mechanistic perspective. Am J Clin Nutr. 2007;85(2):346–54.

Hill J, Wing R. The National Weight Control Registry. Perm J. 2003;7:34–7.

Hooper L, Abdelhamid A, Moore HJ, Douthwaite W, Skeaff CM, Summerbell CD. Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. BMJ. 2012;345:e7666.

Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. Cochrane Database Syst Rev. 2015;(8):CD011834.

Jenkins DJ, Wolever TM, Taylor RH, et al. Rate of digestion of foods and postprandial glycaemia in normal and diabetic subjects. Br Med J. 1980;281(6232): 14–7.

Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34(3):362–6.

Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;99(1):14–23.

Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA. 2014;312(9):923–33.

Kelly SA, Hartley L, Loveman E, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;8:Cd005051.

Keys A, Keys M. How to eat well and stay well the Mediterranean way. New York: Doubleday; 1975.

Kirk S, Hill A. Exploring the food beliefs and eating behaviour of successful and unsuccessful dieters. J Hum Nutr Diet. 1997;10:331–41.

Kramer FM, Jeffery RW, Snell MK. Monetary incentives to improve follow-up data collection. Psychol Rep. 1986;58(3):739–42.

Lean M, Brosnahan N, McLoone P, et al. Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity. Br J Gen Pract. 2013;63(607): e115–24.

Lean ME, James WP. Prescription of diabetic diets in the 1980s. Lancet. 1986;1:723–5.

Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541–51.

Lent MR, Vander Veur SS, Peters JC, et al. Initial weight loss goals: have they changed and do they matter? Obes Sci Pract. 2016;2(2):154–61.

Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. N Engl J Med. 1992;327(27):1893–8.

Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54(10):2506–14.

Linne Y, Hemmingsson E, Adolfsson B, Ramsten J, Rossner S. Patient expectations of obesity treatment-

the experience from a day-care unit. Int J Obes Relat Metab Disord. 2002;26(5):739–41.
Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic review of the Mediterranean diet for long-term weight loss. Am J Med. 2016;129(4):407–15. e4
Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, et al. Benefits of the Mediterranean diet: insights from the PREDIMED study. Prog Cardiovasc Dis. 2015;58(1):50–60.
McMillan-Price J, Brand-Miller J. Low-glycaemic index diets and body weight regulation. Int J Obes. 2006;30(Suppl 3):S40–6.
Meisel SF, Wardle J. Responses to FTO genetic test feedback for obesity in a sample of overweight adults: a qualitative analysis. Genes Nutr. 2014;9(1):374.
Michie S. Talking to primary care patients about weight: a study of GPs and practice nurses in the UK. Psychol Health Med. 2007;12(5):521–5.
Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241–7.
Miller W, Rollnick S. Motivational interviewing: preparing people to change. New York: The Guildford Press; 2002.
Miller W, Rollnick S. Motivational interviewing: helping people change. New York: Guildford Press; 2013.
Nackers LM, Ross KM, Perri MG. The association between rate of initial weight loss and long-term success in obesity treatment: does slow and steady win the race? Int J Behav Med. 2010;17(3):161–7.
National Institute for Clinical Excellence. Obesity: identification, assessment and management of overweight and obesity in children young people and adults. NICE clinical guideline: National Institute for Clinical Excellence; 2014.
National Institute for Clinical Excellence. Eating disorders: recognition and treatment; 2017.
Nolan C, Deehan A, Wylie A, Jones R. Practice nurses and obesity: professional and practice-based factors affecting role adequacy and role legitimacy. Prim Health Care Res Dev. 2012;13(4):353–63.
Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166(3):285–93.
Noronha JC, Mejia SB, Braunstein CR, et al. Liquid meal replacements improve glycemic control: a systematic review and meta-analysis of randomized controlled trials image 9. Can J Diabetes. 2016;40(5):S14.
Paisey RB, Frost J, Harvey P, et al. Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. J Hum Nutr Diet. 2002;15(2):121–7.
Pedersen LR, Olsen RH, Jurs A, et al. A randomised trial comparing weight loss with aerobic exercise in overweight individuals with coronary artery disease: the CUT-IT trial. Eur J Prev Cardiol. 2015;22(8):1009–17.
Peneau S, Menard E, Mejean C, Bellisle F, Hercberg S. Sex and dieting modify the association between emotional eating and weight status. Am J Clin Nutr. 2013;97(6):1307–13.
Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. The influence of the type of dietary fat on postprandial fat oxidation rates: monounsaturated (olive oil) vs saturated fat (cream). Int J Obes Relat Metab Disord. 2002;26(6):814–21.
Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. Br J Nutr. 2003;90(3):717–27.
Prentice AM, Black AE, Coward WA, et al. High levels of energy expenditure in obese women. BMJ. 1986;292(6526):983–7.
Puhl R, Brownell KD. Ways of coping with obesity stigma: review and conceptual analysis. Eat Behav. 2003;4(1):53–78.
Rollnick S, Mason P, Butler C. Health behaviour change. Edinburgh: Churchill Livingstone; 1999.
Sackner-Bernstein J, Kanter D, Kaul S. Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A meta-analysis. PLoS One. 2015;10(10):e0139817.
Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation. 2017;136(3):e1–e23.
Schlundt DG, Hill JO, Sbrocco T, Pope-Cordle J, Sharp T. The role of breakfast in the treatment of obesity: a randomized clinical trial. Am J Clin Nutr. 1992;55(3):645–51.
Scientific Advisory Committee on Nutrition. SACN energy requirements working group draft report; 2009.
Scottish Intercollegiate Guidelines Network. Obesity in Scotland 1996. A national guideline for use in Scotland. Edinburgh: SIGN; 1996.
Scottish Intercollegiate Guidelines Network. Management of obesity. A national clinical guideline; 2010.
Sloth B, Astrup A. Low glycemic index diets and body weight. Int J Obes. 2006;30(Suppl 3):S47–51.
Sloth B, Krog-Mikkelsen I, Flint A, Tetans I, Astrup A, Raben A. Repy to J Brand Miller. Am J Clin Nutr. 2005;81:723.
Snel M, Jonker JT, Hammer S, et al. Long-term beneficial effect of a 16-week very low calorie diet on pericardial fat in obese type 2 diabetes mellitus patients. Obesity (Silver Spring). 2012;20(8):1572–6.
Soares MJ, Cummings SJ, Mamo JC, Kenrick M, Piers LS. The acute effects of olive oil v. cream on postprandial thermogenesis and substrate oxidation in postmenopausal women. Br J Nutr. 2004;91(2):245–52.
Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337:a1344.
Spitzer RL, Yanovski S, Wadden T, et al. Binge eating disorder: its further validation in a multisite study. Int J Eat Disord. 1993;13(2):137–53.

Taylor R, Barnes AC. Translating aetiological insight into sustainable management of type 2 diabetes. Diabetologia. 2018;61(2):273–83.

The Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care. 2002;25(12):2165–71.

The Look Ahead Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring). 2014;22(1):5–13.

Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev. 2009;(1):Cd006296.

Thomas D, Elliot E, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev. 2007;(3):CD005105.

Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3(12):968–79.

Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599–608.

Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring). 2006;14(8):1283–93.

Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343–50.

Unick JL, Leahey T, Kent K, Wing RR. Examination of whether early weight loss predicts 1-year weight loss among those enrolled in an Internet-based weight loss program. Int J Obes. 2015;39(10):1558–60.

Wadden TA, West DS, Neiberg RH, et al. One-year weight losses in the Look AHEAD study: factors associated with success. Obesity (Silver Spring). 2009;17(4):713–22.

Wadden TA, Neiberg RH, Wing RR, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. Obesity. 2011;19(10):1987–98.

Wansink B. Mindless eating: environmental contributors to obesity. In: Cawley J, editor. The Oxford handbook of the social science of obesity. New York: Oxford University Press; 2011.

Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337(13):869–73.

White MA, Masheb RM, Rothschild BS, Burke-Martindale CH, Grilo CM. Do patients' unrealistic weight goals have prognostic significance for bariatric surgery? Obes Surg. 2007;17(1):74–81.

Willett WC, Sacks F, Trichopoulou A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995;61(6 Suppl):1402S–6S.

Wyatt HR, Grunwald GK, Mosca CL, Klem ML, Wing RR, Hill JO. Long-term weight loss and breakfast in subjects in the National Weight Control Registry. Obes Res. 2002;10(2):78–82.

56 Assessment of the Patient with Obesity and Bariatric Surgical Interventions

Saira Hameed and Harvinder Chahal

Contents

56.1 **Assessment of the Patient with Obesity** 1087

56.2 **Clinical Assessment** 1088
56.2.1 Clinical History and Obesity Staging/Scoring Systems 1088
56.2.2 Physical Examination 1090
56.2.3 Diagnostic Tests 1090

56.3 **Identification of Patients for Bariatric Surgery** 1091
56.3.1 The Right Patient 1091
56.3.2 The Right Operation 1092
56.3.3 Important Information for Patients Undergoing Assessment for Bariatric Surgery 1094
56.3.4 The Right Time 1094
56.3.5 Multi-disciplinary Decision-Making 1094

56.4 **Preparing a Patient for Bariatric Surgery** 1095
56.4.1 Assessment of Pre-operative Micronutrient Status 1095
56.4.2 Pre-operative Diet 1095
56.4.3 Smoking 1095
56.4.4 Alcohol Consumption 1095

56.5 **Post-operative Follow-Up** 1096
56.5.1 Post-operative Micronutrient Status 1096
56.5.2 The Post-operative Diet and Food Choices 1096
56.5.3 Medication Changes 1096

56.6 **Conclusions** 1097

56.7 **Key Points to Provoke Readers' Critical Thinking** 1097

References 1098

S. Hameed · H. Chahal (✉)
Imperial Weight Centre, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

Investigative Medicine, Division of Diabetes, Endocrinology and Metabolism, Imperial College London, London, UK
e-mail: s.hameed@imperial.ac.uk; h.chahal@imperial.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_56

Abstract

The worldwide prevalence of obesity has been described as an 'epidemic' by the World Health Organization (WHO). For the first time in human history, the prevalence of obesity and overweight now exceeds that of underweight and malnutrition and it is predicted that obesity could reverse the trend for increased life expectancy that has, to date, been realised by successive generations. The seriousness of the problem has led the Chief Executive of the UK National Health Service (NHS) to describe obesity as 'the new smoking'.

Obesity is associated with physical and mental health comorbidities including cardiovascular disease, type 2 diabetes, certain cancers, joint pathology, obstructive sleep apnoea, depression and anxiety. These comorbidities impact both on the individual patient and society as a whole through loss of economic productivity and increased healthcare costs.

Assessment of the patient with obesity requires a whole team, multi-disciplinary team (MDT) approach including, but not limited to, specialist nurses, endocrinologists, dieticians, psychologists, psychiatrists, surgeons and anaesthetists. This allows for a holistic review of the patient's physical and mental health status and an MDT treatment plan.

The treatment options for obesity include lifestyle and behavioural modification and/or pharmacotherapy and/or bariatric surgery. Of all of these treatment modalities, there is clear evidence of the superior efficacy of bariatric surgery for weight loss, long-term weight maintenance, and amelioration of obesity associated comorbidities.

Despite the significant number of obese patients that would benefit from it, in most countries bariatric surgery remains a limited treatment option. In the UK, where 25% of the adult population are obese, just 5000 bariatric operations are carried out annually which means that currently less than 1% of those who could benefit get treatment. For those patients who do undergo weight-loss surgery, the most commonly performed bariatric procedures are gastric banding, Roux-en-Y gastric bypass and sleeve gastrectomy. Specialist pre- and post-operative nursing care including long-term post-surgery follow-up are essential to good patient outcomes and overall surgical success.

Keywords

Obesity · Obesity associated comorbidities · Bariatric surgery · Gastric band · Roux-en-Y gastric bypass · Sleeve gastrectomy

Abbreviations

AUD	Alcohol use disorder
BMI	Body mass index
BOMSS	British Obesity and Metabolic Surgery Society
CPAP	Continuous Positive Airways Pressure (ventilation)
ECG	Electrocardiogram
EOSS	Edmonton Obesity Staging System
FBC	Full blood count
GORD	Gastro-oesophageal reflux disease
HADS	Hospital Anxiety and Depression Scale
KOSC	King's Obesity Staging Criteria
LFTs	Liver function tests
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ODG	Oesophago-gastro-duodenoscopy
RYGB	Roux-en-Y gastric bypass
SF-36	Short Form (36) Health Survey
VLCD	Very low calorie diet
WHO	World Health Organization

Key Terms

- **Bariatric surgery**: Surgical procedures to induce weight loss.
- **EOSS**: Edmonton obesity staging system; grading of the obesity for guiding treatment decisions.
- **KOSC**: King's obesity staging criteria; tool for the assessment of the obese patient.
- **Obesity staging**: A method of grading to allow for specific treatment planning.
- **Obesity**: A body mass index of >30 kg/m^2.

- **Roux-en-Y gastric bypass, gastric banding, sleeve gastrectomy**: Mechanism of creating a physical restriction to the volume of food and liquid that the patient can consume.

Key Points

- The worldwide prevalence of obesity is increasing.
- Assessment of the obese patient includes the medical history, physical examination, diagnostic tests, and identification and management of obesity associated comorbidities.
- Bariatric surgery is the most efficacious treatment for obesity achieving weight loss, long-term weight maintenance and amelioration of obesity associated comorbidities.
- The selection of obese patients for bariatric surgery aims to identify 'the right patient for the right operation at the right time'. These decisions should be taken within a specialist multi-disciplinary team setting.
- Assessment of the obese patient, pre-operative preparation and long-term post-operative follow-up require specialist, holistic nursing care.

56.1 Assessment of the Patient with Obesity

Obesity is a chronic condition of excess adiposity associated with insulin resistance and other metabolic abnormalities that both establish and then perpetuate the condition (Heymsfield and Wadden 2017). Obesity is associated with physical and mental health comorbidities and it is these that often determine the need for both clinical intervention and consideration of bariatric surgery. The improvements in these conditions after surgery have led some to consider bariatric surgery to be a 'metabolic' as opposed to a 'weight-loss' operation (Rubino et al. 2014).

The common obesity associated comorbidities are listed in Table 56.1.

Awareness of these is essential because assessment of the patient with obesity involves identifying and managing these conditions in order to improve the health of the obese patient and to optimise these comorbidities both before and after bariatric surgery.

Obesity is defined according to body mass index (BMI) which is the weight in kilogrammes divided by the height in metres squared. A BMI of greater than 30 kgm^2 is diagnostic of obesity. The use of BMI has been endorsed by the WHO which further sub-classifies obesity into obese class 1 (BMI 30.0–34.9 kgm^2), obese class 2

Table 56.1 Common obesity associated comorbidities listed by system

Endocrine	*Cardiovascular*	*Respiratory*
Type 2 diabetes Metabolic syndrome Reduced fertility (men and women) Amenorrhoea Polycystic ovarian syndrome Hirsutism (women) Erectile dysfunction	Hypertension Dyslipidaemia Ischaemic heart disease Cerebrovascular disease Venous thromboembolism	Obstructive sleep apnoea Asthma Obesity hypoventilation syndrome
Gastro-intestinal	*Renal*	*Musculoskeletal*
Gall stones Non-alcoholic fatty liver disease Abdominal wall hernias Gastro-oesophageal reflux disease	Chronic kidney disease	Osteoarthritis Mechanical back pain
Central nervous system	*Mental health*	*Oncological*
Idiopathic intracranial hypertension	Depression Anxiety Psychosocial problems arising as a consequence of the obesity	Six times increased incidence of malignancy particularly oestrogen-mediated cancers such as breast and endometrial

Table 56.2 World Health Organization classification of weight status (WHO 1998)

Weight status	Body mass index (kgm^2)
Underweight	<18.5
Normal range	18.5–24.9
Overweight	25.0–29.9
Obese Class I	30.0–34.9
Obese Class II	35.0–39.9
Obese Class III	≥40.0

(BMI 35.0–39.9 kgm^2), and obese class 3 (BMI ≥40 kgm^2) (WHO 1998) (Table 56.2).

BMI is useful in making the diagnosis of obesity but does not assess obesity associated comorbidity and weight-related functional limitations. This is because the complications of obesity occur in individual patients at vastly different BMIs (Cummings and Cohen 2014). For example, a patient with a BMI of 30 kgm^2 might have type 2 diabetes and obstructive sleep apnoea whereas a patient with a BMI of 40 kgm^2 could be free of comorbidities. In addition, patients from certain ethnic groups, particularly those from the Indian sub-continent, are recognised as being at risk for developing the metabolic consequences of obesity at a lower BMI than that of other racial groups (Rubino et al. 2017).

The limitations of BMI in the assessment of an obese patient has led to the development of obesity clinical staging or scoring systems. These serve several purposes. Firstly, they allow the healthcare provider to organise the assessment of the patient so that all physical and mental health comorbidities as well as functional and social factors are systematically considered. In addition, these approaches allow for consistency in the re-assessment of the obese patient either after a period of time has elapsed and/or an intervention such as bariatric surgery has taken place.

Lastly, because these assessment systems take into account obesity associated comorbidities and functional limitations, they help to identify which patients are most in need of medical intervention as well as identifying patients that will experience the greatest benefit from bariatric surgery.

56.2 Clinical Assessment

56.2.1 Clinical History and Obesity Staging/Scoring Systems

The patient's history can be taken 'free-hand' or a structured obesity assessment tool can be used. The two most frequently used systems for the assessment of the obese patient are the Edmonton Obesity Staging System (EOSS) (Sharma and Kushner 2009) and the King's Obesity Staging Criteria (Aylwin and Al-Zaman 2008).

56.2.1.1 Edmonton Obesity Staging System (EOSS)

Using findings from the history, examination and commonly used diagnostic tests, the EOSS comprises a five-stage system that allows for the grading of obesity which then guides treatment decisions (Table 56.3).

Limitations of EOSS include subjectivity in the assessment of the psychological and functional impact of the obesity and variability in the cut-offs for the definition of obesity associated comorbidities such as dyslipidaemia and hypertension.

56.2.1.2 King's Obesity Staging Criteria (KOSC)

A second frequently used tool for the assessment of obese patients is the King's Obesity Staging Criteria (KOSC). KOSC consists of nine health domains, addressed in alphabetical order, that comprise the following: Airway, Body mass index, Cardiovascular disease, Diabetes, Economic complications, Functional limitations, Gonadal axis, Health status (perceived), and body Image. The extended KOSC also includes assessment of Junction (assessment of symptoms of gastro-oesophageal reflux disease), Renal function (Kidneys), Liver function and Medications.

Assessment in each domain is made through a combination of the medical history, physical examination findings, e.g. blood pressure and the results of diagnostic tests, e.g. HbA1c. Each domain is then assigned a score from zero to three. Zero indicates normal health, one 'at risk', two

Table 56.3 Edmonton Obesity Staging System (EOSS) (from van Strien et al. 1986)

Stage	Description	Management
0	Patient has no apparent obesity-related risk factors (e.g. blood pressure, serum lipids, and fasting glucose within normal range), no physical symptoms, no psychopathology, no functional limitations and/or impairment of well-being	Identification of factors contributing to increased body weight. Counselling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity
1	Patient has obesity-related subclinical risk factor(s) (e.g. borderline hypertension, impaired fasting glucose, elevated liver enzymes), mild physical symptoms (e.g. dyspnoea on moderate exertion, occasional aches and pains, fatigue), mild psychopathology, mild functional limitations, and/or mild impairment of well-being	Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status
2	Patient has established obesity-related chronic disease(s) (e.g. hypertension, type 2 diabetes, obstructive sleep apnoea, osteoarthritis, gastro-oesophageal reflux disease, polycystic ovarian syndrome, anxiety disorder), moderate limitations in activities of daily living and/or well-being	Initiation of obesity treatments including considerations of all behavioural, pharmacological, and surgical treatment options. Close monitoring and management of comorbidities as indicated
3	Patient has established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitation(s), and/or impairment of well-being	More intensive obesity treatment including consideration of all behavioural, pharmacological, and surgical treatment options. Aggressive management of comorbidities as indicated
4	Patient has severe (potentially end-stage) disability/ies from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitation(s), and/or severe impairment of well-being	Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy, and psychosocial support

'established disease', and three 'advanced disease. For example, in the 'diabetes domain', a patient without diabetes would score zero, a patient with pre-diabetes or impaired fasting glucose would score one, a patient with established diabetes would score two and a patient with advanced diabetes (e.g. the presence of diabetes-related complications) would score three. Advantages of KOSC are high reproducibility when the same patient is assessed by more than one healthcare professional (Aasheim et al. 2011) and from a practical perspective, the alphabetical format makes the structure easy to remember and ensures all important areas are covered in the assessment.

56.2.1.3 Further Assessment Beyond EOSS and KOSC

Certain important features of the assessment of the obese patient are not specifically covered by either EOSS or KOSC and these should be specifically addressed in the wider history. These include:

- Any history of very early onset paediatric obesity, hyperphagia from a young age, learning difficulties and consanguineous parentage all of which may point toward a monogenic or syndromic basis to the obesity.
- The timing of the onset of the obesity. Most obesity will come on gradually with the weight slowly increasing over many years. If the obesity is of acute onset with weight rapidly increasing over weeks or months, an underlying cause should be sought, e.g. Cushing's syndrome or a supra-sellar tumour.
- Plans for pregnancy in female patients of childbearing age as this will affect treatment decisions (see below).
- What the patient wants; it is essential to discuss the patient's ideas, concerns, and expectations with respect their obesity, treatment options, and their long-term health and weight goals.

56.2.1.4 Assessment of Psychological State, Quality of Life, and Eating Behaviours

Mental health diagnoses both past and current should be documented including the use of psychiatric medications. Certain psychiatric conditions and, in particular, untreated personality disorder are a contraindication to bariatric surgery and specialist input will be required.

Validated screening tools or questionnaires are frequently used to assess psychological state, quality of life, and eating behaviours. Patients often complete these ahead of the consultation. These screening tools reduce the possibility of subjective assessment. This is particularly important when EOSS or KOSC is used as psychological and functional status contribute to the patient's overall score. Longitudinal use of the same questionnaire also allows for consistency in long-term re-evaluation.

The questionnaires that are frequently used do not require a free text written response, but instead ask the patient to tick a box to indicate their answer or to circle a response. Patients who score highly on any particular assessment tool should be referred to the appropriate specialist for evaluation and treatment.

Quality of life encompasses physical, mental, social and emotional well-being all of which can be affected by obesity and is commonly assessed using the Short Form (36) Health Survey (SF-36) (Jenkinson et al. 1997).

Anxiety and depression are commonly found in obese patients. Whether these conditions predate the obesity and contribute to its pathogenesis or whether they occur as a consequence of the excess weight is not well defined. In clinical practice, a combination of the two scenarios often co-exists. The Hospital Anxiety and Depression Scale (HADS) is widely used to screen patients for these conditions (Zigmond and Snaith 1983). Those who score highly should be referred for further mental health evaluation.

Binge eating, the feeling of being 'addicted' to food and 'emotional eating' are common in obese patients. Useful screening tools to assess for these and other eating behaviours include the Dutch Eating Behaviour Questionnaire (van Strien et al. 1986) and the Yale Food Addiction Scale (Gearhardt et al. 2009). Patients who score highly on screening should undergo specialist assessment.

56.2.2 Physical Examination

A standard multi-systems physical examination should be performed. In particular, this should focus on the following areas:

- Measurement of body weight and height. Calibrated 'bariatric' weighing scales with a suitably high upper weight limit are required. For consistency, the same light clothing should be worn each time the measurement is performed.
- If bio-impedance weighing scales are available, then the percentage body fat can be measured. The patient must have bare feet and should empty their bladder before the measurement is performed.
- Waist and hip circumference measured with a tape measure.
- Measurement of blood pressure.
- Assessment for dysmorphic features that could suggest a monogenic or syndromic cause for the obesity.
- Assessment for signs suggestive of 'endocrine obesity', e.g. Cushing's syndrome, hypothyroidism, or acromegaly.

56.2.3 Diagnostic Tests

In all obese patients, the following investigations form a routine part of the clinical assessment:

- **Blood tests**: full blood count, renal profile (urea, creatinine, potassium, sodium), liver function tests, calcium, phosphate, vitamin D, fasting lipids, fasting glucose, HbA1c, fasting insulin, fasting C-peptide, thyroid function tests, folate, vitamin B12, ferritin, blood group and screen (in patients who will undergo bariatric surgery).
- **Electrocardiogram (ECG)**

Other tests should be performed when indicated (e.g. overnight dexamethasone suppression test in cases of suspected Cushing's syndrome).

Further investigations should be targeted to assess the impact of the obesity on the patient's health and will be guided by the clinical assessment. These additional tests, which are listed below within the domains of the extended KOSC, might include:

- **Airway**: Chest X-ray, lung function tests, sleep study
- **Cardiovascular risk**: Ambulatory blood pressure monitoring; ambulatory heart rate/rhythm monitoring; echocardiography; cardiac 'stress' testing, e.g. dobutamine stress echocardiography; coronary artery angiography
- **Diabetes**: Oral glucose tolerance test (standard or prolonged), continuous blood glucose monitoring
- **Functional limitation**: Joint and musculoskeletal imaging, e.g. plain X-rays, magnetic resonance imaging (MRI)
- **Gonadal dysfunction**: Plasma gonadotropins (luteinising hormone and follicle stimulating hormone), oestrogen, testosterone, sex hormone binding globulin
- Gastro-oesophageal **junction**: Oesophagogastro-duodenoscopy (OGD)
- **Kidney**: Urinalysis; imaging of the renal tract
- **Liver**: Liver imaging, e.g. ultrasound scan

56.3 Identification of Patients for Bariatric Surgery

The selection of obese patients for bariatric surgery aims to identify 'the right patient for the right operation at the right time'. Each of these three components will be discussed below:

56.3.1 The Right Patient

The multi-disciplinary team (MDT) should be satisfied that the patient has tried appropriate non-surgical measures but nevertheless has been unable to achieve or to maintain adequate, clinically beneficial weight loss. In most cases, prior to bariatric surgery, patients will be expected to complete a specialist weight management programme (Welbourn et al. 2016). These programmes typically teach patients about food choices and nutrition and many will also deliver psychological support. Some centres mandate that a certain level of weight loss must be achieved during the weight management programme in order for the patient to be eligible for bariatric surgery; however, such an approach is unstandardised and lacks an evidence base. Patients with a BMI of $\geq$50 kgm^2 are not usually required to participate in such a programme if direct progression to surgery is clinically indicated (National Institute for Health and Care Excellence 2014).

In the UK, eligibility for bariatric surgery is determined according to BMI criteria set out by the National Institute for Health and Care Excellence (NICE) (**National Institute for Health and Care Excellence** 2014). These are that the patient should have a BMI of $\geq$40 kgm^2 or a BMI between 35 and 40 kgm^2 in the presence of obesity associated comorbidity.

Bariatric surgery has been shown to ameliorate and in some cases to reverse type 2 diabetes (Pories et al. 1995). The shorter the duration of diabetes, the higher the likelihood of disease remission (Still et al. 2014). For this reason, a lower BMI threshold of $\geq$30 kgm^2 is set for patients with recent onset type 2 diabetes defined as a diagnosis of type 2 diabetes within the last 10 years.

Patients from certain ethnic groups, particularly those from the Indian sub-continent develop obesity associated comorbidity at a lower BMI than that of other racial groups (Rubino et al. 2017). In these patients, 2.5 kgm^2 BMI points can be subtracted from the above values.

Because of the non-linear relationship between increasing BMI and the presence of comorbidities, some authorities propose that bariatric surgery should be viewed as a 'metabolic' rather than as a 'weight-loss' operation and therefore argue against the centrality of BMI to decisions about who should and should not have surgery (Rubino et al. 2014). Currently, however, most centres will not operate on patients that do not fulfil BMI criteria.

Where a significant comorbidity has been identified, further investigations (see above) may be required either to determine fitness for surgery and/or to optimise the patient's health pre-operatively. In some cases, a specialist opinion, e.g. cardiology,

respiratory, and gastroenterology may be needed in order to further evaluate and treat a comorbidity.

The pre-operative assessment must include psychological evaluation. Screening tools such as those described above help to identify patients in need of psychological or psychiatric assessment. Contraindications to bariatric surgery include untreated personality disorder, active alcohol use disorder (AUD), substance misuse and binge eating disorder. Importantly, mental health can deteriorate after bariatric surgery with patients at risk of AUD substance misuse, depression, self-harm, and suicide (Dixon 2016). Stable pre-operative mental health is therefore essential to good post-operative outcomes.

56.3.1.1 Patient Expectations and Patient Choice

On average, a patient will lose 25–30% of their pre-operative body weight (Sjostrom 2013) but some patients will lose much less than this and some will experience significant post-operative weight regain (Odom et al. 2010). A key part of the pre-operative assessment is to ensure that the patient's goals and expectations of surgery are realistic. In particular, patients must be aware that bariatric surgery is not a panacea and that extensive eating, behavioural and lifestyle changes are required in order to fully recognise the weight loss and health benefits of the procedure. These changes include reducing portion sizes, daily exercise, adequate sleep and the development of non-food-related coping strategies in response to adverse life events. Common features of patients who regain weight after bariatric surgery include, grazing on food throughout the day, a sedentary lifestyle, poor sleep habits and a return to emotional eating in the face of difficult circumstances, e.g. job loss or bereavement. Most centres will offer pre-operative patient seminars that will prepare the patient for life after bariatric surgery.

It should be noted that many people who are eligible for bariatric surgery will choose not to have it. Common reasons cited by patients for not wanting bariatric surgery include fear of having an operation, pain, time off work (and financial repercussions), worry about post-operative life, e.g. food choices and concerns about post-operative complications. All of the patient's reasons for declining bariatric surgery should be explored. This is not so as to change their mind but to ensure that their decision is based on the correct information.

56.3.2 The Right Operation

The most commonly performed bariatric procedures are gastric banding, Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (Fig. 56.1).

All share a common mechanism of creating a physical restriction to the volume of food and

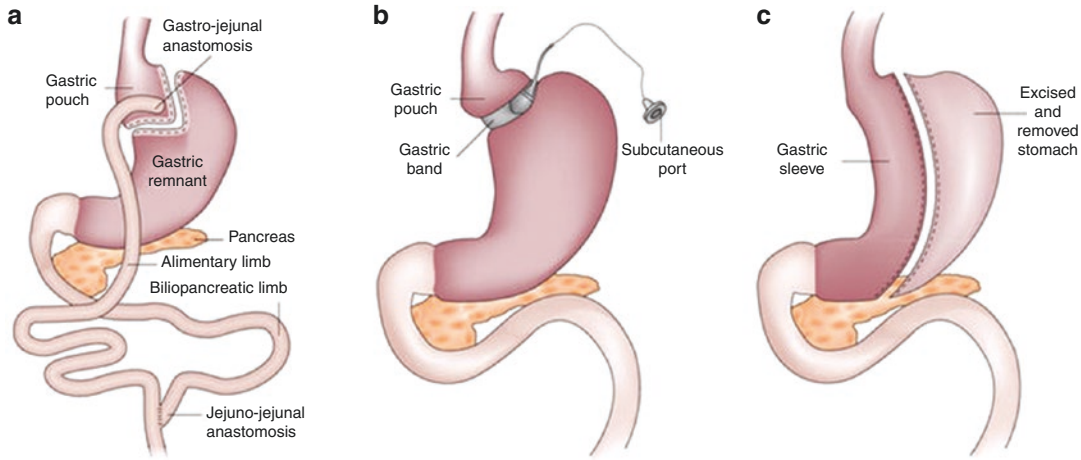


Fig. 56.1 Schemata of anatomy following Roux-en-Y gastric bypass (**a**), gastric banding (**b**), and sleeve gastrectomy (**c**). Credited to: Nat Rev Gastroenterol Hepatol. (2013) 10:575

liquid that the patient can consume. In addition, RYGB reduces the surface area of the small intestine thus producing malabsorption. RYGB and to a lesser extent sleeve gastrectomy also change the secretion of pro-satiety and pro-hunger gut hormones resulting in an enhanced sense of fullness and reduced feelings of hunger (i.e. Roux et al. 2006). This gut hormone effect is particularly strong immediately after the procedure and declines over months or years following the surgery. Therefore, in order for a patient to maximise weight loss and health improvements they must commit to eating and behavioural changes during this 'honeymoon' period.

56.3.2.1 Laparoscopic Gastric Banding

This is a restrictive procedure in which an adjustable plastic and silicon ring is fitted just below the gastro-oesophageal junction. This creates a small pouch of 15–20 mL which can only hold a small volume of food before the patient feels full. This feeling of fullness is further augmented by the slow emptying of the pouch into the rest of the stomach below. A balloon connected to an access port is attached to the plastic-silicon ring which allows the volume of the gastric pouch to be adjusted by injections in a subcutaneous port. Complications include nausea, vomiting, and post-prandial pain. In addition, the band can slip and or migrate, erode into the mucosa, leak or deflate all of which require intervention and in some cases band removal. Although patients can lose up to 15% of their body weight (Sjostrom 2013), the metabolic benefits of bariatric surgery are less commonly realised with gastric banding compared to other procedures (Pournaras et al. 2010).

56.3.2.2 Roux-en-Y Gastric Bypass (RYGB)

In Roux-en-Y gastric bypass (RYGB), the stomach is sub-divided into a small 15–30 mL gastric pouch and a lower gastric remnant. An anastomosis is formed between the gastric pouch and the jejunum. The lower gastric remnant which remains connected to the duodenum and jejunum is joined to the jejunum 75–150 cm distally to the gastro-jejunostomy. The expected weight-loss trajectory is 25–30% of starting body weight over 18–24 months (Sjostrom 2013). There may then be a 5% weight regain before a weight plateau is reached.

RYGB is associated with numerous improvements in comorbidities including remission of type 2 diabetes, reduced blood pressure, resolution of obstructive sleep apnoea and restoration of fertility. Some of these effects, particularly normalisation of blood glucose, occur almost immediately after surgery, before significant weight loss has occurred (Pories et al. 1995).

Complications of RYGB include anastomotic leak or breakdown, ulceration at the gastro-jejunal anastomosis (especially in smokers), gallstones, renal stones, post-prandial hypoglycaemia, dumping syndrome and micronutrient deficiencies. A deterioration in mental health can also occur. The potential for these physical and psychological complications mandate the need for specialist long-term follow-up.

56.3.2.3 Sleeve Gastrectomy

Worldwide, sleeve gastrectomy is now the most commonly performed bariatric procedure (Angrisani et al. 2015). This is a restrictive procedure in which the stomach is vertically divided from top to bottom. Approximately three quarters of the stomach is removed leaving behind a stomach remnant the shape of a banana along the lesser curve of the stomach that empties directly into the small intestine. In addition, the procedure may effect changes in gastric emptying and gut hormone secretion, in particular the suppression of the pro-hunger hormone ghrelin.

The comparative efficacy of sleeve gastrectomy to ameliorate comorbidities relative to RYGB is the subject of intensive debate (Andalib and Aminian 2017). A recent meta-analysis of 14 studies comprising over 5000 patients did not find a difference in comorbidity resolution between the two procedures although patients undergoing sleeve gastrectomy were found to have lost less weight at ≥5 years of follow-up (Shoar and Saber 2017).

Sleeve gastrectomy was initially developed as the first stage of a two-stage approach to the surgical

management of high-risk obese patients with a BMI >60 kgm^2 in who sleeve gastrectomy would be followed, after an interval, by laparoscopic Roux-en-Y gastric bypass (Regan et al. 2003). The efficacy and safety of the procedure however soon led to the establishment of sleeve gastrectomy as a stand-alone operation. Nevertheless, the premise of sleeve gastrectomy makes later conversion to RYGB a possibility for patients who experience poor weight loss or weight regain although issues around funding a second surgery may, in reality, prevent this.

New onset or exacerbation of pre-existing gastro-oesophageal reflux disease (GORD) have been reported after sleeve gastrectomy (Stenard and Iannelli 2015). This is thought to be at least partly due to the modified anatomy of the stomach. Most centres will advise against sleeve gastrectomy in patients with known GORD. Patients who develop *de novo* post-operative GORD or who experience symptomatic deterioration of pre-existing GORD may require conversion to RYGB.

56.3.3 Important Information for Patients Undergoing Assessment for Bariatric Surgery

During assessment for bariatric surgery, the same questions from patients commonly arise. These include the safety of the procedure, time spent in hospital, post-operative complications, and the resumption of everyday life such as working, driving and air travel.

In uncomplicated cases, patients are discharged from hospital on the same day after laparoscopic gastric banding, and can go home 24 h after RYGB or sleeve gastrectomy. Most will be able to return to work within 1–2 weeks of the operation. Once sutures have been removed (usually about 10 days after the operation) the patient can resume driving. Patients are advised to avoid air travel for 3 months after surgery because of the post-operative venous thromboembolic risk.

In a high volume centre, laparoscopic bariatric surgery has a mortality rate of <0.3% which is similar to that of laparoscopic cholecystectomy (Flum et al. 2009).

Patients should be aware that approximately one in five patients will experience a complication after bariatric surgery. These can occur in the immediate post-operative period and include the standard risks of all operations, e.g. infection, bleeding, and venous thromboembolism. More specific risks are described above by procedure type.

The patient should be aware of the risk of excess loose skin which can occur following substantial weight loss. In the UK, surgical removal of the excess skin is not routinely funded by the NHS.

56.3.4 The Right Time

Patients with type 2 diabetes are most likely to achieve diabetes remission if they have had the condition for less than 10 years. Those on insulin are more likely to be free of insulin after bariatric surgery the shorter the duration of pre-operative insulin therapy. This means that in patients with type 2 diabetes, consideration of bariatric surgery early in the disease course will maximise post-operative benefits.

Emerging evidence suggests a higher likelihood of adverse maternal and/or foetal outcomes in women undergoing pregnancy within 2 years of bariatric surgery (Johansson et al. 2015). Women of childbearing age must be advised to wait 12–18 months after surgery before trying to conceive (Mechanick et al. 2013). Those who cannot defer plans for pregnancy, e.g. those of increased age should be advised to complete their family before consideration of bariatric surgery.

In selected patients, the case for an urgent expedited operation arises. This includes patients with severe and deteriorating comorbidities and those who require urgent weight loss ahead of other treatment, e.g. organ transplant (Welbourn et al. 2016).

56.3.5 Multi-disciplinary Decision-Making

Once assessments have been completed, identification of the right patient for the right operation at the right time should be discussed and agreed

within a multi-disciplinary team (MDT) meeting (National Confidential Enquiry into Patient Outcome and Death 2012) comprising a nurse specialist, bariatric physician (usually an endocrinologist); bariatric surgeon, anaesthetist, psychologist/psychiatrist, and a dietician. It is not usual for the patient to attend the MDT meeting but their views, particularly procedure preference should be discussed.

56.4 Preparing a Patient for Bariatric Surgery

56.4.1 Assessment of Pre-operative Micronutrient Status

All bariatric procedures will affect nutritional intake and/or absorption to a greater or lesser extent. Pre-operatively, despite their excess body weight, many obese patients presenting for bariatric surgery are malnourished with micronutrient deficiencies detected during pre-assessment. These include vitamin deficiencies such as vitamin D, lack of minerals including iron and low levels of trace elements such as selenium.

Pre-operative serum micronutrient levels should be measured in order to correct deficiencies before surgery. So as to standardise practice between centres, in 2014, the British Obesity and Metabolic Surgery Society (BOMSS) issued guidelines advocating that the following micronutrients should be routinely measured and corrected as clinically indicated prior to surgery: Full blood count (FBC), ferritin, folate, vitamin B12, 25 hydroxy-vitamin D, calcium, liver function tests (LFTs), and renal function ((BOMSS) British Obesity and Metabolic Surgery Society 2014).

56.4.2 Pre-operative Diet

Prior to both RYGB and sleeve gastrectomy, patients must follow a strict, very low calorie diet (VLCD), consuming no more than 800–1000 kcal/day. The rationale for the pre-operative VLCD is to 'shrink' the liver, that is, to reduce its size through both glycogen depletion and a decrease in intra-hepatic fat stores (Colles et al. 2006). This liver 'shrinkage' makes the gastrointestinal tract more accessible to the surgeon and easier to visualise. Patients follow the VLCD with the support of a nurse specialist and bariatric dietician. If the patient has diabetes, medication down-titration will be necessary with nurse specialist support to reduce the risk of hypoglycaemia during caloric restriction. In most patients, the pre-operative diet is for the 2 weeks immediately prior to the operation date. In patients with a very high BMI (usually taken as a BMI of greater than 50 kgm^2), the MDT may advocate a 6-week pre-operative diet.

56.4.3 Smoking

Smoking increases the risk of peri-operative complications including prolonged intubation, re-intubation, pneumonia, and sepsis (Haskins et al. 2014). In addition, smoking is a specific contraindication to RYGB because of the risk of ulceration at the gastro-jejunal anastomosis. All centres will mandate that the patient stops smoking and some may require referral to a smoking cessation service. The duration of smoking cessation before surgery varies according to local guidelines but will usually be for at least 3 months. In cases where there is doubt as to whether the patient has stopped smoking, a carbon monoxide breath test can be performed although this will give a 'non-smoker' reading within 24–48 h of the last cigarette that was smoked.

56.4.4 Alcohol Consumption

The number of units of alcohol consumed per week including a history at any time of AUD must be assessed. AUD affects a minority of patients seeking bariatric surgery but if present is a contraindication to surgery by most programmes and in published guidelines (Mechanick et al. 2013). In its 2016 guidance, the American Society for Metabolic and Bariatric Surgery advocated a period of abstinence from alcohol before weight-loss surgery (Parikh et al. 2016). Almost all centres will require this of patients although the duration of pre-operative alcohol cessation varies between centres.

It is recognised that bariatric surgery and in particular RYGB can, in some patients, be associated with an increased risk of developing *de novo* post-operative AUD or AUD relapse (King et al. 2017). Of note, male sex, baseline smoking, and baseline alcohol consumption are independently related to an increased likelihood of AUD after bariatric surgery (Svensson et al. 2013).

Patients must be informed that post-operatively, particularly following RYGB, they should expect accelerated alcohol absorption, a higher maximum blood alcohol concentration and an increased time needed to eliminate alcohol (Parikh et al. 2016). These post-operative changes in alcohol pharmacokinetics will have implications for driving and for certain occupations.

56.5 Post-operative Follow-Up

56.5.1 Post-operative Micronutrient Status

After bariatric surgery, all patients must commit to the life-long need to take a complete multivitamin and mineral supplement (Mechanick et al. 2013). In women planning pregnancy, it should be ensured that the multivitamin does not contain vitamin A in order to avoid vitamin A toxicity to the foetus.

The following blood tests are routinely checked to assess for post-operative micronutrient deficiencies: renal profile, LFTs, FBC, ferritin, folate, vitamin B12, calcium, 25 hydroxy-vitamin D, fat soluble vitamins A, E, and K (by measuring prothrombin time), and trace elements (zinc, copper, selenium, magnesium) ((BOMSS) British Obesity and Metabolic Surgery Society 2014).

The frequency of monitoring is determined by the type of bariatric procedure and the circumstances of the individual patient. If micronutrient deficiencies are identified, patient compliance with their multivitamin and mineral supplement must be ascertained in addition to specialist dietetic review. Where necessary, a specific micronutrient might be required in addition to the supplement tablet.

56.5.2 The Post-operative Diet and Food Choices

For the first seven days after surgery, patients can ingest water and fluids, such as a thin soup. Patients are encouraged to take small sips and some may choose to use a straw to help with this. This slow pace of consumption reduces the likelihood of nausea and vomiting. After a week, patients progress on to pureed foods and runny foods such as yogurt for four weeks. If this is tolerated, they move on to eating soft foods such as mashed potato. After six weeks, they can gradually return to eating foods of other textures, building up to a balanced healthy diet. All must receive ongoing support to chew food, to eat slowly and to consume significantly smaller portions compared to pre-operative meal life. In addition, they are advised to stop eating as soon as they feel full. Patients who cannot follow this advice are very likely to experience abdominal pain, nausea, and vomiting.

Evidence suggests that the changes in gut hormone secretion that occur particularly after RYGB not only influence satiety but also reduce interest in high calorie, high sugar foods, an effect that is likely to be centrally mediated (Scholtz et al. 2014).

Those patients who placed an emotional value on food before surgery will require support to develop new coping strategies instead of eating. Post-operatively some patients will experience a ‘mourning’ period at the ‘loss’ of food and this will require specialist support, in particular so that the patient does not turn to other substances such as alcohol.

56.5.3 Medication Changes

Immediately after surgery, the patient’s medication needs change and this transition period requires careful nursing support. Two changes mandate attention. The first is the addition of new medications commonly comprising a vitamin and mineral supplement, a proton pump inhibitor, and ursodeoxycholic acid which alters the enterohepatic circulation of bile salts and may reduce the incidence of post-operative gallstones (Uy et al. 2008).

The second change is the dose reduction or discontinuation of medications that the patient was taking pre-operatively, in particular medications for the treatment of type 2 diabetes and hypertension. Blood glucose and blood pressure will be closely monitored as part of the immediate post-operative care (over the first few days, weeks and months) usually by a nurse specialist and decisions taken regarding optimal pharmacotherapy.

56.6 Conclusions

The worldwide prevalence of obesity is increasing. Obesity is associated with significant physical and mental health comorbidities which may be ameliorated by bariatric surgery. Deciding on who should undergo weight-loss surgery (the right patient), which operation they should have (the right operation) and when (at the right time) is complex and is based upon specialist, often nurse-led, pre-assessment followed by multidisciplinary decision-making. Nurse-led, long-term follow-up using a holistic and patient-centred model of care minimises post-operative complications and optimises long-term health and weight loss.

56.7 Key Points to Provoke Readers' Critical Thinking

Key point 1
Less than 1% of patients who would benefit from a bariatric procedure undergo surgery. What factors do you consider to be barriers to treatment?

Key point 2
Should a patient be mandated to lose a certain amount of weight through a non-surgical weight management programme before being considered eligible for bariatric surgery?

Key point 3
Should patients, who fail to lose weight after bariatric surgery, or who experience weight regain be offered further (revisional) surgery?

Key point 4
Which of these three patients do you think would derive the most benefit from bariatric surgery?

- **Patient 1**: A 73-year-old woman with a BMI of 54 kgm^2 who has severely limited mobility due to her weight and is mainly housebound.
- **Patient 2**: A 39-year-old man with a BMI of 41 kgm^2 who has had type 2 diabetes for 16 years. He has significant diabetes-related complications including end-stage chronic kidney disease and is registered partially sighted because of advanced diabetic retinopathy.
- **Patient 3**: A 24-year-old man of South Asian heritage who has a BMI of 33 kgm^2. He has poorly controlled type 2 diabetes and hypertension treated with two anti-hypertensive medications.

Box 56.1 Case Scenario
A 39-year-old woman with a BMI of 43 kgm^2 presents to the obesity clinic. The KOSC is used to assess her obesity. She smokes ten cigarettes per day. She has symptoms suggestive of obstructive sleep apnoea. She has hypertension for which she takes one anti-hypertensive medication. Type 2 diabetes had been diagnosed 7 years earlier and she had recently been commenced on a long-acting insulin in addition to metformin. She is unemployed. She scores highly on the HADS questionnaire indicating symptoms of depression and anxiety.

She is reviewed by the specialist obesity psychiatrist and is prescribed a selective serotonin reuptake inhibitor (SSRI). She is referred for a sleep study which diagnoses obstructive sleep apnoea and overnight continuous positive airways pressure (CPAP) ventilation is commenced.

She is assessed for bariatric surgery and attends a smoking cessation service. Following MDT discussion, she undergoes Roux-en-Y gastric bypass. On the first

Box 56.1 (continued)

post-operative day, her insulin is discontinued. On review with her nurse specialist one month after surgery, she is found to be normotensive and her blood pressure medication is stopped. Six months after surgery, she undergoes psychiatric review. Her mood has significantly improved and the SSRI is weaned down and then stopped. CPAP is discontinued after a repeat sleep study. One year after the operation, she has lost 27% of her total body weight. She has found a new job which she enjoys. She continues to see her nurse specialist for clinical follow-up and support with post-operative life. Fourteen months after bariatric surgery, she tells her nurse specialist, 'I am a completely different person. Before, I felt tired and unhealthy and I hated the insulin injections. I also felt sad most of the time and I never wanted to go out. It's been hard work but with your help, I have completely changed the way I eat and the way that I think about food. And I exercise every day, no excuses. Now I have energy and I feel good and I love my new job. The operation has changed my life'.

References

Aasheim ET, Aylwin SJ, Radhakrishnan ST, Sood AS, Jovanovic A, Olbers T, et al. Assessment of obesity beyond body mass index to determine benefit of treatment. Clin Obes. 2011;1(2–3):77–84.

Andalib A, Aminian A. Sleeve gastrectomy and diabetes: is cure possible? Adv Surg. 2017;51(1):29–40.

Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric surgery worldwide 2013. Obes Surg. 2015;25(10):1822–32.

Aylwin S, Al-Zaman Y. Emerging concepts in the medical and surgical treatment of obesity. Front Horm Res. 2008;36:229–59.

(BOMSS) British Obesity and Metabolic Surgery Society. BOMSS guidelines on peri-operative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery. 2014. http://www.bomss.org.uk/wp-content/uploads/2014/09/BOMSS-guidelines-Final-version1Oct14.pdf.

Colles SL, Dixon JB, Marks P, Strauss BJ, O'Brien PE. Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. Am J Clin Nutr. 2006;84(2):304–11.

Cummings DE, Cohen RV. Beyond BMI: the need for new guidelines governing the use of bariatric and metabolic surgery. Lancet Diabetes Endocrinol. 2014;2(2):175–81.

Dixon JB. Self-harm and suicide after bariatric surgery: time for action. Lancet Diabetes Endocrinol. 2016;4(3):199–200.

National Institute for Health and Care Excellence. Obesity: identification, assessment and management. Clinical guideline [CG 189]; 2014.

Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med. 2009;361(5):445–54.

Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite. 2009;52(2):430–6.

Haskins IN, Amdur R, Vaziri K. The effect of smoking on bariatric surgical outcomes. Surg Endosc. 2014;28(11):3074–80.

Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376(3):254–66.

Jenkinson C, Layte R, Jenkinson D, Lawrence K, Petersen S, Paice C, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? J Public Health Med. 1997;19(2):179–86.

Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015;372(9):814–24.

King WC, Chen JY, Courcoulas AP, Dakin GF, Engel SG, Flum DR, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surg Obes Relat Dis. 2017;13(8):1392–402.

le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg. 2006;243(1):108–14.

Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis. 2013;9(2):159–91.

National Confidential Enquiry into Patient Outcome and Death. Too lean a service? A review of the care of patients who underwent bariatric surgery; 2012.

Odom J, Zalesin KC, Washington TL, Miller WW, Hakmeh B, Zaremba DL, et al. Behavioral predictors of weight regain after bariatric surgery. Obes Surg. 2010;20(3):349–56.

Parikh M, Johnson JM, Ballem N. ASMBS position statement on alcohol use before and after bariatric surgery. Surg Obes Relat Dis. 2016;12(2):225–30.

Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50; discussion 50–2.

Pournaras DJ, Osborne A, Hawkins SC, Vincent RP, Mahon D, Ewings P, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. Ann Surg. 2010;252(6):966–71.

Regan JP, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient. Obes Surg. 2003;13(6):861–4.

Rubino F, Shukla A, Pomp A, Moreira M, Ahn SM, Dakin G. Bariatric, metabolic, and diabetes surgery: what's in a name? Ann Surg. 2014;259(1):117–22.

Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Obes Surg. 2017;27(1):2–21.

Scholtz S, Miras AD, Chhina N, Prechtl CG, Sleeth ML, Daud NM, et al. Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding. Gut. 2014;63(6):891–902.

Sharma AM, Kushner RF. A proposed clinical staging system for obesity. Int J Obes (Lond). 2009;33(3):289–95.

Shoar S, Saber AA. Long-term and midterm outcomes of laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass: a systematic review and meta-analysis of comparative studies. Surg Obes Relat Dis. 2017;13(2):170–80.

Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219–34.

Stenard F, Iannelli A. Laparoscopic sleeve gastrectomy and gastroesophageal reflux. World J Gastroenterol. 2015;21(36):10348–57.

Still CD, Wood GC, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. Lancet Diabetes Endocrinol. 2014;2(1):38–45.

Svensson PA, Anveden A, Romeo S, Peltonen M, Ahlin S, Burza MA, et al. Alcohol consumption and alcohol problems after bariatric surgery in the Swedish obese subjects study. Obesity (Silver Spring). 2013;21(12):2444–51.

Uy MC, Talingdan-Te MC, Espinosa WZ, Daez ML, Ong JP. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: a meta-analysis. Obes Surg. 2008;18(12):1532–8.

van Strien TF, Frijters JER, Bergers GPA, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restricted, emotional, and external eating behavior. Int J Eating Disord. 1986;5(2):295–315.

Welbourn R, Dixon J, Barth JH, Finer N, Hughes CA, le Roux CW, et al. NICE-accredited commissioning guidance for weight assessment and management clinics: a model for a specialist multidisciplinary team approach for people with severe obesity. Obes Surg. 2016;26(3):649–59.

WHO. Report of a WHO consultation on obesity. Obesity: preventing and managing the global epidemic. Geneva: WHO; 1998.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.

Key Reading

1. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50; discussion 50–2.
2. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219–34.
3. Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, McMahon M, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and non-surgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis. 2013;9(2):159–91.
4. Welbourn R, Dixon J, Barth JH, Finer N, Hughes CA, le Roux CW, et al. NICE-accredited commissioning guidance for weight assessment and management clinics: a model for a specialist multidisciplinary team approach for people with severe obesity. Obes Surg. 2016;26(3):649–59.

Lipid Disorders and Familial Hypercholesterolaemia

57

Alison Pottle

Contents

57.1 **Introduction** 1103

57.2 **Lipid Disorders** 1103
57.2.1 Definition of Lipid Disorders 1103
57.2.2 Types of Lipids 1103
57.2.3 Why Lipids Are Important 1105
57.2.4 Epidemiology 1106
57.2.5 Pathophysiology of Coronary Heart Disease 1106
57.2.6 Treatment Targets 1107

57.3 **Familial Hypercholesterolaemia** 1107
57.3.1 Definition of Familial Hypercholesterolaemia 1107
57.3.2 Background 1107
57.3.3 Prevalence 1108
57.3.4 Diagnosis 1108
57.3.5 Cholesterol Levels 1108
57.3.6 Signs 1109
57.3.7 Cardiovascular Consequences of FH 1109

57.4 **Treatment of Lipid Disorders** 1110
57.4.1 Lifestyle Changes 1110
57.4.2 Lipid-Modifying Drug Therapy 1111
57.4.3 Novel Drug Therapies 1113
57.4.4 Lipoprotein Apheresis 1114

57.5 **Conclusions** 1116

References 1117

A. Pottle (✉)
Royal Brompton and Harefield NHS Foundation Trust, London, UK

Harefield Hospital, Harefield, UK
e-mail: a.pottle@rbht.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_57

Abstract

Raised lipid levels are a significant risk factor for coronary heart disease. Lipids are a heterogeneous group of substances which include cholesterol, triglycerides, lipoproteins and apolipoproteins. The link between increased lipid levels and atherosclerosis has been known since the early 1900s. Optimum levels of total cholesterol and low density lipoprotein cholesterol (LDL) are unknown but the general consensus is 'the lower the better' with some guidelines suggesting that the goal should be an LDL of <1.8 mmol/L (<70 mg/dL).

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic condition which is characterised by elevated levels of cholesterol and an increased risk of premature coronary heart disease (CHD). Patients with heterozygous familial hyperchlosterolaemia typically develop coronary disease 10 years earlier than the general population. The condition remains under diagnosed, and there is a worldwide need for early detection and treatment to be improved.

Statins are the first choice lipid-lowering therapy. However, maximum tolerated doses may not be sufficient to reduce lipid levels to target, and there are a variety of other agents that can be used in combination with statins or as an alternative for patients who are unable to tolerate statin therapy. There are also several novel lipid-lowering therapies that will potentially enable more patients to achieve desired lipid levels. Lipoprotein apheresis, which is a dialysis-like therapy, is another treatment option for those patients whose lipid levels remain elevated despite optimum medical therapy.

Keywords

Lipids · Cholesterol · Lipoproteins · Lifestyle changes · Coronary heart disease · Lipid-lowering therapy · Lipoprotein apheresis

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
Apo A	Apolipoprotein A
Apo B	Apolipoprotein B
BHF	British Heart Foundation
CAD	Coronary artery disease
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	Familial hypercholesterolaemia
HDL	High density lipoprotein
LDL/LDL-C	Low density lipoprotein
Lp (a)	Lipoprotein (a)
MI	Myocardial infarction
MTP	Microsomal triglyceride transport protein
NCEP	National Cholesterol Education Programme
NICE	National Institute for Health and Care Excellence
PCSK9	Proprotein convertase substilisin/kexin type 9
RCT	Randomised controlled trial
TC	Total cholesterol
VLDL	Very low density lipoprotein
WHO	World Health Organisation

Key Terms

- **Tendon xanthoma**: Accumulation of cholesterol rich material found in the tendons of the hands, feet and heels
- **Xanthelasma**: Cholesterol deposits usually on or around the eyelids
- **Corneal arcus**: Cholesterol deposits in the periphery of the cornea
- **Homozygous**: Identical alleles at a gene locus
- Heterozygous—different alleles at a gene locus
- **Receptor negative**: No or minimal receptor activity
- **Receptor defective**: Reduced receptor activity
- **HEART UK**: The cholesterol charity

Key Points

- Coronary heart disease remains the leading cause of death worldwide.
- Raised lipid levels are one of the main risk factors for the development of atherosclerosis.
- Lifestyle and dietary changes are recommended for all patients.
- Familial hypercholesterolaemia is a genetic disorder of lipid metabolism caused by a mutation of the LDL receptor gene.
- Treatment for raised lipid levels includes lifestyle changes, lipid-lowering medications and for a small number of patients, lipoprotein apheresis.

57.1 Introduction

Cardiovascular disease including coronary heart disease (CHD) remains the leading cause of death worldwide (Perk et al. 2012). In the UK, nearly 70,000 deaths annually can be attributed to the CHD. Although mortality from CHD is falling in the UK, more than one in seven men and nearly one in ten women die every year from CHD (BHF British Heart Foundation 2015). Improvements in lifestyle, diet, exercise, smoking cessation, weight control and becoming more health conscious as well as the new developments in lipid-lowering medications and therapies are part of the reason behind the reduction (Ellegård et al. 2007).

Three risk factors—elevated cholesterol, smoking and hypertension or combinations of these factors are responsible for more than 75% of all cardiovascular disease worldwide (WHO). Elevated cholesterol carries the greatest attributable risk for CHD (Wilson et al. 1998).

This chapter will describe the various lipids and examine why abnormal levels cause health problems. Familial hypercholesterolaemia (FH), a genetic disorder of lipid metabolism will be described, together with the treatments available to treat raised lipid levels. The first section will concentrate on definitions, the types of lipids, epidemiology and pathology.

57.2 Lipid Disorders

57.2.1 Definition of Lipid Disorders

Lipids are basically fats however there is no unifying structure. Included in lipids are substances in which fatty acids are an essential component such as triglycerides but also other substances which have varied structures such as cholesterol. Lipids are a heterogeneous group of substances which have a low solubility in water but are more readily soluble in a mixture of chloroform and ethanol (Durrington 2007). Lipids are not in themselves bad as they are essential to life, however if levels become elevated the risk of CHD increases.

The World Health Organisation classification of hyperlipidaemia is shown in Table 57.1.

57.2.2 Types of Lipids

57.2.2.1 Cholesterol

Cholesterol is the predominant sterol in vertebrates. It is an essential component of cell membranes where it is present as free cholesterol, as is most of the cholesterol in the body. It is also the precursor for steroid hormones and vitamin D. Cholesterol esters are more of a storage form which are prevented from interacting with cell

Table 57.1 WHO classification of hyperlipidaemia

Type	Lipoproteins elevated	Lipids elevated
I	Chylomicrons	Triglycerides and cholesterol
IIa	LDL	Cholesterol
IIb	VLDL and LDL	Cholesterol and triglycerides
III	β-VLDL	Triglycerides and cholesterol
IV	VLDL	Triglycerides
V	Chylomicrons and VLDL	Triglycerides and cholesterol

Durrington and Sniderman (2000)
LDL low-density lipoprotein, *VLDL* very low-density lipoprotein

membranes. In the plasma and extracellular fluid, cholesterol is present in lipoproteins, largely as cholesterol esters. The role of cholesterol within the phospholipid layer of the cell membrane appears to be to regulate and stabilise its fluidity. This may influence important properties such as permeability (Durrington 2007).

Cholesterol is absorbed from the gut; however, this absorption is not complete and usually only about 30–60% of the amount ingested is actually absorbed. Cholesterol is both absorbed from the gut and excreted back into it as part of bile. The body synthesises at least as much cholesterol as is ingested each day. Almost all tissues in the body can synthesise cholesterol but it is the liver, gut and central nervous system which synthesise the majority in the adult. Cholesterol synthesis is immensely complex. The cholesterol molecule is constructed from acetyl-CoA obtained from β-oxidation of fatty acids or from carbohydrate breakdown. The full process contains 37 steps which is beyond the scope of this chapter (Durrington 2007). An important step in the process is when 3-hydroxy-methylglutaryl CoA is converted to mevalonic acid. The enzyme responsible for this process, HMG-CoA reductase, can be inhibited by physiological factors such as the intracellular level of cholesterol. Tissues which are supplied with cholesterol in large quantities from the liver and gut will therefore down-regulate their own cholesterol biosynthesis (Durrington and Sniderman 2000). Statins, are HMG-CoA reductase inhibitors, which will be described later in the chapter, also act on this enzyme. The average cholesterol level of adults living in England and Scotland is 5.3 mmol/L (205 mg/dL) (BHF/HEART UK 2011).

57.2.2.2 Triglycerides

Triglycerides constitute the main energy source of the body. An average lean adult male has about 15 g of triglyceride stored which represents an energy store to survive starvation for about 3 months (Durrington and Sniderman 2000). Triglyceride is stored in adipose tissue which has an important role in protecting the vital organs. Subcutaneous adipose tissue also provides a layer of thermal insulation.

Triglycerides are digested in the gut to fatty acids and monoglycerides which are then absorbed into the enterocyte and synthesised into chylomicrons to be transported to the tissues (Durrington and Sniderman 2000). The liver also has the ability to synthesise triglycerides from fatty acids in the circulation or synthesised from glucose. These triglycerides are then assembled into very low density lipoprotein particles (VLDL) and released into the circulation.

The release of fatty acids from adipose tissue is under the control of an enzyme called lipase. Once released from the glycerol to which they are bound, the fatty acids move out of the adipose cell and are transported to other tissues.

57.2.2.3 Lipoproteins

Lipoproteins are macromolecular complexes of lipids and proteins, the protein components of which are apolipoproteins or enzymes. A major function of lipoproteins is to transport lipids through the vascular and extravascular body fluids. The principle sources of lipoproteins are the liver and the gut. Chylomicrons are the largest of the lipoproteins and are produced by the gut following the absorption of the products of fat digestion. The absorption of fat is usually complete within a few hours of a meal and the chylomicron concentration fluctuates related to this. Following the ingestion of food, there is a postprandial rise in triglycerides which is due to chylomicrons. This rise may be only modest in fit, healthy people but may be marked in others (Durrington and Sniderman 2000).

Lipoprotein lipase is the enzyme that is responsible for removing the triglyceride component from chylomicrons. It hydrolyses triglyceride to monotriglycerides and fatty acids. The monoglycerides are then broken down to glycerol and fatty acids by other tissue lipases. These fatty acids and glycerol are then taken up by the cells and either respired or resynchronised back into triglycerides for storage (Durrington and Sniderman 2000).

57.2.2.4 Low Density Lipoprotein

Low density lipoprotein (LDL) is a smaller triglyceride-rich particle then very low density lipoprotein (VLDL). LDL is described as being respon-

sible for supplying cholesterol to the tissues especially during growth. There is great heterogeneity in LDL particle composition caused by the differences in the amount of cholesterol in each LDL particle (Durrington and Sniderman 2000). LDL is often described as 'bad cholesterol' as it is one of the major causes of coronary atherosclerosis.

57.2.2.5 High Density Lipoprotein

Approximately two thirds of serum cholesterol is present in LDL, a small amount is present in VLDL but the majority of the remainder is in high density lipoprotein (HDL). HDL is a small molecule compared with the other lipoproteins and so can easily cross the vascular endothelium. Its concentration in the tissue fluids is much closer to its intravascular concentration than for LDL (Durrington 2007). HDL is able to receive excess cholesterol from the tissues which is then transferred out of HDL to the liver to other lipoproteins. Low levels of HDL are associated with an increased risk of CHD. HDL is believed to have a protective role against atherosclerosis possibly due to the ability of HDL to promote the transfer of cholesterol from tissues to the liver, the so-called reverse cholesterol transport (Durrington and Sniderman 2000). HDL is therefore often referred to as 'good cholesterol'.

57.2.2.6 Apolipoprotein A

The main apolipoproteins of HDL are apolipoprotein A (Apo A) of which there are two major ones in humans—apolipoprotein AI and apolipoprotein AII. Of the two, apolipoprotein AI is the most abundant and is present in health in the plasma in concentrations which usually exceed apolipoprotein B. In the tissue fluid, apolipoprotein AI is the apolipoprotein with the greatest concentration (Durrington 2007). Apolipoprotein AI and AII are secreted from the gut and the liver.

57.2.2.7 Apolipoprotein B

Apolipoprotein B (Apo B) is central to the lipoprotein transport system. It is the most abundant protein in LDL. Apolipoprotein B is essential for the assembly and secretion of chylomicrons and VLDL and also for the removal of LDL via the LDL receptor. This is because apolipoprotein B is the part of LDL that is recognised by the LDL receptor (Durrington and Sniderman 2000). There are two types of Apo B–Apo B100, which is produced by the liver and Apo B48, which is produced by the gut in humans. This has approximately 48% of the weight of Apo B100, hence its name, and does not bind to lipoprotein receptors (Durrington 2007).

57.2.2.7.1 Apolipoprotein (a)

Apolipoprotein (a) is present in a Lipoprotein called lipoprotein (a) [Lp(a)] and was discovered by Berg in the 1960s (Berg 1963). It is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100 and an additional protein, apolipoprotein (a), attached via a disulphide bond. Lp(a) does not appear to have a triglyceride-rich lipoprotein precursor and is thought to be secreted by the liver. The level of Lp(a) is higher in people whose ancestors originated in Africa or the Indian subcontinent then in those of European origin, suggesting an ethnic difference (Durrington 2007).

57.2.3 Why Lipids Are Important

The first discovery of the link between cholesterol and atherosclerosis was described in 1913 in a rabbit model by Anitchkow (1913). Then, in the same year, Bacmeister and Henes reported for the first time, an association between raised levels of cholesterol and atherosclerosis in humans (Bacmeister and Henes 1913). In the past 30 years, several trials have been carried out which have demonstrated the benefit of reducing levels of cholesterol and therefore the event rate for CHD. One of the first large studies was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). This showed that an 8% reduction in total cholesterol for a mean of 7.4 years was associated with a 19% reduction in myocardial infarction or CHD death (LRC 1984). Since 1989 there have been a series of large-scale prospective interventional trials which have established that lowering LDL reduces the risk of CHD and diminishes mortality and morbidity in both primary and secondary prevention (Packard et al. 1998; Scandinavian Simvastatin Survival Study Group 1994; Pfeffer et al. 1995).

57.2.4 Epidemiology

The link between the level of cholesterol and CHD has been confirmed in a large number of prospective epidemiological studies and has been shown to be accounted for by the LDL component of circulating cholesterol (Anderson et al. 1987; Law et al. 1994; Assmann et al. 1998). In 2008, the estimated prevalence of raised cholesterol in males in the UK was 65.6% and in the USA it was 53.3%; for females for figures were 65.7% and 56.9%, respectively (WHO 2011). The role of HDL as an independent inverse predictor of CHD has been established in numerous observational epidemiological studies. These studies suggest that the risk of CHD decreases by 2–3% for each 1 mg/dL (0.03 mmol/L) increase in HDL after correction for other CHD risk factors (Gordon et al. 1989). The exact physiological role of raised Lp(a) in not totally understood; however, it has emerged that an elevated level of more than 600 mg/L is an important independent risk factor and is predictive of adverse outcomes in atherosclerotic disease (Cremer et al. 1994; Danesh et al. 2000).

57.2.5 Pathophysiology of Coronary Heart Disease

The majority of CHD is caused by atherosclerosis. Atherosclerosis is a complex disorder which is still not fully understood. What is known is that it is caused by a progressive accumulation of lipids, complex carbohydrates, blood, blood products and calcific deposits within the intimal layer of the artery wall with infiltration and increased production of vascular smooth muscle cells. These processes result in atheroma (Pottle 2012). Atheroma tends to be distributed in focal areas of the artery in plaques which often occur around branching vessels or areas where there is arterial curvature suggesting that haemodynamic stressors may play a part in initiating the process. Atherosclerotic plaques may occur as three presentations: fatty streaks, fibrous plaques and advanced lesions. Fatty streaks are flat, lipid-rich lesions which are thought to be benign and cause little or no obstruction to the coronary artery. They are, however, the precursor to advanced atheromatous lesions. Conversion of the fatty streaks to atheroma is dependent on the proliferation of vascular smooth muscle cells into fibroblasts (Pottle 2012).

White fibrous plaques are produced which protrude into the lumen of the artery. This is followed by further proliferation of vascular smooth muscle cells which results in the formation of a tough fibrous cap. A 'lipid-rich' pool then develops underneath which are released when foam cells die. Advanced lesions are composed of fibrous tissue, lipids, blood products and fibrin. The lipid-rich core in these lesions may increase in size and become calcified (Fig. 57.1). Atherosclerotic plaques may be described as concentric, where the plaque is distributed around the circumference of the artery or eccentric where they do not involve the entire circumference of the artery. This results in an area of normal or

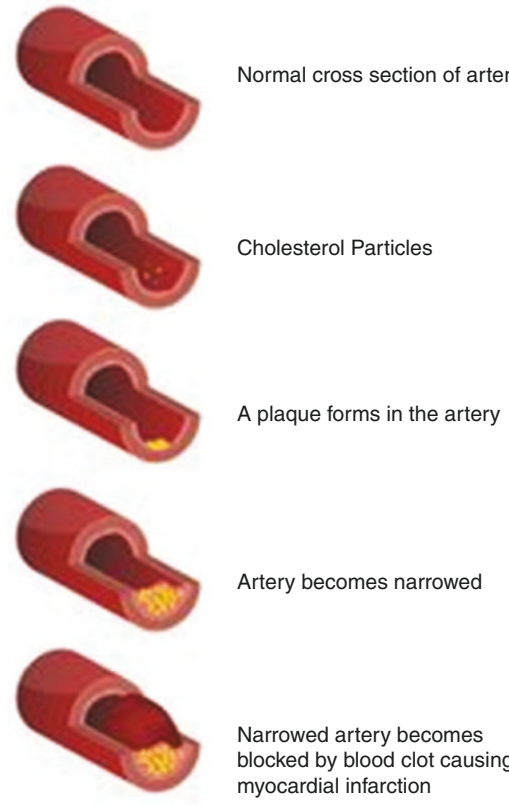


Fig. 57.1 The process of atherosclerosis development

near normal artery wall (Waller et al. 1992). The majority of fatal CHD events are thought to be caused by eccentric plaques (Waller 1989).

57.2.6 Treatment Targets

The treatment targets for lipid management are primarily based on results from clinical trials. In most trials, the LDL level has been used as the target for therapy and so this is the primary target in management of dyslipidaemia. The ESC/EAS guidelines on management of dyslipidaemia recommend modulating the intensity of the preventative intervention according to the level of the total cardiovascular risk (ESC/EAS 2011). Every 1.0 mmol/L (40 mg/dL) reduction in LDL is associated with a 22% reduction in cardiovascular mortality and morbidity (Baigent et al. 2010). The ESC/EAS recommended targets for LDL are shown in Table 57.2.

The American ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults were updated in 2013 (Stone et al. 2014). These guidelines are based solely on the results of randomised controlled trials (RCT) with atherosclerotic cardiovascular disease outcomes. Observational studies and those with less than 18 months follow-up were excluded. The main difference between these guidelines and the European ones is that the American guidelines do not support the use of specific LDL targets. Clinicians are recommended to use a new Pooled Cohort Equation to estimate the 10-year atherosclerotic cardiovascular risk to accurately identify those people at high risk. Statin therapy can therefore be focused on those who are most likely to benefit (Stone et al. 2014). Recent guidance from the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine (Nordestgaard et al. 2016) recommend that non-fasting blood samples should routinely be used for assessment of plasma lipid profiles.

Table 57.2 The ESC/EAS recommended targets for LDL

Level of risk	Target LDL level
Very high CVD risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD, SCORE level of >10%	<1.8 mmol/L (<70 mg/dL) and or >50% reduction when target level cannot be reached
High CVD risk (markedly elevated single risk factors, a SCORE level of >5 to <10%	<2.5 mmol/L (<100 mg/dL)
Moderate CVD risk (SCORE level >1 to <5)	<3.0 mmol/L (<115 mg/dL)

Adapted from ESC/EAS (2011)
CVD cardiovascular disease, *CKD* chronic kidney disease, *LDL* low-density lipoprotein, *SCORE* Systematic Coronary Risk Evaluation, *ESC* European Society of Cardiology, *EAS* European Atherosclerosis Society

57.3 Familial Hypercholesterolaemia

This section will describe familial hypercholesterolaemia, explain how it can be diagnosed and discuss the consequences of this condition.

57.3.1 Definition of Familial Hypercholesterolaemia

Familial hypercholesterolemia (FH) is an autosomal dominant disorder usually resulting from a mutation in the LDL receptor gene that leads to receptor absence or malfunction (Goldstein et al. 1983). The genetic basis of this disorder was discovered by Goldstein and Brown in 1979 who demonstrated mutations in the gene encoding the LDL receptor; one allele being affected in the heterozygote and both alleles in homozygotes (Goldstein and Brown (1979). Other genetic causes of FH include familial defective apolipoprotein B100, autosomal recessive hypercholesterolaemia and FH3, caused by gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (Radar et al. 2003). The gene for the LDL receptor is located on chromosome 19 (Durrington 2007).

57.3.2 Background

FH is characterised by increased hepatic cholesterol production, and decreased clearance of LDL

which result in accumulation of LDL in the plasma. The mutation of the LDL receptor prevents it from participating effectively in LDL uptake. It cannot be transported to the cell surface, cannot bind properly to LDL once it gets to the cell surface, cannot be internalised and is not released from the endosome. A wide range of mutations of the LDL receptor have already been found and the number continues to increase.

57.3.3 Prevalence

It has previously been estimated that the prevalence of heterozygous FH in Northern America and Europe was 1:500 and of homozygous FH, 1:1,000,000 but more recent data indicates that the frequency of heterozygotes in Europe may be as high as 1:200 (Nordestgaard et al. 2013) and of homozygotes 1:300,000 (Sjouke et al. 2015). In societies which have arisen relatively recently from a small number of settlers or migrants, the frequency of FH may be even higher and it may be caused by a smaller number of mutations. As an example, as many as 1:80 South Africans of Dutch or French decent have FH and the majority have one of only three different LDL-receptor mutations (Durrington and Sniderman 2000). Two of the mutations can be traced back to two of the early Dutch settlers and the other to a Huguenot migrant.

57.3.4 Diagnosis

Patients with heterozygous FH often come to medical attention due to the markedly elevated incidence of cardiovascular disease, clinical symptoms developing in the third or fourth decade of life (Marais 2004). Alternatively, they may be identified through cascade testing in affected families or during routine lipid screening. Identification of the 'index' patient is important because it represents the starting point for family tracing or 'cascade testing' by which the majority of cases of FH can be detected (Hadfield et al. 2009). This is important because it enables early intervention including lifestyle measures and management of other major cardiovascular risk factors.

There are several diagnostic tools for the clinical diagnosis of FH including those from the Dutch Lipid Clinics, Simon Broome Registry and the US MEDPED Programme. There are, however, no internationally agreed criteria for the phenotypic diagnosis of FH. The Simon Broome Criteria for FH (1991) is widely used in the UK and is shown in Table 57.3.

Secondary causes of hypercholesterolaemia such as primary hypothyroidism, proteinuria, cholestasis and medications such as corticosteroids must be excluded, but it is important to note that FH may co-exist with other cardiovascular risk factors especially metabolic syndrome and diabetes.

57.3.5 Cholesterol Levels

Serum cholesterol in FH is raised from birth. Serum cholesterol rises in the first year of life to a mean of 4.1 mmol/L (160 mg/dL) and persists

Table 57.3 Simon Broome criteria for FH

Definite FH
Raised cholesterol:
In children (<16 years): Total cholesterol >6.7 mmol/L
OR LDL >4.0 mmol/L
In adults (>16 years): Total cholesterol >7.5 mmol/L
OR LDL >4.9 mmol/L
AND
Tendon xanthomata in the patient or in a first- or second-degree relative
OR
DNA-based evidence of an LDL receptor, familial defective Apo B100 or PCSK9 mutation
Possible FH
Raised cholesterol:
In children (<16 years): Total cholesterol >6.7 mmol/L
OR LDL >4.0 mmol/L
In adults (>16 years): Total cholesterol >7.5 mmol/L
OR LDL >4.9 mmol/L
AND one of the following:
Family history of premature myocardial infarction
MI at <50 years in second degree
MI at <60 years in first-degree relatives
OR
Family history of raised cholesterol
In adults (>16 years), first- or second-degree relatives: Total cholesterol >7.5 mmol/L
In children (<16 years), first-degree relatives: Total cholesterol >6.7 mmol/L

until the early teens with the mean levels being similar in boys and girls before puberty (Durrington and Sniderman 2000). The normal range for cholesterol has little variation with age during childhood which allows a diagnostic threshold for childhood FH to be defined.

Homozygous FH has historically been diagnosed on the basis of an untreated plasma LDL level of >13 mmol/L (>500 mg/dL) or a treated LDL concentration of ≥8.0 mmol/L (≥300 mg/dL) and the presence of cutaneous or tendon xanthomas before the age of 10 or the presence of untreated elevated LDL levels consistent with heterozygous FH in both parents (Cuchel et al. 2014).

LDL levels are typically four times and about two times higher in family members with homozygous FH and heterozygous FH, respectively, when compared to non-affected family members (Soutar and Naoumova 2007). The range of LDL levels may overlap significantly between heterozygous FH and homozygous FH and untreated LDL levels of <13 mmol/L (<500 mg/dL) can be found in patients with genetically confirmed homozygous FH (Bertolini et al. 2013).

57.3.6 Signs

Tendon xanthomata are localised infiltrates of lipid containing foam cells that histologically resemble atheroma and are the diagnostic hallmarks of FH. Xanthelasma of the soft connecting tissues of the eyelids and corneal arcus may also occur but are not specific for FH; however, they often occur earlier in life in those with FH than patients with more common polygenic raised cholesterol. Corneal arcus that occurs in the third of fourth decade of life may indicate FH. Xanthelasma frequently occur in women with previously normal cholesterol levels in their first pregnancy. In heterozygous FH, xanthomata rarely develop before adulthood (less than 10%) and are completely absent in a considerable proportion of patients (Assmann et al. 1999). In homozygous FH, xanthomata may be present at birth and usually develop before the age of 2 years.

The most common sites for xanthomas are the tendons overlying the knuckles, the Achilles tendons, the pre-tibial insertion of the patellar tendon and the elbows (Fig. 57.2). The skin over the xanthomas is normal in colour and the xanthomata feel hard. The cholesterol accumulation is deep within the tendons and a large amount of the swelling is fibrous.

57.3.7 Cardiovascular Consequences of FH

FH is a treatable disease but aggressive lipid lowering is required to achieve the target LDL reduction of 50%. However despite the prevalence of

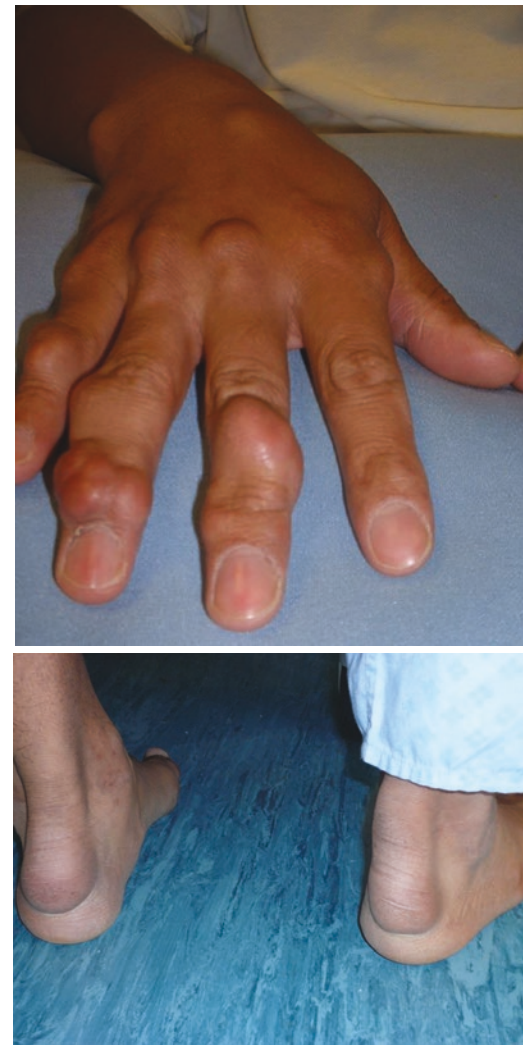


Fig. 57.2 Tendon xanthomas on the knuckles and Achilles

the disease and the availability of effective options, FH remains underdiagnosed and undertreated particularly in children. Some estimates suggest that only approximately 20% of patients are diagnosed and of these only a small number receive appropriate treatment (Goldberg et al. 2011).

The median age for the development of CHD in patients with heterozygous FH in men is approximately 50 and for women it develops about 9 years later (Durrington and Sniderman 2000). In homozygous FH, the first major cardiovascular event often occurs during adolescence although in patients who are receptor negative, angina, myocardial infarction and death have been reported in early childhood (Kolansky et al. 2008). Untreated homozygous FH patients who are LDL receptor negative rarely survive beyond the second decade and although those who are LDL receptor defective have a better prognosis, they almost all develop significant CHD by the age of 30 (Cuchel et al. 2014). Homozygous FH is characterised by the development of accelerated atherosclerosis which typically affects the aortic root, compromising the coronary ostia and also the carotid, descending aorta, renal and ileo-femoral arteries (Raal and Santos 2012).

57.4 Treatment of Lipid Disorders

57.4.1 Lifestyle Changes

Approximately six in ten adults in England have a total cholesterol (TC) level above the target of 5.0 mmol/L (200 mg/dL) (Townsend et al. 2012). Lipid-lowering medication is the mainstay of cholesterol reduction; however; it is important that individuals also adhere to a healthy diet if they are to achieve desired levels of cholesterol. There are a variety of guidelines available to assist in the advice and treatment that patients should receive however patient-specific differences may necessitate an individualised approach to cardiovascular disease management.

57.4.1.1 Dietary Management of Raised Cholesterol

In many patients, lipid disorders can be successfully managed with lifestyle changes. Detailed recommendations and guidelines for weight control, physical activity levels, smoking cessation and diet have been developed by numerous national and international organisations and professional societies. Dietary modifications are the cornerstone of therapy for patients with raised lipid levels. The National Cholesterol Education Programme Guidelines recommend a decrease in the level of saturated fat intake to <7% of calories, a decrease in cholesterol intake to <200 mg/day and an increase in soluble fibre intake to 10–25 g/day and plant sterols/stanols (2 g/day) (NCEP 2002). There is a need for a diet that is not only realistic, but one that delivers impactful cholesterol lowering results such as 'the ultimate cholesterol lowering plan' (HEART UK n.d.). With good adherence to dietary changes, reductions in cholesterol levels of 5–10% can be achieved (BHF/HEART UK 2011). Patients with homozygous FH should receive dietary counselling by a registered dietician (Gidding et al. 2009).

For patients with raised triglyceride levels, emphasis must be given to raising the ratio of monounsaturated to saturated fatty acids and on increasing the energy intake from complex carbohydrates without increasing all carbohydrates as carbohydrates, saturated fat and alcohol can all contribute to elevated plasma triglyceride concentrations (Gotto et al. 2003).

A high level of HDL (>60 mg/dL/≥1.6 mmol/L) is considered to be a negative risk factor for CHD whereas an HDL level of <40 mg/dL/<1.0 mol/L increases the risk of the development of CHD (NCEP 2002). HDL levels are however, little affected by the type of dietary fatty acids. The key lifestyle changes to increase HDL are weight loss in those who are overweight, increased physical activity and smoking cessation. With smoking cessation, HDL levels increase by 6–8 mg/dL (0.15–0.20 mmol/L) on average and significant improvements can occur within as little as 30 days (Gotto et al. 2003).

Estruch et al. (2013) studied Spanish patients who were at high cardiovascular risk but who had no cardiovascular disease on enrolment. They showed that for those patients at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts, reduced the incidence of major cardiovascular events.

There are a variety of foods which can actively help in lowering cholesterol levels including, pulses, fruit and vegetables soy protein and plant sterols and stanols (Hark and Deen 2005). Oats and barley are both fat soluble fibres. Beans, peas, chickpeas and lentils have fat soluble fibres in addition to vegetable protein, folic acid and other antioxidants. They all have a very low glycaemia index resulting in lowering of blood pressure, improvement in the lipid profile and also blood sugar control (Abeysekara et al. 2012).

Apples, strawberries and grapes all have antioxidant properties. Avocados contain monounsaturated fatty acids, dietary fibre, essential nutrients and phytochemicals which can help to improve overall diet quality, nutrient intake and reduce the risk of metabolic syndrome (Fulgoni III et al. 2013). Raw carrots cause an increase in serum carotene levels which helps in reducing cholesterol levels (Robertson et al. 1979).

Soy protein has a modest LDL-C lowering effect (3–5%) (Dewell et al. 2006). Fish is low in saturated fat. Cold water fish are rich in omega-3 fatty acids which lower plasma triglyceride levels and may improve the coagulation profile as it reduces clot formation. A randomised controlled trial in Japan examined the effect of omega-3 fatty acid supplements in Japanese hypercholesterolaemia patients (18,645) with and without coronary artery disease (CAD) (Yokoyama et al. 2007). Twenty-six percent of the total number of recruits in the study had CAD, of which 21% had a prior history of myocardial infarction, 61% had angina and 18% were recruited following revascularisation. Analysis of the results for patients without CAD found that omega-3 fatty acid supplementation had no effect on the primary outcome, or any of the secondary outcomes compared with no supplementation. Fish oil supplementation is no longer recommended and the National Institute for Health and Care Excellence in the UK no longer recommends that patients include oily fish in their diet as a means of reducing preventing CHD (NICE 2014).

Plant sterols and stanols are compounds which occur naturally in plant-based foods and aid digestion. They imitate the way cholesterol works thereby reducing the amount of cholesterol absorbed by the body. Plant sterols are structurally similar to cholesterol and can be divided into phytosterols and phytostanols. They work by mimicking cholesterol and competing with it for space in fatty particles that are absorbed from the gut. The result is less cholesterol and less bile absorbed into the body. This prompts the liver to take more cholesterol from the circulation and to recycle it as cholesterol-rich bile, which serves as an aid to digestion. The daily consumption of 2 g of phytosterols can effectively lower total cholesterol and LDL by 7–10% in humans and have little effect on HDL and triglyceride levels when consumed with the main meal (Abumweis et al. 2008). Currently, there are no data available indicating that cholesterol lowering through plant sterol ingestion results in prevention of CVD. The NICE guidance (2014) states that patients should not be advised to take plant sterols and stanols to prevent CVD; however, they remain in the NCEP guidelines and they may still be recommended for patients with FH (Moruisi et al. 2006).

Red yeast rice is a source of fermented pigment used in China as a food colourant and flavour enhancer. The possible bioactive effects of red yeast rice are related to a statin-like mechanism of inhibition of HMG-CoA reductase. Different preparations have different concentrations of monacolins, the bioactive ingredients which lower total cholesterol and LDL although long-term safety of consumption of these products is not fully understood. One randomised study from China in patients with CAD showed that a particularly purified extract of red yeast rice reduced recurrent events by 45% (Lu et al. 2008).

57.4.2 Lipid-Modifying Drug Therapy

If lipid goals have not been achieved in primary prevention despite lifestyle changes, then drug therapy may be indicated to supplement the life-

style modifications. In secondary prevention, lipid-modifying drug therapy is almost always indicated.

Statins are the most widely recommended treatment for hypercholesterolaemia. Statins reduce the production of cholesterol in the liver by blocking the enzyme 3-hydroxyl-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Their principle effect is to lower plasma LDL although there may be modest increases in HDL and variable decreases in triglycerides dependant on the agent and dose used. A number of large-scale clinical trials have demonstrated that statins substantially reduce cardiovascular morbidity and mortality in both primary and secondary prevention (Downs et al. 1998; Scandinavian Simvastatin Survival Study Group 1994). The 4S study was the first landmark trial in which simvastatin was given to patients with moderately raised cholesterol levels who were known to have CHD. Total mortality was significantly reduced as was the rate of coronary events. In the Cholesterol Treatment Trialist's meta-analysis of individual participant data from >170,000 participants in 26 randomised trials of statins, a 10% proportional reduction in all-cause mortality and 20% proportional reduction in CVD death per 1.0 mmol/L (approx. 40 mg/dL) LDL-C reduction was reported (Baigent et al. 2010).

Statins are the first-line treatment for most people with high cholesterol. Side effects are rare but can include intestinal problems, liver damage, muscle tenderness, asymptomatic increases in liver transaminases and myopathy. Drugs in this class may also interact with other medications such as calcium channel blockers and some antibiotics due to the metabolic pathway used. This can result in significant increases in the plasma levels of statins, increasing the potential for adverse effects. Patients taking statins need to be advised to avoid grapefruit as it is metabolised through the same cytochrome P450 system. There is also some evidence that statins have a number of properties beyond LDL lowering that may contribute to their benefits. These properties are often referred to as pleotropic effects and include improvement in endothelial function, anti-inflammatory effects, antioxidant effects and plaque stabilisation (Davignon and Laaksoen 1999). Current NICE guidance in the UK recommends the use of atorvastatin 20 mg for primary prevention and atorvastatin 80 mg for secondary prevention (NICE 2014).

Statins are generally safe and well tolerated. They do, however cause a rare side effect called myositis which is defined as muscle symptoms in association with a substantially elevated serum creatine kinase concentration. The European Atherosclerosis Society has published a consensus statement on how this condition should be assessed and managed (Stroes et al. 2015).

Bile acid sequesterants or resins act by irreversibly binding the bile produced by the liver. Bile helps the digestion and absorption of fats in the intestine. The depletion in the bile acid pool leads to a greater breakdown of cholesterol to form bile salts. This then promotes up-regulation of the LDL receptors in the liver to maintain the cholesterol pool in the liver. The LDL lowering is 10–20% (Durrington and Sniderman 2000). Although this process can effectively reduce LDL, it can aggravate production of triglycerides. Bile acid sequesterants interfere with the absorption of fat soluble vitamins and supplements of these may be required. At the top dose of 24 g of cholestyramine or 4.5 g of cholestagel, a reduction in LDL-C of 18–25% has been observed. No major effect on HDL has been reported, while triglycerides may increase in some predisposed patients (ESC/EAS 2011).

Fibrates have a much weaker effect on LDL than statins and act mainly by decreasing serum triglycerides and inhibiting lipoprotein lipase activity (The FIELD Study Investigators 2005). The overall efficacy of fibrates on CVD outcomes is much less robust than of statins. Recent meta-analyses have reported that fibrate therapy reduced major CVD events by 13%, the benefits being most evident in patients with elevated triglyceride levels (>2.3 mmol/L/90 mg/dL) (Jun et al. 2010).

Cholesterol absorption inhibitors lower cholesterol by inhibiting the intestinal absorption of dietary and biliary cholesterol by blocking the passage across the intestinal wall. They favourably affect triglyceride and HDL levels in mono-

therapy and in combination with statins (Gagné et al. 2002). The IMPROVE-IT study examined the addition of ezetimibe to statin therapy in patients who had been hospitalised for an acute coronary syndrome within the previous 10 days. The study concluded that when added to statin therapy, ezetimibe resulted in incremental lowering of the LDL level and improved cardiovascular outcomes (Cannon et al. 2015). Ezetimibe is recommended to be used as monotherapy for patients in whom statin therapy is contraindicated or co-administered with a statin if the LDL is not adequately controlled after dose titration of the statin or if dose titration is limited by statin intolerance (NICE 2016).

Nicotinic acid is a B vitamin that markedly reduces VLDL and LDL and substantially increases HDL. It also is the only hypolipidaemic agents that reduces Lp(a). Its mechanism of action is not fully known but reduces VLDL secretion by the liver (Durrington and Sniderman 2000). Although successful in reducing cholesterol levels, this group of drugs are not well tolerated and the main drugs available have recently been withdrawn in the UK and Europe due to their side effect profile.

57.4.3 Novel Drug Therapies

In the last few years, a variety of novel lipid-lowering agents with different mechanisms of action have been developed which have the potential to further improve the management of hypercholesterolaemia.

57.4.3.1 Mipomersen

Mipomersen is a second-generation antisense oligonucleotide which targets the messenger ribo-nucleic acid (mRNA) of Apo B. It is administered by subcutaneous injection and acts by reducing the translation of Apo B mRNA and the synthesis by the ribosome leading to reduced secretion of VLDL (Crooke and Geary 2013). In a placebo-controlled double-blind study of patients with homozygous FH, weekly injections of mipomersen resulted in further reductions from baseline at 26 weeks in plasma levels of LDL (mean 25% reduction), Apo B (mean 27% reduction and Lp(a) (mean 31% reduction) versus placebo. A significant number of patients reported injection site reactions (76%) some of which were long-lasting. Other adverse reactions included flu-like symptoms which typically appeared 2 days after the injection (Raal et al. 2010). Mipomersen has been approved by the Food and Drug Administration in the USA for patients with homozygous FH; however, the licence for use in Europe was withdrawn due to the adverse event profile.

57.4.3.2 Lomitapide

Lomitapide is an inhibitor of the microsomal triglyceride transport protein (MTP) which is a key protein in the assembly and secretion of Apo B containing lipoproteins in the liver and intestine. An open-label trial of maximally tolerated doses in homozygous FH patients showed reduction in LDL of approximately 50% and Lp(a) of approximately 15% at 26 weeks in addition to standard care including lipoprotein apheresis. The LDL reductions were maintained over a further 12 months follow-up (Cuchel et al. 2013). The most frequently observed side effects were gastrointestinal and liver fat accumulation. The gastrointestinal effects were reduced by using a gradual dose-escalation regimen combined with adherence to a very low-fat diet (<20% of energy from fat). Lomitapide is licenced for use in homozygous FH adults in the USA and Europe although the high cost of the drug may limit its use.

57.4.3.3 PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce circulating LDL levels by preventing the degradation of LDL receptors when bound to PCSK9. Studies with monoclonal antibodies to PCSK9 have shown that the addition of these agents to moderate or high intensity statins in patients with primary hypercholesterolaemia resulted in additional LDL lowering. Most patients achieved LDL levels of less than 1.8 mmol/L (70 mg/dL) at 12 weeks. Adverse events were reported in 36%

of patients and were most commonly musculoskeletal or headaches (Robinson et al. 2014). The safety and efficacy of one of the PCSK9 inhibitors has been evaluated at 52 weeks demonstrating that added to diet alone, to low dose statin or high dose statin with or with ezetimibe there was a significant reduction in LDL levels in patients with a range of cardiovascular risks (Blom et al. 2014). PCSK9 inhibitors have been licenced since 2016 and their use is increasing for patients who fail to reach target cholesterol levels despite maximum tolerated statins or those who are statin intolerant.

57.4.3.4 Cholesterol Ester Transfer Protein Inhibitors

Cholesterol ester transfer protein (CETP) reduces circulating HDL levels by transferring cholesterol ester from HDL to larger lipoproteins such as chylomicrons, VLDL and LDL in exchange for triglyceride. It creates a smaller, cholesterol-depleted HDL, therefore remodelling the HDL which is potentially beneficial in removing excess tissue cholesterol together with a small, cholesterol-depleted LDL which is highly atherogenic (Durrington 2012). CETP activity is elevated in dyslipidaemia and early onset CAD (Bhatnagar et al. 1993). It is known that there is an inverse relationship between HDL and CVD which has led to the hypothesis that therapies that raise HDL levels may ameliorate future CVD risk. Inhibiting CETP is one potential mechanism of achieving this.

There are four CETP inhibitors which have reached late-stage clinical development. The development of one of these—torcetrapib was halted after studies showed an increase in cardiovascular events and total mortality; however, it was not felt that these affects were due to CETP inhibition (Vergeer et al. 2008). Anacetrapib given in addition to statins was seen to increase the HDL level by approximately 140% with no observable adverse effects on cardiovascular outcomes (Cannon et al. 2010). Similar studies with dalcetrapib also showed no adverse cardiovascular effects but the increase in HDL was more modest at approximately 30% (Robinson 2010). The lack of positive outcome data for CETP inhibitors has resulted in them not yet being used in routine clinical practice. Further studies on the class of drug are required together with development of novel drugs to identify their exact place in the management of raised cholesterol.

Figure 57.3 shows the development of lipid-lowering therapy over the past 60 years.

57.4.4 Lipoprotein Apheresis

Lipoprotein apheresis is a selective extracorporeal treatment, similar to renal dialysis, which removes atherogenic Apo B 100 containing lipoproteins from the circulation. It can be used to treat raised cholesterol levels in patients with FH and non-familial hypercholesterolaemia who have failed to reach target levels with maximum tolerated diet and medication.

The first successful use of plasma exchange to treat homozygous FH was described in 1975 (Thompson et al. 1975). Lipoprotein apheresis is now accepted as the treatment of choice for patients with homozygous FH and for heterozygotes with cardiovascular disease refractory to lipid-lowering drug therapy. Lipoprotein apheresis should also be considered for patients with accelerated coronary disease and significantly raised Lp(a) whose LDL cholesterol remains raised despite maximal drug therapy.

There are a several guidelines for the use of lipoprotein apheresis worldwide which all vary slightly, as do the number of patients receiving treatment. The National Lipid Association Expert Panel on Familial Hypercholesterolaemia (Ito et al. 2011) recommend the use of apheresis in patients who, after 6 months, do not have an

Fig. 57.3 Development of lipid-lowering therapy

adequate response to maximum tolerated drug therapy in the following cases:

- Functional homozygous FH patients with LDL cholesterol ≥300 mg/dL (7.7 mmol/L) (or non-HDL cholesterol ≥330 mg/dL/8.5 mmol/L).
- Functional heterozygous FH patients with LDL cholesterol ≥300 mg/dL (7.7 mmol/L) (or non-HDL cholesterol ≥330 mg/dL/8.5 mmol/L) and 0–1 risk factors.
- Functional heterozygous FH patients with LDL cholesterol ≥200 mg/dL (5.1 mmol/L) (or non-HDL cholesterol ≥230 mg/dL/5.9 mmol/L) and high-risk characteristics such as ≥2 risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay.
- Functional heterozygotes with LDL cholesterol ≥160 mg/dL (4.1 mmol/L) (or non-HDL cholesterol ≥190 mg/dL/4.9 mmol/L) and very high-risk characteristics (established CHD, other cardiovascular disease or diabetes) (Ito et al. 2011)

In Germany, LDL apheresis is recommended for all patients with homozygous FH and LDL >500 mg/dL (12.9 mmol/L) and for patients with severe hypercholesterolaemia when maximal diet and drug therapy for more than 1 year has failed to lower the LDL sufficiently (Working Party on medical treatment of the Federal Committee 2009). Some German centres also recommend considering apheresis treatment to patients with Lp(a) >600 mg/L with progressive CHD despite optimal control of other risk factors (Heigl et al. 2009).

In the UK, the LDL Apheresis Working Group of HEART UK has recommended that LDL apheresis should be considered for:

- All patients with homozygous FH older than 7 years of age with a total cholesterol of >350 mg/dL (9.0 mmol/L) or a decrease of less than 50% on drug therapy
- Patients with heterozygous FH or a family history of premature cardiac death with significant progression of coronary disease if the LDL is more than 200 mg/dL (5.2 mmol/L) or a decrease of less than 40% on maximal drug therapy
- Patients with Lp(a) >600 mg/L with progression of CAD if the LDL is >125 mg/dL (3.2 mmol/L) despite maximal drug therapy (Thompson et al. 2008).

Despite these recommendations, lipoprotein apheresis is widely underused and the frequency varies across Europe and the rest of the world. It is estimated that 12 per million of the population receive apheresis in Germany, three per million in Sweden, two per million in France and Italy and 0.6 per million in the UK (Thompson et al. 2008). In the USA, there were approximately 250 patients being treated in 35 apheresis centres in 2006 (Nordestgaard et al. 2013).

There are several methods available for lipoprotein apheresis. Initial methods involved the separation of plasma from red blood cells prior to the removal of LDL and Lp(a). These include immunoadsorption, double filtration, dextran sulphate cellulose adsorption and heparin-induced extracorporeal LDL-cholesterol precipitation. Newer methods such as direct adsorption of lipoproteins and direct haemoperfusion remove the lipoproteins from whole blood.

Although there are technical differences between the different methods, studies have demonstrated no significant differences in reduction of lipoproteins or in clinical outcomes (Julius et al. 2008). Treatment duration varies depending on the system used but is usually between 1.5 and 4.0 h. Factors which affect treatment duration include the blood flow achieved, method of venous access used, target volume of blood/plasma to be treated and the patient's condition. Treatment requires the insertion of two large gauge vascular access catheters into the patents peripheral veins or via an arterio-venous fistula. Occasionally, insertion of a long-term central line is required if the two previous methods of vascular access fail.

Lipoprotein apheresis treatment is generally well tolerated with side effects and adverse events being reported in approximately 3–5% of treatments (Gordon et al. 1998). Overall, it is a safe and effective treatment but there is a need to

expand the availability of the therapy in many countries of the world.

57.5 Conclusions

Raised lipid levels are an important risk factor for CHD. Patients with FH have an increased risk of premature coronary disease and it is important that they receive optimum therapy to reduce the likelihood of them experiencing coronary events. There are a variety of interventions that can reduce lipid levels including lifestyle changes, medication and lipoprotein apheresis. Each patient needs to be individually assessed in order to determine the most appropriate management plan to achieve target lipid levels.

Case Study 1

Mr Smith is a 55-year-old man. He was admitted to a tertiary cardiac centre as an emergency with an acute myocardial infarction (MI). He had no previous medical history but was a smoker. He was treated with primary angioplasty and underwent insertion of 2 drug eluting stents to his left anterior descending coronary artery. Prior to discharge he was reviewed by one of the cardiac rehabilitation nurses who gave him advice on smoking cessation and on a low-fat diet.

His cholesterol level was checked during his admission and was found to be 6.7 mmol/L (260 mg/dL). As part of his secondary prevention treatment, he was started on Atorvastatin 80 mg od. Mr Smith was concerned about taking a statin as he had read reports in the press that they had side effects. He was counselled by one of the pharmacists who explained the importance of cholesterol reduction following his MI and also explained that side effects were rare but that it was important that he should inform his GP of any problems he had with any of his medication. He was also advised to have his cholesterol level rechecked in 3 months to ensure that his level had been reduced adequately.

Case Study 2

Mrs Brown is a 50-year-old lady who was diagnosed with familial hypercholesterolaemia (FH) when she was 40 years old. Her father had died from a myocardial infarction when he was 38 years old, and her paternal grandfather and uncle had also died before the age of 50. Her raised cholesterol level was found during a health check at work. and she was then sent to the regional cardiac centre for genetic testing. This had shown that she had a mutation of the LDL receptor. Mrs Brown has two children who are 25 and 27 years old who have also been tested for FH. Neither of them has been found to have the mutation. Mrs Brown's LDL level was 6.0 mmol/L (190 mg/dL) when she was diagnosed. She was prescribed Atorvastatin 80 mg od which reduced her LDL to 3.0 mmol/L (115 mg/dL). As this level remains higher than the target for someone with FH, she has recently been started on Ezetimibe 10 mg od in addition to her statin. She has also had a discussion with her lipidologist about one of the newer drugs that can be used for raised cholesterol. They have agreed that if her LDL level continues to be greater than 1.8 mmol/L (70 mg/dL) on statin and Ezetimibe combination therapy she will try a PCSK9 inhibitor. She is concerned that this new medication is given by injection and has decided that she would prefer to try other oral lipid-lowering therapy first.

Nursing process in the management of patients with lipid disorders and FH

- Identify patients with raised lipid levels
- Provide information and advice regarding diet and lifestyle changes that patients can make to help reduce lipid levels
- Identify patient knowledge deficits and areas for additional education
- Advise patients on how frequently they should have their lipid levels checked
- If patients have xanthelasma or tendon xanthomas and are not known to have FH, facilitate referral to a lipid specialist
- Discuss the need for lipid-lowering therapy with patients
- Provide advice on potential side effects of medication and the action to be taken if patients think they are experiencing side effects
- Ensure patients are aware that lipid-lowering therapy is lifelong

- Allow time for patients to express their possible concerns about lipid-lowering therapy to facilitate adherence
- Evaluate the patients response to lipid-lowering therapy and give advice on the need to increase or add additional medication as necessary
- Identify patients whose lipid levels remain above target and ensure they are referred to a lipid specialist
- Discuss the need for cascade testing with patients who are diagnosed with FH
- Advise women of child bearing age of the need to stop lipid-lowering therapy prior to planning a pregnancy
- Refer any patient known to have raised lipids who develops symptoms of chest discomfort to a cardiologist for further evaluation
- Provide information about patient support groups and websites for patients with raised lipids
- Provide emotional support to patients and their families when diagnosed with, or being investigated for FH
- Be aware of new medications being used or under investigation for use in patients with raised lipid levels

References

Abeysekara S, Chiliback PD, Vatanparast H, Zello GA. A pulse based diet is effective for reducing total and LDL-cholesterol in older adults. Br J Nutr. 2012;108:S103–10.

Abumweis SS, Barake R, Jones PJ. Plant sterols/stanols as cholesterol lowering agents: a met-analysis of randomised controlled trials. Food Nutr Res. 2008;52. https://doi.org/10.3402/fnr.v52io.1811.

Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. JAMA. 1987;257:2176–80.

Anitchkow N. Über die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose. Beiträge zur pathologischen Anatomie und zur allgemeinen. For Pathol. 1913;56:379–404.

Assmann G, Cullen P, Schulte H. The Münster Heart Study (PROCAM)—results of follow-up at 8 years. Eur Heart J. 1998;19:A2–11.

Assmann G, Cullen P, Gotto AM. Treatment of elevated low density lipoprotein cholesterol: the role of LDL apheresis. Osaka: Medical Science Publications Inc; 1999.

Bacmeister A, Henes E. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Erkrankungen. Deutche Med Wochensch. 1913;39:544–6.

Baigent C, Blackwell L, Emberson J, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 17,0000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

Berg K. A new serum type system in man: the Lp system. Acta Pathol Microbiol Scand. 1963;59:369–82.

Bertolini S, Pisciotta L, Rabacchi C, et al. Spectrum of mutations and phenotypic expression in patients with autosomal dominant hypercholesterolaemia identified in Italy. Atherosclerosis. 2013;227:342–8.

Bhatnagar D, Durrington PN, Channon KM, et al. Increased transfer of cholesterol esters from high density lipoproteins to low density lipoproteins and very low density lipoproteins in patients with angiographic evidence of coronary artery disease. Atherosclerosis. 1993;98:25–33.

BHF British Heart Foundation. Cardiovascular disease statistics, UK factsheet. 2015. http://www.bhf.org.uk/research/heart-statistics.

Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidaemia. N Engl J Med. 2014;2014(370):1809–19.

British Heart Foundation, HEART UK. Inherited heart conditions. London: BHF; 2011.

Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med. 2010;363:2406–515.

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.

Cremer P, Nagel D, Labrot B, et al. Lipoprotein Lp(a) as a predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factors: results from the Prospective Gottingen Risk Incidence and Prevalence Study (GRIPS). Eur J Clin Investig. 1994;24:444–53.

Crooke ST, Geary RS. Clinical pharmacological properties of mipomersen (Kynamro) a second generation antisense inhibitor of apolipoprotein B. Br J Clin Pharmacol. 2013;76:269–76.

Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381:40–6.

Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146–57.

Danesh J, Collins R, Peto R. Lipoprotein (a) and coronary heart disease. Meta-analysis of prospective studies. Circulation. 2000;102:1082–5.

Davignon J, Laaksoen R. Low-density lipoprotein-independent effects of statins. Curr Opin Lipidol. 1999;10:543–59.

Dewell A, Hollenbeck PL, Hollenbeck CB. A critical evaluation of the role of soy protein and isoflavone supplementation in the control of plasma cholesterol concentrations. J Clin Endrocrinol Metab. 2006;91:772–80.

Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFACPS/TexCAPS. JAMA. 1998;279:1615–22.

Durrington PN. Hyperlipideamia, diagnosis and management. 3rd ed. London: Hodder Arnold; 2007.

Durrington PN. Cholesterol ester transfer protein (CETP) inhibitors. Br J Cardiol. 2012;19:126–33.

Durrington P, Sniderman A. Hyperlipidaemia. Abingdon: Health Press; 2000.

Ellegård LH, Andersson SW, Normén AL, Andersson HA. Dietary plant sterols and cholesterol metabolism. Nutr Rev. 2007;65:39–45.

ESC/EAS. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–818. https://doi.org/10.1093/eurheartj/ehr158.

Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. NEJM. 2013;368:1279–90.

Forms of Therapeutic Hemopheresis. Summary report of the working party on medical treatment of the federal committee of physicians and health insurance companies on the deliberations pursuant to § 135 para 1 of the Code of Social Law, vol V (SGB V); 2009.

Fulgoni VL III, Dreher M, Davenport AJ. Avocado consumption is associated with better diet quality and nutrient intake and lower metabolic syndrome risk in US adults: results from National Health and Nutrition Examination Survey (NHANES) 2001-2008. Nutr J. 2013;12:1–6.

Gagné C, Bays H, Weiss S, et al. Efficiency and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolaemia. Am J Cardiol. 2002;90:1084–91.

Gidding SS, Lichenstien AH, Faith MS, et al. Implementing American Heart Association paediatric and adult nutrition guidelines: a scientific statement from the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular Disease in the Young, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Councilon Cardiovascular Nursing, Council on Epidemiology and Prevention and Council for High Blood Pressure Research. Circulation. 2009;119:1161–75.

Goldberg A, Hopkins P, Toth P, et al. Familial hypercholesterolaemia: screening, diagnosis and management of paediatric and adult patients. J Clin Lipidol. 2011;5:133–40.

Goldstein JL, Brown MS. The LDL receptor locus and the genetics of familial hypercholesterolaemia. Annu Rev Genet. 1979;13:259–89.

Goldstein JL, Kita T, Brown MS. Defective lipoprotein receptors and atherosclerosis. Lessons from an animal counterpart of familial hypercholesterolaemia. N Engl J Med. 1983;309:288–96.

Gordon DJ, Probstfield JL, Garrison RJ, et al. High density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. Circulation. 1989;79:8–15.

Gordon BR, Kelsey SF, Dau PC, et al. Long-term effects of low-density lipoprotein apheresis using an automated dextran sulphate cellulose adsorption system. The Liposorber Study Group. Am J Cardiol. 1998;81:407–11.

Gotto AM, Amarenco P, Assmann G, et al. Dyslipideamia and coronary heart disease. 3rd ed. New York: International Lipid Information Bureau; 2003.

Hadfield SG, Horara S, Starr BJ, et al. Family testing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health familial hypercholesterolaemia cascade testing project. Ann Clin Biochem. 2009;46:24–32.

Hark L, Deen D. Nutrition for life. 1st ed. London: Dorling Kindersley; 2005.

HEART UK. The nation's cholesterol charity. n.d. www.heartuk.org.uk/healthyliving/healthy-living-resources.

Heigl F, Hettich R, Lotz N, et al. Indication and implementation of lipidapheresis, rheopheresis or immunoadsorption (lesions learnt from Germany's largest apheresis centre). Atheroscler Suppl. 2009;10:137–41.

Ito MK, McGowan MP, Moriarty PM. Management of familial hypercholesterolaemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolaemia. J Clin Lipidol. 2011;5:S38–45.

Julius U, Frind A, Tselmin S, et al. Comparison of different LDL apheresis methods. Expert Rev Cardiovasc Ther. 2008;6:629–39.

Jun M, Foote C, Lu J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010;375:1875–84.

Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolaemia. Am J Cardiol. 2008;102:1438–43.

Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. BMJ. 1994;308:363–6.

Lipid Research Clinics Program. The Lipid Research Clinics Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–74.

Lu Z, Kou W, Du B, et al. Chinese Coronary Secondary Prevention Study Group. Effect of Xuezhikang,

an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol. 2008;101:1689–93.
Marais AD. Familial hypercholesterolaemia. Clin Biochem Rev. 2004;25:49–68.
Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolaemic subjects: a systematic review with meta-analysis. J Am Coll Nutr. 2006;25:41–8.
National Cholesterol Education Programme (NCEP). Third report of the National Cholesterol Education Programme (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification CG181. 2014. www.nice.org.uk/guidance/cg181.
National Institute for Health and Care Excellence. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Technology appraisal guidance 385. 2016. www.nice.org.uk/guidance/ta385.
Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90.
Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine. E Heart J. 2016;37(25):1944–58. https://doi.org/10.1093/eurheartj/ehw152.
Packard CJ, Shepherd J, Cobbe SM, et al. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation. 1998;97:1440–5.
Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. Eur Heart J. 2012;33:1635–701.
Pfeffer MA, Sacks FM, Moyé LA, et al. Cholesterol and recurrent events: a secondary prevention trial for normolipidemic patients. Am J Cardiol. 1995;76:98C–106C.
Pottle A. Understanding coronary heart disease. In: Bullock I, Macloed Clark J, Rycroft-Malone J, editors. Adult nursing practice—using evidence in care. Oxford: OUP; 2012. p. 97.
Raal FJ, Santos RD. Homozygous familial hypercholesterolaemia; current perspectives on diagnosis and treatment. Atherosclerosis. 2012;223:262–8.
Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:998–1006.
Radar DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolaemia: new insights in pathogenesis and treatment. J Clin Invest. 2003;111:1795–803.
Robertson J, Brydon WG, Tadesse K, et al. The effect of raw carrot on serum lipids and colon function. Am J Clin Nutr. 1979;32:1889–92.
Robinson JG. Dalcetrapib: a review of phase II data. Expert Opin Investig Drugs. 2010;19:795–805.
Robinson JG, Nedergaard BS, Rogers WJ. Effect of evolocumab or ezetimibe added to moderate-or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolaemia. The LAPLACE-2 randomised clinical trial. JAMA. 2014;311:1870–82.
Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disaease; the Scandinavian Survival Study. Lancet. 1994;344:1383–9.
Scientific Steering Committee, Simon Broome Registry Group. Riask of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. Br Med J. 1991;303:893–6.
Sjouke B, Kusters M, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship and clinical outcome. Eur Heart J. 2015;36:560–5.
Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolaemia. Nat Clin Pract Cardiovasc Meds. 2007;4:214–25.
Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1–45.
Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on assessment, aetiology and management. Eur Heart J. 2015;36(17):1012–22. https://doi.org/10.1093/eurheartj/ehv043.
The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–61.
Thompson GR, HEART UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. Atherosclerosis. 2008;198:247–55.
Thompson GR, Lowenthal R, Myant NB. Plasma exchange in the management of homozygous familial hypercholesterolaemia. Lancet. 1975;1:1208–11.

Townsend N, Wickramasinghe K, Bhatnagar P, et al. Coronary heart disease statistics. 2012th ed. London: British Heart Foundation; 2012. www.bhf.org.uk.

Vergeer M, Bots ML, van Leuven SI, et al. Cholesterol ester transfer protein inhibitor torcetrapib and off-target toxicity: a pooled analysis of the rating atherosclerotic disease change by imaging with a new CETP inhibitor (RADIANCE) trials. Circulation. 2008;118:2515–22.

Waller BF. The eccentric coronary atherosclerotic plaque: morphologic observations and clinical relevance. Clin Cardiol. 1989;12(1):14–20.

Waller BF, Orr CM, Slack DJ, et al. Anatomy, histology and pathology of coronary arteries: a review relevant to new interventional and imaging techniques—part III. Clin Cardiol. 1992;15(8):607–15.

Wilson P, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.

World Health Organisation. Non communicable diseases country profiles 2011. France: World Health Organisation; 2011. http://whqlibdoc.who.int/publications/2011/9789241502283_eng.pdf.

Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.

Key Reading

1. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012).
2. Cardiovascular disease: risk assessment and reduction, including lipid modification NICE guidelines [CG181] Published date: July 2014 Last updated: January 2015. https://www.nice.org.uk/guidance/cg181.
3. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
4. www.heartuk.org.
5. Durrington PN. Hyperlipidaemia, diagnosis and management. 3rd ed. London: Hodder Arnold; 2007.

Part X

Late Effects of Cancer Treatment in Relation to Endocrinology

Cecilia Follin

Transition of Childhood Cancer Survivors

58

Tanya L. Urquhart-Kelly and Jerry K. Wales

Contents

58.1 Introduction 1124
58.2 What Is Transition? 1126
58.3 Barriers to Transition 1127
58.4 Conclusions 1127
References 1131

Abstract

More than three quarters of children treated for cancer survive into adulthood with this number continuing to rise. Successful transition is now recognised as an important facet of care in both paediatric and adult medicine. It encompasses "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems" (Blum et al. 1993). It is not simply transfer of care to another provider but should be a gradual process taking into account physical and psychological maturity as well as the availability and structure of local resources.

Childhood cancer survivors (CCS) have to cope not only with the late effects of treatment but also come to terms with their initial diagnosis, the uncertainty about relapse and the risk of second malignancies. Specialist nursing skills are required to deal with these issues, the emphasis of this being support, screening and clinical review, ensuring a swift referral process for suspected second malignancy or late effects (LE) requiring specialised care, i.e. cardiomyopathy, hypothyroidism, and premature ovarian failure.

Keywords

Transition · Survivors · Survivorship care plans · Childhood cancer · Collaboration Multidisciplinary · Adolescents · Young adults

T. L. Urquhart-Kelly (✉)
Sheffield Hallam University, Sheffield, UK
e-mail: t.urquhart-kelly@shu.ac.uk

J. K. Wales
Lady Cilento Children's Hospital,
Brisbane, QLD, Australia
e-mail: jerry.wales@health.qld.gov.au

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_58

Abbreviations

ACTH	Adrenocorticotropic hormone
B	Breast
CCS	Childhood cancer survivors
CHN	Complex health needs
DDAVP	Desmopressin
GH	Growth hormone
GHD	Growth hormone deficiency
GP	General practitioner
LE	Late effects
PH	Pubic hair
RSG	Ready steady go
SCP	Survivorship care plan
UFC	Urinary free cortisol
YP	Young person

Key Terms

- **Late effects**: Complications due to cancer treatment.
- **PanCare**: Pan-European network to improve the care of childhood cancer survivors.
- **Survivorship care plan**: Cancer treatment history and recommended follow-up plan.
- **Transition**: An active, planned, coordinated comprehensive process to enable transfer from child-centered to adult-oriented health care system.

Key Points

- The number of childhood cancer survivors is growing.
- This patient population may be at risk of premature morbidity or mortality due to their previous cancer treatments or the cancer itself and are at risk of second malignancies.
- There are a paucity of transition programmes for childhood cancer survivors to enable a successful transfer from child-orientated health care services to adult-orientated healthcare.
- Transition is specific to each individual survivor and needs to be considered from the following perspectives; developmental stage and understanding, medical, psychological, educational, and vocational.
- It requires a multidisciplinary approach.
- Patients should be empowered to be collaborative in their transition process.

58.1 Introduction

The overall 5-year survival rate following childhood cancer is now greater than 80% in developed European countries (Winter et al. 2015) and (M Van Laar 2013). For some cancers, such as acute lymphoblastic leukaemia and Hodgkin's disease, cure rates exceed 90% (Cohen 2005). Consequently, the cohort of CCS is increasing worldwide, year on year presenting a significant challenge for service provision. This not only impacts paediatric services but also adult services as these children mature into adolescence and adulthood. Although these survival rates are a positive aspect of the speciality, childhood cancer survivorship is known to be associated with adverse long-term physical and psychological LE. Whilst some will manifest in childhood, others may manifest many years, even decades following completion of treatment and into adulthood. CCS who fail to successfully transition to adult-orientated LE clinics will miss out on their risk-based LE follow-up and potentially experience late morbidity and early mortality (Klassen et al. 2014).

LE following cancer treatment in childhood is presented in Chap. 2. The most common impacts of the primary three treatments for childhood cancer (chemotherapy, radiation therapy, and surgery) are on growth, endocrine function, fertility, neuropsychology, and the cardiac system. Two thirds of childhood cancer survivors will experience at least one LE with the endocrine system commonly involved. Another third of patients will develop two or more LE which may be severe or life-threatening (Oeffinger et al. 2006). Therefore, transition services for CCS must include competent health professionals from multiple disciplines with insight and an understanding of the potential LE following childhood cancer. This prevalence of endocrine disorders amongst CCS combined with increased survival rates for this patient cohort will all add to the

demand for lifelong endocrine input for CCS (Brignarello et al. 2013). Indeed a study by Sadak et al. (2013) suggested that CCS preferred a paediatric health care professional known to them or one with knowledge of childhood cancer to remain part of the clinical team in transition.

Another element of successful transition is that early detection of LE using planned surveillance with a focus on prevention and detection may reduce psychological and health problems. Endocrinopathies are now well recognised and common amongst survivors of childhood cancer. Thus, LE follow-up requires endocrinologists and endocrine nurses to be part of their survivorship teams (Patterson et al. 2012). Furthermore, the research by Sadak et al. (2013) identifies that adult survivors of childhood cancer rated their comprehensive survivorship care as the most beneficial aspect of their wider LE care. They also suggested that preferences for transition may be multifactorial and include the role of parents in continuing to attend LE follow-up appointments (Kinahan et al. 2008), cultural sensitivities associated to race and ethnicity, and the importance of the role of nuclear families (Casillas et al. 2010).

Models of shared care survivorship have been proposed and are often developed to suit local services with consideration of available facilities, systems, and professionals. The logistics of professionals facilitating clinics across adult and paediatric hospital sites can be complex. Furthermore, paediatric settings often lack developmentally appropriate facilities for adolescents (Blum 2002). That said, the exact location of good LE follow-up may be located in either paediatric or adult out-patient settings depending on local circumstance. In some areas, specialised childhood LE clinics exist which are only able to deliver appropriate risk-based follow-up for children and young people following completion of their cancer treatment but may be unable to provide ongoing LE follow-up care once these patients move into adulthood. If this is the case, these patients may then be discharged back to their general practitioner (GP) in primary care. If this model needs to be adopted, it is essential that a summary of the patient's treatment and individualised care plan for future screening is appended to their discharge summary. This will allow the GP or primary care physician to continue to provide this screening, assessment, and management of LE.

These documents are commonly referred to as survivorship care plans (SCP). The accurate information included in these care plans together with the nature of the individual's current problems and a realistic view of the future are all essential. However, McClellan et al. (2013) identified that many young adult survivors of childhood cancer do not have an SCP. Furthermore, the provision of an SCP is seen by many health professionals as a costly and time-consuming addition to a patients care pathway (Hewitt 2007). The Institute of Medicine (2006) recommends that certain core components be universally present in SCPs, with the provision on SCPs being the second recommendation in their adult survivors report (Hewitt et al. 2005; Alfano and Rowland 2016). The core components expected to be listed in any post-treatment care plan are: details of diagnosis and treatment, potential consequences, recommendations for type and timing of follow-up, and recommendations for preventative services, e.g. psychosocial resources if locally available.

Evaluation of SCPs in adult bowel cancer survivors demonstrated that 80% of respondents were likely to engage with them if one was made available with 30% commenting on how useful it would be for continuity of care at follow-up appointments (Baravelli et al. 2009). This is echoed in work undertaken by Slater (2010) where a participant responded "showing my SCP to whichever physician I see will save a lot of messing around and repetition". Clearly this is transferable to the care for CCS due to their requirement to continue follow-up lifelong and across multi-professional teams. A standardised approach to the SCP format has demonstrated an improvement in the early detection, intervention, and management of recurrent disease and LE (Earle 2007).

Negative aspects of SCPs have also been addressed, with 17% of survivors raising concern about information regarding recurrence and family risk, although all agreed it should be retained despite the potential distress (Slater 2010). They have also described themselves as being overwhelmed at the end of active treatment, receiving

so much information they could not absorb it all (Hewitt 2007). Overall however SCP's can be viewed as a successful tool to pre-empt or address individual issues before they arise whilst at the same time offering survivors a source of control, shared knowledge, and a free flow of information and transparency about their continuing health journey (Hewitt 2007).

A scoping exercise to identify successful models of transitional care for young people (YP) with a variety of complex health needs (CHN) was undertaken in the UK in 2011 (Watson et al. 2011). This demonstrated a paucity of evidence to inform best practice about both the process of and what constitutes effective transitional care. From this work a transition programme named "Ready, Steady, Go" (RSG) was devised (National Institute of Health and Care Excellence (NICE) 2017). RSG is a suite of resources designed to deliver high-quality transition for young people (YP) across all subspecialties. The objective of RSG is to deliver high-quality transition thereby improving patient and young people's experience and ability to manage their healthcare independently in a cost-effective manner.

58.2 What Is Transition?

Transition is a phenomenon that occurs in all of our everyday lives, independent of health status and age (Mulder et al. 2016). Examples of these transitions are starting school, puberty, moving away from home to study, and gaining employment. Without doubt adolescence is a significant time in our lives for all adolescents and not just those with an underlying chronic health condition. It is a point in life where individuals strive to move from dependence and seek their own identity. The end point is cited by (Evans 1996) as being a time when "adolescents are expected to emerge into adult life with a positive sense of self-worth and an established identity, a comfortable body image, and the ability to form relationships with others of the same and opposite sexes. They should have an ability to think in abstract terms, to verbalise conceptually, and to have attained emotional and practical independence". Thus, adolescence can be described as a time of tension and uncertainty as the individual strives to establish an identity and plan for the future (Hollis and Morgan 2001). As children and young people grow and mature, their cognitive, medical, and social needs for information also change. These combined health and psychosocial needs must be responded to by the LE team in a timely and developmentally appropriate way. Myelination and maturation of the central nervous system is not normally complete until the middle of the third decade and may be incomplete or abnormal in some LE patients (see below). For this reason, risk-taking behaviour is more common (including non-adherence to therapies) and explanations or educational material should be appropriate for the developmental age of the young person. Likewise, achievement of peak bone mass is not until a similar age and so treatments to improve bone health such as growth hormone at a reduced dose on attainment of adult height remains an "active" medical issue.

Children undergoing treatment for cancer achieve a number of other transitions during their treatment journey. The first is upon completion of active treatment and entering a period of clinical surveillance which follows their immediate end of treatment where the emphasis is primarily on screening for recurrence. This follow-up is usually performed by the treating oncologist/haematologist. The second transition is to a specific LE follow-up clinic, often with new personnel although others will link from the earlier acute clinical period. The third transition is to a transition LE service either in paediatric or adult services or discharge to primary care. Where local adolescent medical specialists are available, there may even be other transitions to adult care and eventually care of the elderly!

Core specialists within LE teams usually include: Consultant paediatric oncologist, Specialist LE nurse, Consultant Endocrinologist, Psychologist, and a specific multidisciplinary team co-ordinator. Nurse specialists' benefit from an oncology background as their knowledge of cancer treatment is fundamental to ongoing assessment and patient education. In the UK, the Royal College of Nursing competencies identify the core knowledge and skills required (RCN 2011). There also need to be rapid referral pathways to fertility, orthopaedic, ophthalmology,

and other sub-specialisms to deal with specific late effects of some treatments.

It is also important to understand what transition is NOT; it is not simply a transfer process to an equivalent adult specialist from a paediatric specialist. The consequences of not undertaking transition in a structured way involving a multiprofessional team leaves the patient at significant risk of harm (Mulder et al. 2016).

Recently, PanCare, a multidisciplinary pan-European network of professionals, survivors, and their families that aims to reduce the frequency, severity, and impact of late side-effects of the treatment of children and adolescents with cancer (https://www.pancare.eu) provided a definition of transition of care of childhood cancer survivors: "Transition of childhood cancer survivors is an active, planned, coordinated, comprehensive, multidisciplinary process to enable childhood and adolescent cancer survivors to effectively and harmoniously transfer from child-centred to adult-oriented health care systems. The transition of care process should be flexible, developmentally appropriate and consider the medical, psychosocial, educational and vocational needs of survivors, their families and care-givers, and promote a healthy lifestyle and self-management" (Mulder et al. 2016). The definition highlights the importance of the guided process of transition starting early in follow-up and including the multidisciplinary team involved in the care before and after transition. PanCare is currently working on evidence-based guidelines to help implementing transition in follow-up.

58.3 Barriers to Transition

Adolescents, when asked to identify their individual barriers to transition cited their level of maturity, readiness to assume responsibility for their own future health and lack of knowledge of their health condition and its implications as factors (Granek et al. 2012). Furthermore, due to the very nature of some cancer treatments used in childhood and the toxicity they cause, memory and learning function may be affected. Thus, the ability of some CCS to have the cognitive and developmental maturation to fully understand and engage with transition is lowered. This also impacts on information giving, not only around transition but also around their previous cancer journey and potential future health risks. In the majority of cases, this continues to be facilitated through the parents/carers participation in consultations.

It is suggested widely that transition should begin at age 11+ years but should always take into account the needs of the families and patient. A study in the UK of transition process (Downing et al. 2017) demonstrated that parents tend to monopolise questioning in the consultation until around 16 year of age and that there was some benefit in allowing the young person to set an agenda for their own consultation. Actively discussing early on the need to separate young people from their parents during the consultation to allow them to discuss topics such as sexuality is a very important part of the process. The provision of a personalised record with space to record questions that occur between appointments and the provision of web-based material targeted at their specific conditions may also aid effective communication (Downing et al. 2017). It is also important to try to individualise follow-up arrangements taking into account tertiary education, jobs, and relationships as these develop. If these issues are not taken into account when scheduling appointments at a new hospital there is a 30% loss to follow-up of patients in the first year of transition with patients who cancel or do not attend appointments in the first year of the process being 14 times more likely to be completely lost to follow-up (Downing et al. 2013).

58.4 Conclusions

Childhood cancer survivorship brings with it many challenges for children, young people, the family, and those providing care. This chapter has provided a comprehensive overview of the considerations and principles required by health care professionals and multidisciplinary teams to ensure safe, evidence-based, individualised, and holistic transitional care for this patient cohort.

Case Studies

Sophie

Diagnosis	Rhabdomyosarcoma of the naso-pharynx
Age at diagnosis	6
Treatment	Chemotherapy and adjuvant radiotherapy (pituitary involved in radiation field)
Age at transition	16
Late effects/known endocrinopathies at transition	Growth hormone deficiency Primary hypothyroidism Adrenal insufficiency (delayed presentation age 15)
Medication	Growth hormone (GH) until age 12 when she achieved "final adult height" and no longer wanted to receive "daily injection" Thyroxine Hydrocortisone (Oral daily replacement and emergency IM injection)
Follow-up in TYA LE service	Annual endocrine screening bloods demonstrate a low IGF1, Sophie reluctant to restart GH therapy
Age 17	Presents to clinic with concerns re central adiposity, enlarging breasts and struggling to keep pace with her peers; re-tested for GHD using adult protocol and found to be GH deficient with a peak of just 0.10 μg/L and drifting IGF1
Age 18	Sophie presents with pain and swelling of oropharynx ? Disease recurrence Low threshold for imaging Nothing on imaging, under close review and patient knows to contact service if further problems between appointments
Ongoing issues	This case demonstrates the longitudinal nature of endocrine late effects and the danger of patients being lost to follow-up, especially given this young woman's delayed presentation of adrenal insufficiency Furthermore, it highlights an increasing and ageing population of childhood cancer survivors, emphasising the need for knowledge sharing and education regarding late effects with nurses practising in adult clinical settings

Tom

Diagnosis	Craniopharyngioma
Age at diagnosis	13 ***June 2004***
Treatment	Neuroendoscopic fenestration and drainage of cystic components ***August 2004*** Further fenestration ***July 2005*** due to ↑ in size of cystic components and surgical resection of solid component ***August 2005*** 6 weeks of radiation therapy for recurrence of disease ***February 2009***
Age at transition	16
Known endocrinopathies at transition	***Pan-hypo-pituitarism*** Growth hormone deficiency Primary hypothyroidism Adrenal insufficiency Diabetes insipidus Hypogonadism
Known late effects	Reduced visual fields Memory and learning difficulties Impaired quality of life
Potential late effects—radiation specific	Secondary malignancy Neuropsychological dysfunction Hypothalamic/pituitary dysfunction Reduced bone mineral density **Site Specific** **Skin and hair** Pigmented skin lesions, hypoplasia, fibrosis, atrophy, telangiectasia **Soft tissue** Hypoplasia, fibrosis, atrophy **Any major artery** Atheroma, stenosis

Diagnosis	Craniopharyngioma
Medication	***Full replacement therapy*** Thyroxine Hydrocortisone (Oral daily replacement and emergency IM injection) Testosterone (gel preparation swapped to long-acting depot injection) Desmopressin (DDAVP) Growth hormone
Follow-up in TYA LE service	Annual endocrine screening bloods demonstrate poor compliance with medication. Tom is a shift worker and requires support from his keyworker and consultant in managing his replacement medications around his frequently changing working hours
Age 17	Greater difficulties with short-term memory—referred to psychological services
Ongoing issues	This case demonstrates the common endocrine pathway for a complex patient, but also highlights the importance of oncology knowledge or oncology input into the multi-professional clinic

Adam

Diagnosis	Hodgkin Lymphoma
Age at diagnosis	14 ***May 2006*** Recurrence ***October 2006***
Treatment	Excision biopsy ***Nov06*** **Chemotherapy** ***Initial diagnosis*** Gonadotoxic and cardio toxic agents ***Recurrence*** Further gonadotoxic and respiratory affecting agents **Radiotherapy** At time of recurrence—whole neck 25 Gy in 14 fractions. Whole anterior and posterior neck
Age at transition	16
Known endocrinopathies at transition	Hypothyroidism
Known late effects	Nil currently
Potential late effects—radiation specific	Impaired quality of life Secondary malignancy Cardiac dysfunction Gonadal dysfunction Respiratory dysfunction—exposure to 100% O_2 therapy hazardous **Radiation—Site Specific** **Skin and hair** Pigmented skin lesions, hypoplasia, fibrosis, atrophy, telangiectasia, secondary malignancy **Soft tissue** Hypoplasia, fibrosis, atrophy **Any major artery** Atheroma, stenosis ***Thyroid (Neck)*** Thyroid dysfunction, nodules, and/or malignancy
Medication	Thyroxine
Follow-up in TYA LE service	GP and Primary care team in the transition LE clinic screen thyroid bloods annually Annual follow-up with palpation of thyroid gland assessing for any nodules Questioning re sexual function and desire to undergo sperm assessment at a time when Adam is ready to explore this further Adam aware of seeking medical advice if he feels any new "lumps or bumps"
Ongoing issues	Adam's case demonstrates the complexities of being a childhood cancer survivor with an isolated endocrinopathy, whilst being at risk of other significant treatment-related sequelae

Kate

Diagnosis	Adrenal tumour
Age at diagnosis	4.5 years
Presentation	Sudden onset of obesity Tired Unable to sit from prone Height 75% Weight 90% PH2 B1 No cliteromegaly Vague mass below liver Cushingoid appearance
Investigations and results	Midnight cortisol 647 Undetectable ACTH Raised urinary free cortisols (UFC) USS and CT scan showed right adrenal mass with no calcification 7 × 5 cm
Treatment	***Initial Surgery*** Resection attempt abandoned due to highly vascular tumour with extensive blood loss Cushing's syndrome remained Commenced ***ketoconazole***, ***metyrapone*** with ***radiotherapy*** to tumour Cortisol and UFC remained high so commenced on ***mitotane*** but remained Cushingoid Concurrent episode of meningococcal sepsis requiring intensive care ***Aminoglutethimide*** added to the regimen with biochemical response and metyrapone was withdrawn but Kate felt very unwell on ***ketoconazole, aminoglutethimide,*** and **mitotane** Thus ***aminoglutethimide*** withdrawn and biochemical remission continued with symptomatic improvement and ***ketoconazole*** at a reduced dose along with continued ***mitotane***
14 months later, age 6	Kate developed mitotane-related encephalitis with ataxia, slurred speech, and reduced conscious level so mitotane was withdrawn and her neurological symptoms resolved Whilst just on ketoconazole Kate had asystolic cardiac arrest with long QT interval so ketoconazole withdrawn and Cushing's syndrome reappeared Interventional radiology attempted embolisation of the tumour and reduced blood supply to superior 50% of the mass
22 months from presentation	Second ***surgery*** was successful and "cure" achieved
Puberty	Early puberty at age 9 with menarche at age 12 despite potential for gonadal failure 2^0 to mitotane chemotherapy
Age at transition	Gradual process involving multi-professionals from the age of 16
Issues at transition	Intensive psychological support for Kate and her mother was required to allow them to attend hospital appointments and recognise that future life without an adrenal tumour was possible Dexa scans confirmed only minor reduction in bone mineral density She experienced 1 Addisonian crisis with gastroenteritis and steroid replacement was continued Striae were treated with topical retinoids Weight reduction advice was unsuccessful until she entered a relationship and her BMI fell to 50%
Late effects and/or known endocrinopathies at transition	Adrenal insufficiency

Diagnosis	Adrenal tumour
Potential late effects	Impaired quality of life Secondary malignancy Cardiac dysfunction Gonadal dysfunction **Radiation—Site Specific** **Skin and hair** Pigmented skin lesions, hypoplasia, fibrosis, atrophy, telangiectasia, secondary malignancy **Soft tissue** Hypoplasia, fibrosis, atrophy **Any major artery** Atheroma, stenosis **Abdomen** Abdominal Adverse pregnancy outcome Gastrointestinal dysfunction, diarrhoea Gastrointestinal fibrosis, stricture Hepatic dysfunction Hepatic fibrosis, cirrhosis Splenic dysfunction Renal hypoplasia Glomerular dysfunction Proteinuria Hypertension
Medication	Replacement hydrocortisone
Follow-up in TYA LE service	She began training as a midwife and despite management with an oral contraceptive she became pregnant and delivered a healthy boy at 19 years of age
Age 30	Receives annual USS surveillance of the tumour area but remains well with no sign of second malignancy
Ongoing considerations/issues	This case illustrates the issues that may be faced by a survivor of an extremely dramatic and rare medical problem in early life with multiple life-threatening events but eventual "cure"

References

Alfano CM and Rowland JH. Recovery issues in cancer survivorship: A new challenge for supportive care. Cancer Journal. 2016;12(5):432–43.

Baravelli C, Krishnasamy M, Pezaro C, et al. The views of bowel cancer survivors and health care professionals regarding survivorship care plans and post treatment follow up. J Cancer Surviv. 2009;3:99–108.

Blum RW. Improving transition for adolescents with special health care needs from paediatric to adult-centred health care. Paediatrics. 2002;110:1301–3.

Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP, Slap GB. Transition from child-centered to adult health-care systems for adolescents with chronic conditions: a position paper of the Society for Adolescent Medicine. J Adolesc Health. 1993;14(7):570–6.

Brignarello B, Felicetti F, Castiglione A, Chiabotto P, Corrias A, Fagiolo F, Ciccone G, Boccuzzi G. Endocrine health conditions in adult survivors of childhood cancer: the need for specialised adult-focused follow-up clinics. Eur J Endocrinol. 2013;168:465–72.

Casillas J, Khan KL, Doose M, et al. Transitioning childhood cancer survivors to adult-centred healthcare: insights from parents, adolescent and young adult survivors. Psychooncology. 2010;19:982–90.

Cohen LE. Endocrine late effects of cancer treatment. Endocrinol Metab Clin North Am. 2005;34:769–89.

Downing J, Gleeson HK, Clayton PE, Davis JRE, Wales JK. Transition in endocrinology: the challenge of maintaining continuity. Clin Endocrinol. 2013;78:29–35.

Downing J, Gleeson H, Clayton PE, Davis JRE, Dimitri P, Wales J, Young B, Callery P. Communication with young people in paediatric and adult endocrine consultations: an intervention development and feasibility study. BMC Endocr Disord. 2017;17(1):33. https://doi.org/10.1186/s12902-017-0182.

Earle C. Long term care planning for cancer survivors: a health services research agenda. J Cancer Surviv. 2007;1:64–7.

Evans M. Interacting with teenagers with cancer. In: Selby P, Bailey C, editors. Cancer and the adolescent. London: BMJ Publishing Group; 1996. p. 251–63.

Granek L, Nathan P, Rosenberg-Yunger ZRS, et al. Psychological factors impacting transition from paediatric to adult care by childhood cancer survivors. J Cancer Surviv. 2012;6:260–9.

Hewitt ME. Perspectives on post treatment cancer care; qualitative research with survivors, nurses and physicians. J Clin Oncol. 2007;25(16):2270–3.

Hewitt ME, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition. Washington, DC: The National Academics Press; 2005.

Hollis R, Morgan S. The adolescent with cancer – at the edge at no man's land. Lancet Oncol. 2001;2:43–8

Institute Of Medicine. From cancer patient to cancer survivor: lost in transition/Committee on Cancer Survivorship: Improving Care and Quality of Life, National Cancer Policy Board; Maria Hewitt, Sheldon Greenfield, and Ellen Stovall, editors. [online]. 2006. https://www.nap.edu/download/11468.

Kinahan KE, Sharp LK, Amston P, et al. Adult survivors of childhood cancer and their parents: experiences with survivorship and long term follow-up. J Paediatr Hematol Oncol. 2008;30:651–8.

Klassen AF, Rosenberg-Yunger Z, D'Agostino NM, et al. The development of scales to measure childhood cancer survivors' readiness for transition to long-term follow-up care as adults. Health Expect. 2014;18:1941–55.

McClellan W, Kemp J, Krebill H, et al. Understanding the functional late effects and informational needs of adult survivors of childhood cancer. Oncol Nurs Forum. 2013;40(3):254–62.

Mulder RL, Van Der Pal HJH, Levitt GA, Skinner R, Kremer LCM, Brown MC, Bardi E, Windsor R, Michel G, Frey E. Transition guidelines: an important step in the future care for childhood cancer survivors. A comprehensive definition as groundwork. Eur J Cancer. 2016;54:64–8.

van Laar M, Glaser A, Phillips RS, Feltbower RG, Stark DP. The impact of a managed transition of care upon psychosocial characteristics and patient satisfaction in a cohort of adult survivors of childhood cancer. Psychooncology. 2013;22(9):2039–45.

National Institute for Health and Care Excellence. Implementing transition care locally and nationally using the 'Ready Steady Go' programme [online]. 2017. https://www.nice.org.uk/sharedlearning/implementing-transition-care-locally-and-nationally-using-the-ready-steady-go-programme. Accessed 5 May 2017.

Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572–82.

Patterson BC, Wasilewski-Masker K, Blythe Ryerson A, Mertens A, Meacham L. Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program. J Clin Endocrinol Metab. 2012;97(3):810–8.

Royal College of Nursing. An integrated career and competence framework for nurses working in the field of long-term follow-up and late effects care of children and young people after cancer. [online]. 2011. https://www2.rcn.org.uk/__data/assets/pdf_file/0005/408254/004172.pdf. Accessed 5 May 2017.

Sadak KT, DiNofia A, Reaman G. Patient-perceived facilitators in the transition of care for young adult survivors of childhood cancer. Pediatr Blood Cancer. 2013;60:1365–8.

Slater A. Treatment summary record an survivor care plan. National Cancer Survivorship Initiative. Providing the evidence to achieve improvements for patients. CYP cancer survivorship. 2010;22 [online].

Watson R, Parr JR, Joyce C, May C, Le Couteur AS. Models of transitional care for young people with complex health needs: a scoping review. Child Care Health Dev. 2011;37(6):780–91.

Winter J, Kenborg L, Byrne J, et al. Childhood cancer survival cohorts in Europe. Acta Oncol. 2015;54:655–68.

Endocrinopathy After Childhood Cancer Treatment

59

Cecilia Follin

Contents

59.1 **Pathophysiology of Radiation Damage** 1135

59.2 **Hypopituitarism After Radiotherapy** 1135
59.2.1 Growth Hormone Deficiency 1136
59.2.2 Gonadotropin Secretion 1137
59.2.3 ACTH Deficiency 1137
59.2.4 TSH Deficiency 1138
59.2.5 Abnormalities of Prolactin Secretion 1139

59.3 **Metabolic Disorders** 1139
59.3.1 Obesity 1140

59.4 **Bone Health** 1141
59.4.1 Radiation Damage and Bone Health 1141

59.5 **Fertility** 1142
59.5.1 Male Fertility 1142
59.5.2 Female Fertility 1143

59.6 **Follow-up and Nursing Perspectives** 1144

59.7 **Conclusions** 1145

References 1146

Abstract

Due to remarkable improvements in treatment and supportive care over the past several decades, survival rates for childhood cancer currently exceed 80%. Nevertheless, survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications, and cardiovascular morbidity. Research report that 40–50% of survivors will develop an endocrine disorder over their lifetime. Deficiencies of one or more anterior pituitary hormones have been described following therapeutic CRT for primary brain tumors, nasopharyngeal tumors, and following prophylactic CRT for childhood acute lymphoblastic leukemia (ALL). For at risk-survivors, new endocrinopathies can develop decades following cancer treatment, and

C. Follin (✉)
Department of Oncology, Skane university hospital, Lund, Sweden
e-mail: Cecilia.follin@med.lu.se

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_59

lifelong surveillance is mandatory. Studies have consistently shown a strong correlation between the total radiation dose and the development of pituitary deficits. Further, age at treatment and also time since treatment has strong implications on pituitary hormone deficiencies. Risk factors for low BMD include high dose methotrexate, cumulative doses of glucocorticoids, male gender, and low physical activity. Any combination of these factors may result in osteopenia, not reaching optimal peak bone mass and osteoporosis later in life. Infertility is an important potential consequence of treatment for childhood cancer and identification of survivors for whom strategies to preserve fertility are required. Women treated with radiotherapy affecting ovarian and uterine function are at high risk of acute ovarian failure, premature menopause, complications including spontaneous abortion and preterm labor. Radiotherapy to the gonads, total body irradiation, and high dose chemotherapy may result in a number of effects on the male reproductive system in survivors. Detailed information about the past cancer treatment including surgery, the type and cumulative doses of chemotherapy, and radiotherapy volumes and doses are needed to estimate health risks associated with childhood cancer. A risk-based care approach, for all childhood cancer survivors, should include a systematic plan for lifelong screening, surveillance, and prevention that incorporates risk estimates.

Keywords

Childhood cancer survivors · Cranial radiotherapy · Late complications · Hypothalamic-pituitary insufficiency · Long-term morbidity Bone mineral density · Infertility

Abbreviations

ACTH	Adrenocorticotropic hormone
ALL	Acute lymphoblastic leukemia
BIA	Bioelectrical impedance measurement
BMD	Bone mineral density
CCS	Childhood cancer survivors
CRT	Cranial radiotherapy
DEXA	Dual-energy X-ray absorptiometry
FSH	Follicle stimulating hormone
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone releasing hormone
Gy	Grey
H-P	Hypothalamic-pituitary
IGF-1	Insulin like growth factor
ITT	Insulin tolerance test
LH	Luteinizing hormone
PRL	Prolactin
RT	Radiotherapy
TSH	Thyrotropin stimulating hormone

Key Terms

- **Anthracyclines:** Chemotherapy known to affect the cardiac function.
- **BMD:** Bone mineral density.
- **Cranial radiotherapy**: Whole brain radiotherapy.
- **GHD:** growth hormone deficiency.
- **Hypothalamus:** Important for energy balance and food intake.
- **Metabolic complications:** Obesity, lipid abnormalities, insulin resistance.
- **Survivorship care plan**: Comprehensive treatment summary with information about potential cancer-related health risks.

Key Points

- Childhood cancer survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications, and cardiovascular morbidity.
- For at risk-survivors, new endocrinopathies can develop decades following cancer treatment, and lifelong surveillance is mandatory.
- Hypothalamus is more radiosensitive than the pituitary. With lower doses of CRT (<30 Gy), the primary site of radiation damage is the hypothalamus and this usually causes isolated GH deficiency (GHD).
- Survivors exposed to CRT are at particularly high metabolic risk and increased risk of cardiovascular diseases later in

life. Risk factors for these complications include obesity, physical inactivity, lipid abnormalities, and insulin resistance.

- Survivors of ALL and of tumors in the pituitary-hypothalamic area are at greatest risk for obesity. CRT can cause CNS damage, in particular hypothalamic. This may promote obesity via a number of possible mechanisms: growth hormone deficiency, leptin resistance or hypothalamic regulation of food intake, and energy expenditure.
- The survivors should be provided with a comprehensive treatment summary, a systematic survivorship care plan for lifelong screening, surveillance, and prevention.

59.1 Pathophysiology of Radiation Damage

The pathophysiology of radiation damage remains poorly understood. Direct injury to the hypothalamic-pituitary (H-P) cells, rather than reduced hypothalamic blood flow, is the major cause of progressive H-P dysfunction after fractionated cranial radiotherapy. Direct neuronal damage has been shown in studies of rat pituitary cell survival and growth hormone (GH) secretion after in vitro irradiation of pituitary cell cultures (Hochberg et al. 1983). They recorded a marked sensitivity of the somatropes to single doses of radiation. Further, differential radiosensitivity of H-P function, including dose and time dependency of anterior pituitary hormone deficiencies have been demonstrated in rats. GH and PRL were most sensitive and decreased by more than 90% after irradiation and ACTH was the most robust hormone (Robinson et al. 2001). In humans, the neurotoxicity of any radiation therapy is a function of the total radiation dose, the fraction size, and the time between the duration of the radiation schedule. Using no more than 2 Gy per fraction and no more than 5 fractions per week will minimize the damage to a healthy hypothalamic-pituitary axis. Higher doses of radiotherapy (>60 Gy) causes damage to both hypothalamus and pituitary resulting in early multiple anterior pituitary hormone deficiencies (Lam et al. 1991). Direct stimulation with exogenous GHRH, LHRH, or TRH will demonstrate impaired GH, LH/FSH, and TSH secretion from pituitary. On the other hand, verified hypothalamic dysfunction is shown by delayed responses to LHRH and TRH tests (Lam et al. 1991) and also by different GH stimulation tests. The convincing test of diagnosing GH deficiency in the early years after CRT in ALL survivors is the insulin tolerance test as it reveals dysfunction of the entire hypothalamus-pituitary axis compared to GHRH-arginine test stimulating the pituitary direct (Björk et al. 2005). The presence of hyperprolactinemia due to a reduction in hypothalamic release of the inhibitory neurotransmitter, dopamine, has been described in those intensively irradiated for brain tumors, but less frequently in those treated for leukemia with less intensive radiation schedules (Lam et al. 1991).

Given the differential radiosensitivity of H-P function with GH axis as the most sensitive, variable degrees of GHD are usually seen in isolation after lower radiation doses used in leukemia survivors (18–24 Gy). With higher radiotherapy doses used in nasopharyngeal carcinoma and skull base tumors (>60 Gy) anterior pituitary hormones are affected with an early and multiple pituitary hormone deficits. (Lam et al. 1991)

Age influences the impact of radiation on H-P function such as younger age increases vulnerability to radiation damage. Younger children treated with prophylactic cranial radiotherapy for childhood ALL are more sensitive to radiation-induced GHD than older children (Link et al. 2004). In patients treated with high radiation dose (>40 Gy) for tumors of head and neck, it was shown that children younger than 15 years of age had higher risk of GHD a short time after treatment compared to older patients. However, the patients older than 15 years showed increased risk of ACTH and LH deficiency (Samaan et al. 1982).

59.2 Hypopituitarism After Radiotherapy

The most commonly diagnosed chronic conditions after cranial radiotherapy (CRT) involves the endocrine system and in particular the hypothalamic-pituitary axis (Brignardello et al.

2013; Chemaitilly et al. 2015). Deficiencies of one or more anterior pituitary hormones have been described following therapeutic CRT for primary brain tumors, nasopharyngeal tumors, and following prophylactic CRT for childhood acute lymphoblastic leukemia (ALL). Studies have consistently shown a strong positive correlation between the total radiation dose and the development of pituitary deficits (Sklar and Constine 1995). Further, age at treatment and also time since treatment has strong implications on pituitary hormone deficiencies (Link et al. 2004). It has become apparent that the pituitary hormone deficiencies can develop after many years after radiotherapy and studies have suggested that the damage might be at the level of hypothalamus (Littley et al. 1988). There is a difference in the incidence of anterior pituitary hormone deficiencies, with secretion of growth hormone (GH) being the most frequently affected followed by gonadotropin, adrenocorticotropic hormone (ACTH), and thyroid stimulating hormone (TSH). Prolactin (PRL) insufficiency is probably an early occurring insufficiency (Fig. 59.1). The most important predictive factors to deficient hormone axes are dose of CRT, age at CRT, and time since CRT. Hypopituitarism is an important diagnosis to make correctly and endocrine nurses and endocrinologists should be involved at an early stage of patient management. It has been shown that untreated pituitary deficiency is associated with poor health.

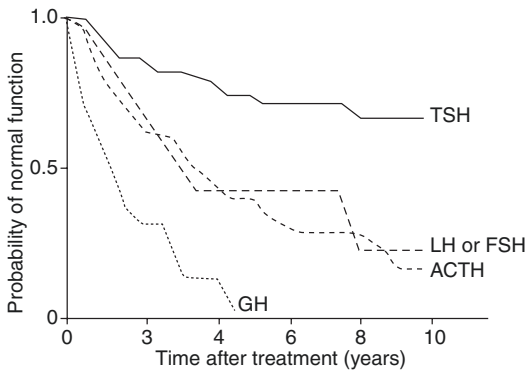


Fig. 59.1 Probability of a normal hypothalamic-pituitary axis after cranial radiotherapy (Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumors in adults. Q J Med 1988;262:145–160)

59.2.1 Growth Hormone Deficiency

GH deficiency (GHD) is usually the first and often the only established endocrine sequel of CRT (Littley et al. 1988). CRT in children frequently causes abnormal hypothalamic-pituitary function later in life (Link et al. 2004) and growth deficits have been reported consistently after doses of >24 Gy cranial radiotherapy (Link et al. 2004; Sklar and Constine 1995). However, GHD has also been shown during childhood in ALL patients after low doses of <20 Gy (Brennan et al. 1998), but these data are less consistent.

Based on the background to hypothalamic-pituitary disease, different GH tests must be carefully considered (Björk et al. 2005). There are clear cut-off levels for GH when a GHD is diagnosed, i.e., for the insulin tolerance test (ITT) the level is GH < 3 μg/L (or 9 mU/L) and for the growth hormone releasing hormone (GHRH)-arginine test which is BMI dependent, we used the same cut-off levels (Björk et al. 2005). Thus, Björk et al. (2005) recorded that the ITT clearly reflected the presence of early radiation-induced GHD, but this was not always the case with the GHRH-arginine test, which more confirmed the diagnosis later in life. The GHRH-arginine test is more a stimulation test directly on the pituitary, reflecting the pituitary GH secretion. However, when the GH response to GHRH-arginine was low we considered the patient to be clearly GHD (Björk et al. 2005). Thus, it would appear that primarily the hypothalamus and then later direct pituitary damage from CRT was the cause of GH deficiency among the former ALL patients.

Brennan et al. (1998) investigated GH secretion after CRT in 32 adults, 6.8–28.6 (median 17.8 years) years since CRT. Nine of the patients were severely GHD (peak GH response <9 mU/L to both provocative agents arginine and ITT) and a further 12 patients were GH insufficient (peak GH response <20 mU/L to both tests with at least one peak GH response >9 mU/L). They had all received between 18 and 24 Gy. A group of 44 childhood ALL with a median of 25 years (19–32) of whom all were treated with CRT median 24 Gy (range 18–24 Gy) were investigated. They were treated with CRT at a median age of 5 years

(range 1–18) and 17 years had passed since ALL treatment and CRT (Link et al. 2004). According to the ITT and/or the GHRH-arginine test 91% were considered GHD. All patients with a peak GH 3.9 μg or more on the GHRH-arginine test performed an ITT.

Among 310 childhood cancer survivors, the most frequent hormone deficiency was gonadal, primary hypothyroidism, and GHD (Brignardello et al. 2013). GHD was evaluated using standard GH tests. GHD was found among 16.13%, where the most frequent background diagnosis was brain tumors, followed by hematological malignancies.

In a recent paper from Chemaitilly et al. (2015) on a mixed population of adults with childhood cancer, with 72% leukemia diagnosis, about 46.5% were diagnosed with GHD. However, GHD was defined only as a measurement of morning serum IGF-I < −2.0 *z*-score. This is probably a strong underestimation as serum IGF-I is not considered sufficient to set the diagnosis of GHD (Growth hormone research society).

59.2.2 Gonadotropin Secretion

Gonadotropin deficiency in childhood cancer survivors is most frequent after a radiation dose to the hypothalamus-pituitary axis of >40 Gy (Pasqualini et al. 1987) and can be presented with a spectrum from subclinical to severe impairment. It is the second most common anterior pituitary hormone deficiency after CRT. Clinically significant gonadotropin deficiency after CRT is often apparent after long-term follow-up with an incidence of 20–50% (Constine et al. 1993). However, a remarkable increase in incidence is reported following a more intensive radiation schedules with an onset as early as 12 months after radiotherapy (Samaan et al. 1982). Gonadotropin deficiency in CCS can be subtle and detected only by GnRH testing, as well as severe with diminished circulating sex hormone levels. In a mixed population of CCS, LH and FSH deficiency was recognized in 11% of the total cohort of survivors 27 years after cancer diagnosis. After CRT doses more than 40 Gy, the prevalence of LH and FSH deficiency was 23% and 8% after CRT doses of less than 40 Gy (Chemaitilly et al. 2015). Male sex, CRT dose >22 Gy and BMI > 30 kg/m were associated with higher odds of LH and FSH deficiency (Chemaitilly et al. 2015). In another study, only including men, of 199 childhood cancer survivors showed that 13 survivors had central hypogonadism 14 years after cancer diagnosis (Brignardello et al. 2013). The risk of hypogonadism was higher in survivors treated with CRT. Radiation doses of <50 Gy may cause premature activation of the H-P gonadal axis resulting in precocious puberty (Brauner and Rappaport 1985). ALL survivors treated with a moderate dose of CRT of 18–24 Gy have an increased risk of precocious puberty, but almost exclusively in girls (Leiper et al. 1987). GHD is almost always present in irradiated children which makes the outcome of precocious puberty worse as the pubertal growth spurt will be further attenuated. In addition, the window of opportunity to treat the child with GH is reduced in the GHD child who is already pubertal. The mechanism of early puberty after radiotherapy is related to damage at the level of hypothalamus with increased frequency and amplitude of GnRH pulsatile secretion by the hypothalamus. Other results have also been reported; a large study of 949 female ALL survivors found craniospinal radiotherapy to be associated with an increased risk of late-onset menarche (Chow et al. 2009). Thus, both early and delayed puberty can be seen.

59.2.3 ACTH Deficiency

The hypothalamic-pituitary-adrenal (HPA) axis appears to be relatively resistant to radiotherapy in patients treated for childhood cancer. Clinically apparent ACTH deficiency is uncommon after cranial radiotherapy. After a total radiation dose of <50 Gy to the H-P axis around 3% of childhood brain tumor survivors present with ACTH deficiency short time after (3–10 years) after diagnosis (Constine et al. 1993). After radiation doses of >50 Gy, the frequency of ACTH deficiency is significantly increased in

survivors with head and neck tumors with rates of 27–35% up to 15 years after treatment (Lam et al. 1991). In a study including 310 childhood cancer survivors, the authors found 4 survivors with central hypoadrenalism. Among the 310 survivors, 74 were treated with cranial radiotherapy in childhood (Brignardello et al. 2013). Chemaitilly et al. (2015) investigated a mixed population of CCS, 27 years after CRT, and found that 4% of the survivors was ACTH deficient. In a group of ALL survivors, treated with a moderate dose of CRT (18–24 Gy), Follin et al. (2014) report ACTH insufficiency. Thirty-eight percent ALL survivors had a subnormal cortisol response to an insulin tolerance test (ITT) (257–478 nmol/L) while there was no significant difference in basal cortisol levels between ALL survivors and healthy matched control subjects. ALL women, but not ALL men had significantly lower ACTH levels compared to gender matched controls. However, only a few survivors needed regular hydrocortisone replacement. GHD might mask the presence of a hidden central adrenal insufficiency. If GH therapy is introduced, there will be an increase in the conversion of hormonally active cortisol to inactive cortisone and a decrease in cortisol levels can be apparent. An increased awareness of the risk for adrenal insufficiency is of importance and in particular when the survivors start GH therapy.

59.2.4 TSH Deficiency

The H-P-thyroid axis appears to be the most robust hormone to radiation damage. The incidence of TSH deficiency has been reported to be as low as 3–5% in childhood brain tumors (Livesey et al. 1990), but also more frequent recorded among CCS treated with an intensive radiotherapy schedule with doses >50 Gy (Pai et al. 2001). In ALL survivors treated <30 Gy, there are conflicting results in early studies, with no risk or an increased risk (Lando et al. 2001) of central hypothyroidism after CRT. After a follow-up of an average of 6 years after ALL treatment, one out of the 33 children was found to have a papillary carcinoma of the thyroid. Thyroid function was normal in all patients, with the exception of one case which showed high basal levels TSH levels, but normal response to TRH. This hormonal alteration was later normalized. In a study with 8 years of follow-up of survivors of childhood ALL treated with prophylactic CRT no adverse effect on hypothalamic-pituitary-thyroid function was recorded (Lando et al. 2001).

Hypothalamic-pituitary-thyroid dysregulation after CRT, identified by a TRH-stimulation test or TSH surge, has been recognized in as many as 15% of former ALL patients 10 years after CRT (Chow et al. 2009). In a study from Follin et al. (2013) with a median of 20 years of follow-up, no significant difference in basal TSH and only slight disparity of free T_4 levels (higher), which indicates no known clinical significance, was shown. However, a slightly lower TSH response to a TRH test, shown in 13 ALL patients, might be an early indication of TSH dysfunction. This is in contrast to Darzy and Shalet (2005) who 11.5 years after cancer treatment (with mixed diagnosis), found increased TRH-stimulated TSH levels in cranially irradiated patients with GHD as compared to matched controls. Disparity in results may be due to differences in radiation dose, type of cancer, age at cancer diagnosis, and particularly in follow-up time. Further, GHD plays a role in the regulation of thyroid hormone metabolism, with both a central effect, with an increase in somatostatin inhibition of TSH secretion, and a peripheral effect with an increased conversion of free T_4 to free T3.

Among 310 CCS, the most frequent hormone deficiency was gonadal, primary hypothyroidism, and GHD, after a median time of 16 years since diagnosis (Brignardello et al. 2013). They documented at least one endocrine disease among 50% of CCS. Primary hypothyroidism was diagnosed among 18%, whereas seven patients had central hypothyroidism. A study from the USA investigated a mixed population of adults with childhood cancer with a mean of 27 years after treatment and 7.5% were considered TSH deficient (Chemaitilly et al. 2015).

59.2.5 Abnormalities of Prolactin Secretion

Hyperprolactinemia after treatment with CRT for childhood cancer has been reported in studies investigating children treated with a dose >40 Gy after a short follow-up (Constine et al. 1993; Livesey et al. 1990). The hyperprolactinemia is due to the reduction in the neurotransmitter, dopamine, which has an inhibitory effect on prolactin secretion. Hyperprolactinemia after radiotherapy has no significant biological impact on the vast majority of the patients. In rare cases, high levels of prolactin can cause impaired gonadotropin secretion and pubertal delay in children (Littley et al. 1988) On the other hand, hypoprolactinemia has also been recorded in ALL survivors after CRT, but after long-term follow-up (Follin et al. 2013). It has been suggested that severe prolactin (PRL) deficiency occurs late after all other anterior pituitary insufficiencies in the evolution of hypopituitarism and that very low levels of PRL is related to the severity of hypopituitarism (Mukherjee et al. 2006). Littley et al. (1988) showed that after CRT to adults basal PRL showed an early rise, followed by a gradual decline after a few years. CRT seems to cause a primarily diminished inhibition of PRL secretion resulting in increased basal PRL levels, followed by a slowly developing lactotroph dysfunction. In contrast, in rats exposed to non-fractionated CRT, GH and PRL were shown to be most sensitive of all pituitary hormones, with a dramatic decrease with time and dose after irradiation (Robinson et al. 2001). It has been shown that PRL deficiency, thus very low PRL levels, was independently associated with reduced levels of serum IGF-I in severely GHD adults and that PRL deficiency can act as a surrogate marker for the severity of GHD (Mukherjee et al. 2006). Follin et al. (2013) recorded significantly lower basal PRL levels and PRL area under the curve (AUC) after GHRH-arginine stimulation test in 44 ALL survivors compared to matched controls of both gender. Seven ALL women reported pregnancies during follow-up and six out of seven women reported failure to lactate. Thus, it was reported that ALL patients treated with CRT are not only GH deficient but also PRL insufficient 20 years (8–27) after diagnosis (Follin et al. 2013).

59.3 Metabolic Disorders

Long-term survivors of childhood cancer are at increased risk of cardiovascular disease. In a study from the UK, the authors analyzed a cohort of 4082 survivors and found a fivefold excess of deaths from cardiovascular causes (Hawkins et al. 1994). Survivors of childhood cancer exposed to CRT are at particularly high metabolic risk and increased risk of cardiovascular diseases later in life. Risk factors for these complications include obesity, physical inactivity, lipid abnormalities, and insulin resistance. Further, survivors of childhood ALL and brain tumors with hypothalamic damage are at increased risk for obesity (Lustig et al. 2003). Childhood cancer survivors, treated with CRT have an increased risk of GH deficiency and they can also experience an anthracycline-induced left ventricular dysfunction which are risk factors for developing metabolic complications. Further, the metabolic hormones insulin and leptin, with receptors in the hypothalamus have shown resistance (Link et al. 2004) among the GH-deficient ALL survivors (Link et al. 2004; Brennan et al. 1998), suggesting a radiation-induced hypothalamic dysfunction. Janiszewski et al. (2007) report that ALL survivors treated with CRT have increased abdominal and liver fat, insulin resistance, and dyslipidemia, and these parameters are associated with lower IGF-1 levels. A Swedish study of ALL survivors treated with CRT found a strong correlation between stimulated peak of growth hormone secretion during insulin tolerance test and several cardiovascular risk factors (Link et al. 2004). Survivors of childhood brain tumors have been reported to have an increased blood pressure, waist-hip ratio, LDL cholesterol, and lower HDL cholesterol, and some of these cardiovascular risk factors were most abnormal in those with GHD (Heikens et al. 2000). GH therapy has been beneficial in reducing the prevalence of metabolic syndrome in the ALL survivors (Follin et al. 2010) (Fig. 59.2). The

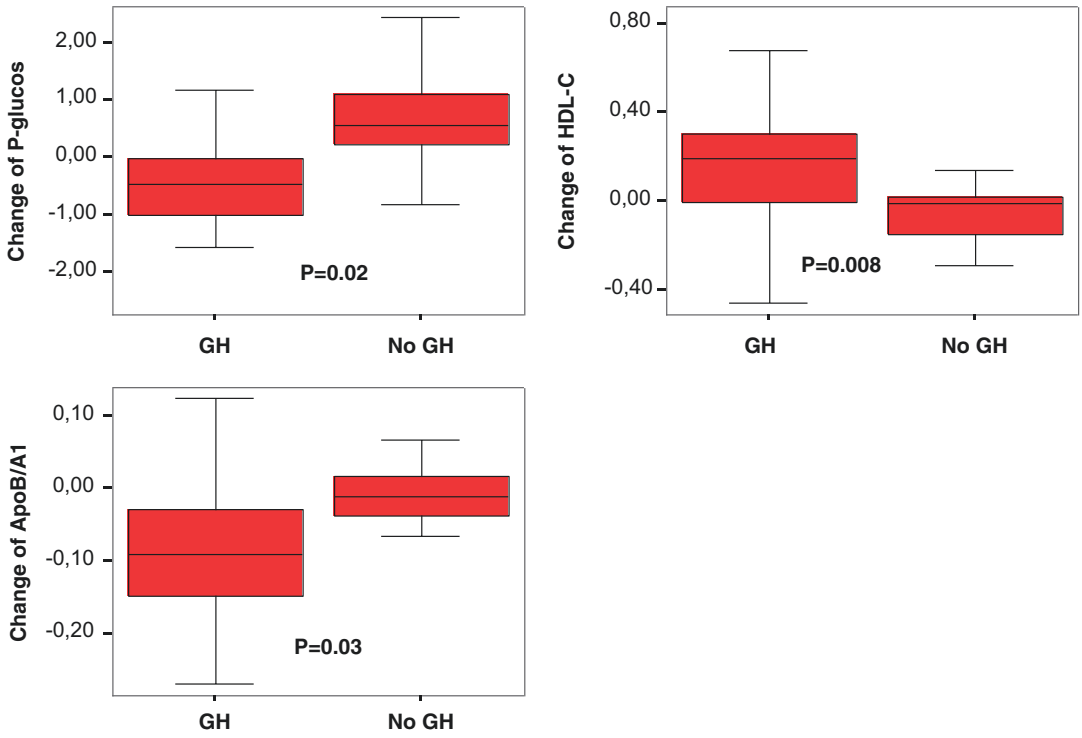


Fig. 59.2 Differences in change of cardiovascular risk factors between GH-treated and non-GH-treated ALL survivors (Follin c J Clin Endocrinol Metab. 2010 Aug;95(8):3726-35. doi: 10.1210/jc.2010-0117. Epub 2010 May 19)

survivors need to be offered multidisciplinary interventions with lifestyle changes and also lipid-lowering medication when necessary.

Survivors of childhood cancer treated with bone marrow transplantation are at particularly high risk of metabolic abnormalities such as greater prevalence of diabetes and increased risk of hypertension (Baker et al. 2007). There was a greater risk for diabetes in those who had undergone total body irradiation in their treatment regimen suggesting an increased insulin resistance.

59.3.1 Obesity

Childhood cancer survivors are at increased risk if obesity and the evidence for the increased prevalence is complex given the variations of the different cancer diseases, treatments and outcomes, and small sample sizes. In clinical routine practice, obesity is most defined using BMI (body mass index). However, in research more direct measures of body fat may be more preferable. Frequently used methods of body composition are dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance measurements (BIA). These methods subdivide body composition into two compartments: fat mass and fat-free mass. Survivors of ALL and of tumors in the pituitary-hypothalamic area are at greatest risk for obesity (more details in Chap. 13). The obesity is a major cause for concern as the survivors also have an increased risk of cardiovascular, metabolic, pituitary, and psychosocial sequelae. Cranial radiotherapy can cause CNS damage (in particular hypothalamic) (Lustig et al. 2003). This may promote obesity via a number of possible mechanisms: growth hormone deficiency, leptin resistance or hypothalamic regulation of food intake, and energy expenditure. Growth hormone deficiency has been shown to be associated with obesity (Carroll et al. 1998) and CCS treated with CRT are known to be GHD. In addition, a

study of 1765 adult survivors of ALL has shown that those who received CRT had an increased risk of obesity, and this risk was greatest for girls treated under the age of 4 years (Oeffinger et al. 2003). This may be related to the effect of CRT on GH secretion and also producing earlier onset of puberty and reduced final height. CNS-directed therapy contributes to the obesity in CCS, but it is not the only determinant of obesity. ALL survivors who did not receive CRT and only treated with chemotherapy are at increased risk of weight gain (Reilly et al. 2000). However, ALL survivors have also received attention reporting evidence for disturbances of energy balance including obesity (Oeffinger et al. 2003). Reduced physical activity has been suggested as one major cause of obesity in ALL survivors. The reasons for reduced physical activity could be motor impairments, musculoskeletal pathology, impairments of exercise capacity. Further, total energy expenditure studies have reported abnormalities in energy balance in ALL survivors (Warner et al. 1998). Identify survivors at particularly high risk of obesity is important as they can be prioritized for interventions such as prevention with healthy lifestyle and physical activity, including treatment of obesity or metabolic risk reduction. Thus, young age at diagnosis and gender (female) are associated with increased risk of obesity. In a large cohort of children with brain tumors, the authors identified risk factors for the development of obesity. These risk factors included, younger age at diagnosis, radiation dose range of 51–72 Gy to the hypothalamus, the presence of endocrinopathy, and location of the tumor at hypothalamus, in particular craniopharyngioma (Lustig et al. 2003). The main consequences of obesity after childhood cancer are presence of cardiovascular risk factors, increased risk of diabetes, increased risk of fatty liver, low health-related quality of life, and lower self-esteem.

59.4 Bone Health

Patients treated for childhood cancer have been exposed to multiple influences that may adversely affect bone health. These include the disease itself, radiotherapy, chemotherapy, poor nutrition, and low physical activity. Some treatments have direct deleterious effects on bone, and some have more indirect effects mediated through endocrine abnormalities. The earlier treatment protocols that included CRT in ALL survivors may result in GHD and low bone mineral density (BMD) in lumbar spine and femoral neck (Follin et al. 2011; Nussey et al. 1991). The risk for fractures, which is the most important outcome in clinical practice, after long-term follow-up is unknown. Another relevant outcome measure is BMD, but this is only a surrogate marker for fracture risk. BMD may be difficult to analyze in CCS who have impaired growth and reduced final height, which may have an impact on bone size. The reported risk factors for low BMD include high dose methotrexate, cumulative doses of glucocorticoids, male gender, and low physical activity. Any combination of these factors may result in osteopenia, not reaching optimal peak bone mass and osteoporosis later in life.

59.4.1 Radiation Damage and Bone Health

Spinal radiotherapy can cause direct damage to vertebrae, and sometimes it takes months or years to become a problem for the survivors. Spinal RT is excluded in most modern treatment protocols, but still craniospinal irradiation is used for certain tumors such as medulloblastomas.

CRT may cause decreased longitudinal bone growth and bone mass, suggesting an effect of pituitary insufficiency and in particular GHD. GH plays a key role in the longitudinal bone growth and the attainment of peak bone mass. A number of cross-sectional studies on BMD after childhood ALL confirm that CRT is a risk factor for low BMD, especially in the lumbar spine (Follin et al. 2011; Gilsanz et al. 1990). A few studies have linked GH status after CRT to BMD and report that survivors with untreated GHD had low BMD in the lumbar spine and femoral neck compared to survivors treated with GH (Follin et al.

2011; Nussey et al. 1991). Further, it has been shown that both GH and IGF-I stimulate osteoblasts resulting in bone formation, but also bone resorption (Ohlsson et al. 1998). Survivors of childhood brain tumors who received CRT and were followed for median 15 years showed that whole body and lumbar spine BMD were lower compared to survivors without CRT (Odame et al. 2006). The negative effect of GHD on BMD can be prevented by treating the survivors with GH, including continuing the treatment into adulthood when peak bone mass is attained (Follin et al. 2011; Nussey et al. 1991). Another effect of insufficient pituitary hormone secretion may be TSH and LH/FSH deficiency which may play a role in some survivors. Thyroid hormone is a major regulator of normal skeletal development and growth before puberty. Untreated primary hypothyroidism, which may occur after neck irradiation as in Hodgkin's lymphoma, may cause bone loss (Sklar et al. 2001). Further, sex steroids are required to achieve a normal growth during puberty and estrogen is necessary to maintain bone health in both genders. In men, testosterone is converted to estrogen which aids normal bone mineral accretion and survivors who are deficient in estrogen or testosterone may develop osteoporosis. Testicular radiotherapy, as in the treatment protocol for ALL with testicular relapse, is related to a high risk of Leydig cell dysfunction with a need of androgen substitution among these survivors. In women, abdominal, pelvic, or spinal irradiation may cause primary ovarian failure and estrogen deficiency.

59.5 Fertility

Infertility in childhood cancer survivors is a potential complication dependent on the treatment during childhood, but also the underlying disease. Gonadal injury is a well-established consequence of cytotoxic chemotherapy and radiotherapy. However, predicting the likelihood of gonadal dysfunction in the individual survivor may be a difficult task. In general, females seem less sensitive to the adverse effects of chemotherapy compared to males. Measuring the gonadotropins and testosterone in pre-pubertal male survivors will not be informative. On the other hand, assessment of growth and puberty is of importance and the presence of secondary sexual characteristics will give information on testosterone production. In females, the normal ovarian function based on the resumption of regular menses after therapy and normal hormone levels does not exclude damage to the ovaries. However, the absence of regular menses does not mean that the survivors will be infertile (Wallace et al. 2005). Women treated with radiotherapy affecting ovarian and uterine function are at high risk of acute ovarian failure, premature menopause, complications including spontaneous abortion and preterm labor. These data are important for family planning and obstetrical management.

59.5.1 Male Fertility

Radiotherapy to the gonads, total body irradiation and high dose chemotherapy, may result in a number of effects on the male reproductive system in long-term survivors. These include direct damage to the gonads and also indirect damage to hypothalamus-pituitary axis. Damage on germ, Sertoli or Leydig cells may result in reduced gonadal function. Impaired germ cells will interfere with spermatogenesis and damage on the supporting Sertoli cells will indirectly affect germ cells and hence spermatogenesis. Recovery of spermatogenesis and sperm production may occur several years after treatment. Effects on Leydig cells may result in failure to produce testosterone, important for initiation of spermatogenesis and the development of secondary sexual characteristics (Meistrich et al. 1992). Male survivors who become azoospermic by cancer treatment have increased FSH and lower inhibin B, including a decrease in testis weight or sperm count, than those who are non-azoospermic. However, survivors treated pre-pubertally may develop secondary sexual characteristics normally despite the fact that

there may be effects on the spermatogenesis. The effect of radiotherapy depends on the dose, target organ, and number of fractions. Radiotherapy of <20 Gy may damage the seminiferous epithelium, affecting spermatogonia leading to oligozoospermia (Wallace and Thomson 2003). Higher doses of >20 Gy may affect the Leydig cells which results in reduced serum testosterone levels and high serum gonadotropins. This is supported by research in survivors of Hodgkin's lymphoma reporting reduced testicular volume including increased FSH levels in these survivors, suggesting damage to the seminiferous epithelium (Pont and Albrecht 1997). Direct radiotherapy to the testis may cause damage to germ cells resulting in permanent azoospermia (Wallace and Thomson 2003). After treatment with fractionated radiotherapy gonadal recovery has been reported in less than 20% of the survivors (Socie et al. 2003).

Chemotherapy has a negative effect on the fertility and the most gonadotoxic agents are procarbazine and alkylating agents such as cyclophosphamide. The damage depends on the dose and the frequency of the administration. Survivors of Hodgkin's lymphoma and Ewing's sarcoma receiving cumulative doses of cisplatin >400 mg/m^2 have an increased risk of impaired spermatogenic function (Pont and Albrecht 1997). ALL survivors and brain tumor survivors treated with surgery only are at low risk of infertility, which means <20%. Brain tumor survivors treated with CRT > 24 Gy and neuroblastoma survivors are at medium risk and of high risk treatment (>80%), which includes total body irradiation or treatment with alkylating agents, are Hodgkin's lymphoma and Ewing's sarcoma.

59.5.2 Female Fertility

A successful pregnancy requires a fully functional hypothalamic-pituitary-ovarian axis, including a uterus capable of growing with the developing fetus to the birth. Childhood cancer treatment may result in fertility defects such as hypothalamic-pituitary insufficiency leading to arrested puberty and primary amenorrhea. If damage occurs after puberty, the survivor will have an increased risk of secondary amenorrhea. Damage direct to the ovaries will result in reduction of the primordial follicles, leading to infertility or premature menopause. The biological ovarian age in childhood cancer survivors is approximately 10 years ahead of their chronological age. Any occurrence of ovarian failure before age 40 is classified as premature menopause and a substantial proportion of the survivors experience premature menopause (Larsen et al. 2003). The negative effects on cancer treatment on female fertility may be mediated through the hypothalamic-pituitary axis, the ovary or the uterus. Radiotherapy is well-known to act on all three of these systems, but direct effects of chemotherapy on the hypothalamic-pituitary axis and the uterus have not been reported. Brain tumor and ALL survivors treated with cranial radiotherapy >24 Gy have an increased risk of delayed puberty or secondary amenorrhea in girls. However, lower doses are associated with early puberty or precocious puberty (Critchley et al. 2002). Livesey et al. (1990) showed that girls who had been treated with craniospinal irradiation developed high gonadotropins suggesting an ovarian dysfunction. Radiotherapy may affect the volume, vascularization, and endometrial thickness of the uterine characteristics, and the degree depends of the radiation dose and the site of the irradiation. The pre-pubertal uterus is more sensitive to irradiation as the development of the uterus is not completed before the onset of puberty. Pelvic irradiation of 20–30 Gy results in impaired uterine development including reduced volume and vascularization (Critchley et al. 2002). Lower doses of radiotherapy, e.g., total body irradiation, also cause reduced uterine volume, impaired blood flow, and absent endometrium and are associated with adverse pregnancy outcome in female survivors. Evidence shows that children of CCS are not at higher risk of congenital abnormalities compared to children of parents without a history of childhood cancer (Edgar and Wallace 2007).

Nevertheless, it has been reported that childhood cancer survivors worry about their fertility and the health of their offspring and that female survivors worry more than the male survivors (Zebrack et al. 2004). Thus, proper scientific information to the survivors is mandatory and can possibly reduce fertility-related anxieties. In addition, some survivors have concerns about their ability to be a good parent, but the survivors also report that their cancer experience as making them better parents.

59.6 Follow-up and Nursing Perspectives

Because of the steady increase in long-term survival rates after childhood cancer, health care professionals caring for CCS should be aware of the unique health risks resulting from the cancer experience. The survivors need to receive appropriate health surveillance and interventions to reduce morbidity and mortality. Further, offering understanding and support with a holistic approach, rather than merely focusing on living with complications, may be a way in which to strengthen the survivors' healthiness. Work, together with the survivors, towards independence for them. Key elements of independence are individual autonomy, be actively involved in decision-making and access to physical and social environment. Offer support in the survivors decision-making by asking "what do you want to do" instead of telling the survivors what they should do. Many CCS experience their daily lives as a struggle and as a complicated issue to cope with. It has been reported that an understanding of the survivors' situation, as well as support for managing daily life is fundamental for the survivors. They also report a lack of understanding and support from the community, and this was connected with a fear for the future. The follow-up of late complications has been shown to be crucial for increasing the survivors' understanding of complications after surviving cancer and they experienced increased self-confidence (Pålsson et al. 2017).

CRT and total body irradiation may cause pituitary insufficiency, primary hypothyroidism, or gonadal insufficiency. Although GHD is the most common deficiency after CRT, it is not always easy to diagnose. A careful follow-up with a combination of growth monitoring through childhood and puberty, regular monitoring of IGF-1 levels and proper stimulation tests for GH are required in these survivors. Long-term monitoring of pituitary hormones including attention to symptoms of pituitary insufficiency is also required in survivors who have been treated with CRT. The health care professionals should be aware of that impaired hormone secretion may occur many years after treatment and hormone substitution can be necessary. In survivors of Hodgkin's lymphoma who have received neck irradiation long-term follow-up of free T4 and TSH is mandatory as they have an increased risk of hypothyroidism.

Survivors of childhood cancer exposed to CRT are at high metabolic risk and increased risk of cardiovascular diseases later in life. Risk factors for these complications include obesity, physical inactivity, lipid abnormalities, and insulin resistance. Reduced physical activity is one major cause of obesity in survivors. It is important to identify survivors at high risk of obesity as they should be prioritized for multidisciplinary interventions such as prevention with healthy lifestyle and physical activity, including treatment of obesity or metabolic risk reduction. The risk for osteopenia or osteoporosis also makes the recommendations of physical activity to the survivors of utmost importance. Weight-bearing activities, such as walking, running, tennis playing, or dancing, causes new bone tissue form and this makes the bones stronger. Monitoring the female survivors at regular intervals after the completion of treatment is of importance. Fertility-related concerns are a major source of distress in many young female survivors and proper information about the facts that the risk of congenital abnormalities are not increased compared to the general population (Fig. 59.3).

- Provide the survivors with a comprehensive treatment summary, a survivorship care plan, which provides information about potential cancer-related health risks.
- Evaluate all aspects of the survivors health status to be able to offer an appropriate plan for lifelong screening, surveillance, and prevention.
- Offer support to strengthen the survivors' healthiness by not focusing on living with complications.
- Plan together with the survivors to work towards an independent life and to be able to manage daily life.
- Ensure long-term monitoring of pituitary hormones including attention to symptoms of pituitary insufficiency.
- Coordinate a careful follow up with a combination of growth monitoring through childhood and puberty, regular monitoring of IGF-1 levels, proper stimulation tests for GH.
- Be aware of that impaired hormone secretion may occur many years after treatment.
- Identify the survivors risk for metabolic complications such as obesity, physical inactivity, lipid abnormalities and insulin resistance.
- Facilitate multidisciplinary interventions such as prevention with healthy lifestyle and physical activity, including treatment of obesity or metabolic risk reduction.
- Act as a key worker and facilitate the contact with the oncologist, endocrinologist, dietician, physiotherapist, psychologist and primary care. Ensure continuity and safety.

Fig. 59.3 Nursing process in the care of childhood cancer survivors

59.7 Conclusions

Detailed information about the past cancer treatment are needed to estimate health risks associated with childhood cancer. Ideally, the childhood cancer survivors will be provided with a comprehensive treatment summary, a survivorship care plan, which provides information about potential cancer-related health risks and health surveillance recommendations, including a systematic plan for lifelong screening, surveillance, and prevention.

CCS exposed to CRT are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications, and cardiovascular morbidity. New endocrinopathies can develop decades following cancer treatment, and lifelong surveillance is mandatory. There is evidence for a strong correlation between the total radiation dose and the development of pituitary deficits. Further, age at treatment and also time since treatment have strong implications on pituitary hormone deficiencies. There is evidence that the hypothalamus is more radiosensitive than the pituitary. Survivors of ALL and of tumors in the pituitary-hypothalamic area are at greatest risk for obesity. The obesity may be promoted via a number of possible mechanisms: growth hormone deficiency, leptin resistance or hypothalamic regulation of food intake, and energy expenditure. Young age at diagnosis and gender (female) are associated with increased risk of obesity. The main consequences of obesity after childhood cancer are presence of cardiovascular risk factors, increased risk of diabetes, increased

risk of fatty liver, low health-related quality of life, and lower self-esteem.

Risk factors for low BMD include high dose methotrexate, cumulative doses of glucocorticoids, male gender, and low physical activity. Any combination of these factors may result in osteopenia, not reaching optimal peak bone mass and osteoporosis later in life. CRT may cause decreased longitudinal bone growth and bone mass, suggesting an effect of pituitary insufficiency and in particular GHD. GH plays a key role in the longitudinal bone growth and the attainment of peak bone mass.

Infertility is an important potential consequence of treatment for childhood cancer and identification of survivors for whom strategies to preserve fertility are required. Women treated with radiotherapy affecting ovarian and uterine function are at high risk of acute ovarian failure, premature menopause, complications including spontaneous abortion and preterm labor. These data are important for family planning and obstetrical management. Radiotherapy to the gonads, total body irradiation, and high dose chemotherapy may result in a number of effects on the male reproductive system in survivors. These include direct damage to the gonads and also indirect damage to hypothalamus-pituitary axis. Recovery of spermatogenesis and sperm production may occur several years after treatment.

References

Baker K, Ness K, Steinberger J, Carter A, Francisco L, Burns L, et al. Diabetes and hypertension and vard-iovascular events in survivors of hematopoetic cell transplantation: a report from bone marrow transplantation survivors study. Blood. 2007;109:1765–72.

Björk J, Link K, Erfurth EM. The utility of the growth hormone (GH) releasing hormone-arginine test for diagnosing GH deficiency in adults with childhood acute lymphoblastic leukemia treated with cranial irradiation. J Clin Endocrinol Metab. 2005;90(11): 6048–54.

Brauner R, Rappaport R. Precocious puberty secondary to cranial irradiation for tumours distant from the hypothalamo-pituitary area. Horm Res. 1985;22:78–82.

Brennan BMD, Rahim A, Mackie EM, Eden OB, Shalet SM. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. Clin Endocrinol. 1998;48:777–83.

Brignardello E, Felicetti F, Castiglione A, Chiabotto P, Corrias A, Fagioli F, et al. Endocrine health conditions in adult survivors of childhood cancer: the need for specialized adult-focused follow-up clinics. Eur J Endocrinol. 2013;68(3):465–72.

Carroll P, Christ E, Bengtsson B, Carlsson L, Christiansen J, Clemmons D, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth hormone research society scientific committee. J Clin Endocrinol Metab. 1998;83:382–95.

Chemaitilly W, Li Z, Huang S, Ness K, Clark K. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime cohort study. J Clin Oncol. 2015;33:492–500.

Chow E, Friedman D, Stovall M, et al. Risk of thyroid dysfunction and subsequent thyroid cancer among survivors of acute lymphoblastic leukemia: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2009;53:32–437.

Constine LS, Woolf PD, Cann D, Mick G, McCormick K, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumours. N Engl J Med. 1993;328: 87–94.

Critchley H, Bath L, Wallace W. Radiation damage to the uterus—review of the effects of treatment of childhood cancer. Hum Fertil (Camb). 2002;5:61–6.

Darzy K, Shalet S. Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. J Clin Endocrinol Metab. 2005;90:6490–7.

Edgar A, Wallace H. Pregnancy in women who had cancer in childhood. Eur J Cancer. 2007;43:1890–4.

Follin C, et al. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab. 2010;95(8):3726–35. https://doi.org/10.1210/jc.2010-0117. Epub 2010 May 19.

Follin C, Link K, Wiebe T, Moell C, Björk J, Erfurth EM. Bone loss after childhood lymphoblastic leukemia: an observational study with and without GH therapy. Eur J Endocrinol. 2011;164(5): 695–703.

Follin C, Link K, Wiebe T, Moëll C, Björk J, Erfurth EM. Prolactin insufficiency but normal thyroid hormone levels after cranial radiotherapy in long-term survivors of childhood leukaemia. Clin Endocrinol. 2013;79(1):71–8.

Follin C, Wiebe T, Moëll C, Erfurth EM. Moderate dose cranial radiotherapy causes central adrenal insufficiency in long-term survivors of childhood leukaemia. Pituitary. 2014;17:7–12.

Gilsanz V, Carlsson M, Roe T, Ortega J. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. J Paediatr. 1990;117:238–44.

Hawkins M, Kingston J, Kinnier Wilson L. Late deaths after treatment for childhood and adolescent cancer. Cancer. 1994;73:3094–102.

Heikens J, Ubbink M, van der Pal H, Bakker P, Fliers E, Smilde T, et al. Long term survivors of childhood

brain tumours have an increased risk for cardiovascular disease. Cancer. 2000;88:2116–21.
Hochberg IC, Kuten A, Hertz P, Tatcher M, Kedar A, Benderly A. The effect of single-dose radiation on cell survival and growth hormone secretion by rat anterior pituitary cells. Radiat Res. 1983;94:508–12.
Janiszewski PM, Oeffinger K, Church T, Dunn A, Eshelman D, Voctor R, et al. Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab. 2007;92:3816–21.
Lam KS, Tse VK, Wang C, Yeung RT, Ho JH. Effects on cranial radiation on hypothalamic-pituitary function—a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med. 1991;78:165–76.
Lando A, Holm K, Nysom K, Rasmussen AK, Feldt-Rasmussen U, et al. Thyroid function in survivors of childhood acute lymphoblastic leukaemia: the significance of prophylactic cranial irradiation. Clin Endocrinol. 2001;55(1):21–5.
Larsen E, Schmiegelow K, Rechnitzer C, Andersen A. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab. 2003;88:5307–14.
Leiper AD, Stanhope R, Kitching P, Chessells JM. Precocious and premature puberty associated with acute lymphoblastic leukemia. Arch Dis Child. 1987;62:1107–12.
Link K, Moëll C, Garwicz S, Cavallin-Ståhl E, Björk J, Thilén U, et al. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. J Clin Endocrinol Metab. 2004;89(10):5003–12.
Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumors in adults. Q J Med. 1988;262:145–60.
Livesey EA, Hindmarsh PC, Brook CG, Whitton AC, Bloom HJ, Tobias JS, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer. 1990;61:622–5.
Lustig R, Post S, Srivannaboon K, Rose SR, Danish RK, Burghen GA, Xiong X, Wu S, Merchant TE. Risk factors for the development of obesity in children surviving brain tumours. J Clin Endocrinol Metab. 2003;88:611–6.
Meistrich M, Wilson G, Brown B, da Cunh M, Lipshultz L. Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer. 1992;70:2703–12.
Mukherjee A, Ryder WD, Jöstel A. Deficiency is independently associated with reduced insulin-like growth factor I status in severely growth hormone-deficient adults. J Clin Endocrinol Metab. 2006;91:2520–5.
Nussey SS, Hyer SL, Brada M, Leiper AD. Bone mineralization after treatment of growth hormone deficiency in survivors of childhood malignancy. Acta Paediatr Suppl. 1991;399:9–15.
Odame I, Duckworth J, Talsma Dm Beaumont L, Furling W, Webber C, Barr R. Osteopenia, physical activity and health-related quality of lie in survivors of brain tumours treated in childhood. Pediatr Blood Cancer. 2006;46:357–62.
Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, Vik TA, Inskip PD, Robison LL, Childhood Cancer Survivor Study. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin Oncol. 2003;21(7):1359–65.
Ohlsson C, Bengtsson BÅ, Isaksson O, Andreassen T, Slootweg M. Growth hormone and bone. Endocr Rev. 1998;19(1):55–79.
Pai HH, Thornton A, Katznelson L, Finkelstein DM, Adams JA, Fullerton BC, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. J Radiat Oncol Biol Phys. 2001;49:1079–92.
Pålsson A, Malmström M, Follin C. Childhood leukaemia survivors' experiences of long-term follow-ups in an endocrine clinic—a focus-group study. Eur J Oncol Nurs. 2017;26:19–26.
Pasqualini T, Escobar ME, Domene H, Muriel FS, Pavlovsky S, Rivarola MA. Evaluation of gonadal function following long-term treatment for acute lymphoblastic leukemia in girls. Am J Pediatr Hematol Oncol. 1987;9:15–22.
Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. Fertil Steril. 1997;68:1–5.
Reilly J, Ventham J, Newell J, Aitchison T, Wallace H, Gibson B. Risk factors for excess weight gain in children treated for acute lymphoblastic leukemia. Int J Obes Relat Metab Disord. 2000;24:1537–41.
Robinson IC, Fairhall KM, Hendry JH, Shalet SM. Differential radiosensitivity of hypothalamo-pituitary function in the young adult rat. J Endocrinol. 2001;169:519–26.
Samaan NA, Vieto R, Schultz PN, Maor M, Meoz RT, Sampiere VA, et al. Hypothalamic, pituitary and thyroid dysfunction after radiotherapy to the head and neck. Int J Radiat Oncol Biol Phys. 1982;8:1857–67.
Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys. 1995;31:1113–21.
Sklar C, Boulad F, Small T, Keman N. Endocrine complications of pediatric stem cell transplantation. Front Biosci. 2001;1:G17–22.
Socie G, Salooja N, Cohen A. Nonmalignant late effect after allogenic stem cell transplantation. Blood. 2003;101:3373–85.
Wallace H, Thomson A. Preservation of fertility in children treated for cancer. Arch Dis Child. 2003;32:366–72.
Wallace W, Anderson R, Irvine D. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6:209–18.
Warner J, Bell W, Webb D, Gregory J. Daily energy expenditure and physical activity in survivors of childhood malignancy. Pediatr Res. 1998;43:607–13.
Zebrack B, Casillas J, Nohr L, Adams H, Zeltzer L. Fertility issues for young adult survivors of childhood cancer. Sychooncology. 2004;13:689–99.

Neurocognitive Dysfunction and Psychosocial Issues

60

Katharina Roser, Gisela Michel, and Katrin Scheinemann

Contents

60.1 **Introduction** 1150

60.2 **Neurocognitive Dysfunction** 1150
60.2.1 Tumor Characteristics 1152
60.2.2 Treatments 1152
60.2.3 Mechanism of Neurocognitive Damage 1153
60.2.4 Moderators: Individual, Genetic and Environmental Variables 1153
60.2.5 Interventions 1153
60.2.6 Future Directions 1155

60.3 **Psychosocial Issues** 1155
60.3.1 Psychological Distress 1155
60.3.2 Post-traumatic Stress Symptoms (PTSS) and Post-traumatic Stress Disorder (PTSD) 1156
60.3.3 Fatigue 1156
60.3.4 Education and Employment 1157

60.4 **Conclusions** 1158

References 1158

Abstract

Childhood cancer is a life-threatening disease and has a major impact on patient and family. Diagnosis is followed by intense treatment putting patients at high risk for late adverse outcomes, including neurocognitive deficits and psychosocial problems, such as psychological distress, post-traumatic stress disorder (PTSD), fatigue, low educational achievement, and unemployment. Psychosocial health in childhood cancer survivors is often interrelated; psychological distress expressed as low mood, depression, and anxiety are associated with insufficient sleep, poor sleep quality and fatigue, as well as with lack of employment and low income. Survivors of central nervous system (CNS) tumors and those who received cranial radiation are at particular high risk for any of these problems, but also women and

K. Roser · G. Michel (✉)
Department of Health Sciences and Health Policy, University of Lucerne, Luzern, Switzerland
e-mail: katharina.roser@unilu.ch; gisela.michel@unilu.ch

K. Scheinemann
Division of Hematology/Oncology, University Children's Hospital Basel (UKBB), Basel, Switzerland

McMaster University, Hamilton, ON, Canada
e-mail: katrin.scheinemann@ukbb.ch

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_60

children who were diagnosed at a younger age. Preventive measures during cancer treatment are important. But also continued support and if necessary treatment during the whole cancer trajectory and into long-term follow-up of adult is necessary to reduce problems and improve quality of survivorship.

Keywords
Radiation therapy · Neuropsychological testing · Neurotoxicity · Depression Anxiety · Fatigue · Follow-up care

Abbreviations

ADHA	Attention deficit/hyperactivity disorder
ALL	Acute lymphoblastic leukemia
CCSS	Childhood Cancer Survivor Study
CNS	Central nervous system
CRP	Cognitive Remediation Program
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
ENT	Ear, nose, throat
MRI	Magnetic resonance imaging
PTSD	Post-traumatic stress disorder
PTSS	Post-traumatic stress symptoms

Key Terms

- **Neurocognitive dysfunction:** changes in cognitive function after a brain insult, particularly in the presence of physical evidence of structural brain changes.
- **Neuroprotective agents**: agents designed to protect the brain from the toxic effects of chemical and imaging treatments.
- **Neuropsychological deficits**: achievement of scores below that of a normative reference standard on psychological testing.

Key Points

- Neurocognitive dysfunction are very common in childhood cancer survivors and highest in CNS tumor survivors.
- Effective interventions to decrease or prevent neurocognitive dysfunctions are under investigation.
- Survivors of childhood cancer are at high risk for psychological distress, post-traumatic stress symptoms, and fatigue.
- Survivors of CNS tumors are at particularly high risk of low educational achievement and unemployment.
- Psychosocial support during treatment and in long-term follow-up should help mitigating these problems.

60.1 Introduction

Cancer in childhood is a very severe and often life-threatening disease, and today it remains the second most common cause of death in children in developed countries. The diagnosis of cancer is usually followed by intense treatment including chemotherapy and/or radiotherapy. Depending on the cancer type, children might have to attend treatment for several years, which has a major impact on their life including family, friends, and school. However, long-term survival of children with cancer has increased over recent decades due to important advances in diagnostics and treatment as well as managing acute and long-term side effects. Accordingly, attention has turned to the quality of survivorship for the increasing population of childhood cancer survivors. Cancer and treatment leave children at a high risk for late adverse outcomes (late effects), such as cardiovascular, pulmonary or endocrine problems, second cancer, but also neurocognitive and psychosocial problems. In this chapter, we are going to summarize long-term neurocognitive and psychosocial consequences of cancer in childhood.

60.2 Neurocognitive Dysfunction

Neuropsychological deficits are unfortunately common, especially within the subgroup of central nervous system (CNS) tumors. Up to 40% of survivors, or even more in survivors of CNS tumors, demonstrate neurocognitive dysfunction (Zeltzer et al. 2009). They often demonstrate some form of deficit either on presenting history/school perfor-

mance or on formal psychological testing, varying from mild learning difficulties to severe impairment (Janzen et al. 2015). One study has shown that around 25% of childhood cancer survivors qualified for special education in school (Ullrich and Embry 2012). Newer findings have estimated that around 40–50% of acute lymphoblastic leukemia survivors and around 70–80% of CNS tumor survivors will require special education services at some point through their school career (Ullrich and Embry 2012). The neurocognitive difficulties persist over time or even increase over time and become more obvious once independent employment should be initiated and established. In adulthood, pediatric CNS tumor survivors report the poorest health-related quality of life among childhood cancer survivors, secondary to neuropsychological and other treatment-related late effects (Zeltzer et al. 2009). Because neuropsychological deficits significantly impact the quality of life, psychosocial functioning, educational attainment, and employment status of childhood cancer survivors, there is urgent need to identify and minimize these deficits in order to optimize functional outcome.

Neuropsychological outcomes for individual childhood cancer survivors are highly variable and depend on multiple, interrelated disease- and treatment-related variables, including age at diagnosis, characteristics of the tumor or metastasis (location within the CNS), required surgical interventions and adjuvant therapy, especially any CNS directed therapy like cranial irradiation or intrathecal chemotherapy. Neuropsychological effects are moderated by the child's individual characteristics gender, pre-morbid functioning and genetics as well as environmental factors. The last two mentioned are still not fully understood and under further investigation. Further, as the mechanisms of treatment-related neurotoxicity have been partially understood, the potential for risk-adapted treatments, neuroprotective agents, and strategies for neuronal repair have emerged, which could substantially reduce morbidity.

Different study groups worldwide have developed guidelines for the identification and intervention of neurocognitive dysfunction in childhood cancer survivors (Nathan et al. 2007). Questionnaires for childhood cancer survivors have been developed to assess neurocognitive functioning (Phillips et al. 2015). Childhood Cancer Survivor Study (CCSS) Neurocognitive questionnaire, a large number of childhood cancer survivors in the aftercare setting have been assessed.

Given the importance of the topic in many of the newer treatment protocols especially for CNS tumors minimizing neurotoxicity is one of the main aims. Tools and investigations for neurocognitive dysfunction measurements are implemented either throughout treatment or after completion of treatment and being in aftercare (Noll et al. 2013).

There is considerable heterogeneity in individual neuropsychological outcomes for childhood cancer survivors given the variety of tumor types and treatments as well as associated time and individual factors. So no single neuropsychological phenotype exits, but many different types varying from no deficits over mild learning or attention deficits to severe limitations in intelligence and adaptive functioning which restrict independent living (Janzen et al. 2015). Overall attention problems are particularly prevalent in the group of leukemia and CNS tumor survivors (Zeltzer et al. 2009).

In the early beginning of neuropsychological testing, general measures of intelligence were tested to predict academic performance. Today, multiple core functions are measured including attention, processing speed, working memory, psychomotor skills and new learning, underlying the ability to learn efficiently and retain information. As the testing is time consuming and requires a patient in good condition the timing of the testing is important. Initial testing—meaning at time of diagnosis—is impossible as the patient is too sick and will require immediate medical attention. So in general the first baseline testing happens quite some time after the initial diagnosis and is already biased by the underlying disease as well as the initiated treatment. Childhood cancer survivors will require multiple testing through their medical journey matching time points of therapeutic interventions as well as academic development, e.g., starting high school, college, or university.

Overall neuropsychological effects appear to be cumulative regardless of the treatment used. Executive functioning impairment has been reported in up to 14% of adult childhood cancer survivors (Zeltzer et al. 2009). Age at diagnosis is a significant predictor of outcome given that brain

structure is injured in the maturation phase. The younger the child at diagnosis is the greater the risk of severe neuropsychological impairment.

60.2.1 Tumor Characteristics

Childhood cancer with CNS location either as primary CNS tumors or metastasis like in leukemias/lymphomas or solid tumors will have a direct impact on the neuropsychological outcome as brain structure is damaged or destroyed. There is an extensive body of literature on neurocognitive dysfunction for survivors of ALL as well as CNS tumors. Special risk factors for children with ALL are cranial radiation therapy, intravenous and intrathecal methotrexate, corticosteroids, and female gender. Main risk factors in CNS tumor patients are cranial radiation therapy, tumor invasion of normal brain, trauma from surgical resection, hydrocephalus, and seizures (Butler and Mulhern 2005). Hydrocephalus as result of a blocked cerebrospinal fluid flow has shown to be a strong predictor of long-term neuropsychological deficits especially the longer the hydrocephalus has been present, e.g., in low grade gliomas of the posterior fossa. Other tumor entities with an increased risk of neurocognitive impairment are acute myelogenous leukemia, non-Hodgkin lymphoma, or tumors of the head and neck undergoing radiation therapy (Nathan et al. 2007).

60.2.2 Treatments

Surgery: Any surgical intervention to the brain is adding an additional risk factor for neuropsychological sequelae. The brain becomes more vulnerable as the blood–brain barrier is damaged.

Postsurgical complications like infection or cerebellar mutism syndrome are adding a further damage. Cerebellar mutism syndrome is a postsurgical complication in around 2.5% of all posterior fossa surgeries. The syndrome is characterized by diminished or absent speech, dysarthria, and linguistic difficulties. It is often accompanied by ataxia, muscular hypotonia, and emotional lability (Janzen et al. 2015). The underlying pathomechanism is not fully understood, and so far no specific treatment has been established. Children who develop this syndrome show significantly lower performance on measures of processing speed, attention, working memory, executive processes, and academic performance which persists over time.

Radiation: Over the past decades, radiation therapy has been identified as the most significant risk factor for long-term neuropsychological deficits. Higher dose (≥3500 cGy) and volume of radiation therapy associated with poorer outcomes, particularly in young children. Due to these facts radiation therapy has been postponed—whenever possible given the underlying disease—until the age of 3 or 4 years or even older. Doses as well as volume were decreased due to newer radiation techniques, but even children with an underlying leukemia receiving cranial low dose radiation of 1200 or 1800 cGy showed neuropsychological deficits. Proton therapy with maximal radiation dose to the tumor and minimal to no dose to the surrounding tissue is now used in children for many tumors whenever a proton facility is available, but so far no long-term data on neuropsychological outcomes exits.

Lots of data has been collected on intellectual decline following whole brain radiation therapy. Losses of 25–30 full-scale IQ points are not uncommon, and the majority of children treated with cranial radiation prior to 7 years of age require special education (Janzen et al. 2015).

Radiation therapy disrupts the protracted process of myelination within the brain, which normally begins prenatally and continues through childhood and adolescence. The resulting white-matter damage is directly related to the nature and severity of neuropsychological impairment.

Chemotherapy: Given the function of the blood–brain barrier, the brain should be protected against most of the chemotherapeutic agents because not many of them can penetrate into the cerebrospinal fluid (CSF) or the brain tissue. But the blood–brain barrier is damaged in primary CNS tumors. A large body of literature exits on the neuropsychological effects of methotrexate from ALL treatment. However, the effect should not be seen in isolation, but in combination with other chemotherapeutic drugs or irradiation.

Glucocorticoid steroids (e.g., prednisone and dexamethasone) are widely used in the treatment of leukemias and lymphomas but also as a potent antiemetic. They are directly associated with acute neurobehavioral difficulties in children and long-term

memory difficulties. Platinum-based chemotherapy is associated with a high risk of hearing loss, vinca alkaloids are associated with peripheral neuropathy resulting in reduced fine motor skills. High dose cytarabine is associated with acute neurotoxicity typically demonstrating in cerebellar dysfunction.

Stem cell transplantation: Given that conditioning treatments for stem cell transplantation are often using similar chemotherapeutic drugs but in higher dosing as well as total body irradiation neurocognitive impairment can be worsened, but has to be seen in combination with the previous treatment as well as the underlying disease. In some clinical studies for brain tumors in young children, high dose chemotherapy and autologous stem cell transplantation are used instead of cranial irradiation, and the neurocognitive outcome seems to be better, but long-term outcome data still have to confirm these preliminary findings.

60.2.3 Mechanism of Neurocognitive Damage

Chemotherapy and radiotherapy are causing mainly white-matter damage especially cortical and subcortical. This results in demyelination and glial cell destruction. This damage can be visualized by specific magnetic resonance imaging sequences (Nathan et al. 2007). Multiple animal models have been established to study the damage mode and to test possible interventions.

Another pathomechanism for radiation damage may be explained by disruption of the microvascular system supplying blood to the brain. This results in calcification of fiber tracts and restriction of blood supply to certain parts of the brain (Nathan et al. 2007).

60.2.4 Moderators: Individual, Genetic and Environmental Variables

The neuropsychological outcome is also influenced by individual factors. Age at the time of diagnosis is a well-established predictor; younger age at diagnosis is correlated with a poorer neuropsychological outcome.

Gender is another individual risk factor. Girls seem to have greater treatment-related neuropsychological impairment than boys, the reason is not quite clear yet.

The neurocognitive outcome is also influenced by the pre-morbid level of functioning. This level is difficult to record as normally formal testing at diagnosis is impossible due to the poor health condition of the child. Indirect assessment of the level is only possible through information of the previous academic performance, but this is dependent on the age of the child at diagnosis as well as the potential diagnostic delay.

Preexisting neurological or developmental conditions such as neurofibromatosis type 1 are an additional risk factor for neurocognitive deficits. Such conditions need to be identified prior to initiation of therapy as in this case treatment modifications (e.g., no radiation therapy) have to be put in place.

Identification of genetic risk factors mainly genetic polymorphisms is in its early stage, but will potentially play a significant role within the next years. In the current focus are enzymes like glutathione S-transferase or enzymes in the folate metabolism pathway that are involved in chemotherapy metabolism and clearance (Nathan et al. 2007).

Genetic polymorphism testing for ototoxicity due to platinum-based chemotherapy or peripheral neurotoxicity due to vinca alkaloid toxicity will hopefully be implemented within the next decade and could dictate individual chemotherapeutic drug dosing.

Family functioning around and after diagnosis can also influence the severity of neurocognitive outcomes as with more support and resources more modified interventions can be put in place. Stress and family conflict can have a negative impact on neurocognitive outcomes (Ullrich and Embry 2012).

Socioeconomic status of the family has been shown to be an important environmental factor. Lower socioeconomic status was associated with greater neurocognitive decline in survivors of ALL and can also impact the outcome in CNS tumor survivors (Ullrich and Embry 2012).

60.2.5 Interventions

Comprehensive neuropsychological evaluations over time are strongly recommended for all child-

hood cancer survivors and are nowadays implemented in many treatment protocols. The treatment centers need to provide the resources in form of qualified personell as well as space and testing tools. Enough time needs to be allocated for discussing the test results with the patient and the caregiver and with professionals involved in possible interventions, e.g., teachers. Especially for this task, counselor-liaison professionals can help with educational planning, advocacy, and coordination of school reentry as they will attend meetings in the clinic as well as in the community (Butler et al. 2008b).

Support in the classroom can help in many areas, e.g., problems with fine motor skills such as handwriting or the use of a computer, problems with slow processing speed such as needing additional time to complete the task or attention problems asking for extra tutoring assistance. Unfortunately as there is clearly a lack of resources and support, parents have to be strong advocates for their children to fulfill their educational and social needs and enhance the knowledge about neuropsychological late effects. Continued career counseling beyond definitive employment is required.

Comorbidities from the disease and treatment like seizures, visual or hearing impairment, and endocrinopathies should be identified and treated as they are co-factors for a worse neurocognitive outcome. Close collaboration with colleagues from neuropediatrics, ophthalmology, endocrinology, and ENT is essential.

Many interventions at different time points (early/during active treatment vs. late/aftercare period) have been developed and tested over the last years. Cognitive Remediation Program (CRP) combines attention training, special education strategies and aspects of cognitive-behavioral therapy. It is a time intense program with moderate intervention-related benefits so far (Butler et al. 2008a).

As attention deficits are prevalent, medication which is used in children with attention deficit/hyperactivity disorder (ADHD) has been tested as stimulants in childhood cancer survivors. So far methylphenidate (Ritalin) has shown some improvement in attention/concentration and neurocognitive side effects, but overall there are quite a few limitations (Butler et al. 2008b). Stimulant medication is only short acting, but improvement after discontinuation of the medication cannot be expected. Secondarily, stimulant medication should not add severe long-term side effects, but long-term safety data on stimulant medication is incomplete so far.

Another promising pharmacological intervention has been run with modafenil in CNS tumor patients from the Children's Oncology Group following completion of multimodal treatment. The medication has been tested over a 6 weeks period and will compare side effects, cognitive function, and fatigue with this alternative stimulant (Noll et al. 2013).

But in summary as pharmacological interventions in this heavily pre-treated group could add potentially severe side effects due to changes in the metabolism pathway (pharmacokinetics), non-medication and feasible home-based interventions have been developed. A computerized cognitive training called Cogmed system was found to be feasible and acceptable to be implemented within the areas of attention deficit and working memory issues. With regular training, improvements in visual working memory can be maintained (Hardy et al. 2013). Again the Children's Oncology Group has run a pilot study in CNS tumor patients receiving cranial radiation using a home-based, computerized cognitive training program.

Results from different regular exercise intervention studies have also shown a positive effect on neurocognitive deficits similar to results on people with dementia. The underlying idea is to promote cell recovery by stimulation of the proliferation and/or differentiation of endogenous stem cells or progenitors. Limitation of a regular exercise intervention is often the severe physical handicaps of the childhood cancer survivors, especially following treatment for a CNS or bone tumor.

Another intervention taking place either during or early after treatment is a specialized rehabilitation in a clinical setting. Children and their parents (depending on the age of the child) are benefiting from a variety of different rehabilitation services, e.g., physiotherapy, occupational therapy, dietician, teacher, psychologist, sports, arts as well as counseling sessions about coping strategies within peer groups. Germany, for example, has quite a few of these specialized rehabilitation clinics and many childhood cancer patients and their parents benefit from such a 4-week intervention.

60.2.6 Future Directions

Whereas currently all interventions are based on already existing deficits, preventative measurements should take place in the near future. Neuropsychological testing needs to be standardized with regard to the tool for different age groups as well as the evaluation points. Assessment should be done computerized as often as possible. Especially in CNS tumor patients, neurocognitive sequelae are part of the neurosurgical planning. Maximum extent of tumor resection should go hand in hand with preserved neurological function. Specific MRI sequences as well as intraoperative monitoring can help facilitating this goal. Endoscopic biopsies have become more and more standard compared to an open biopsy to minimize damage to the normal brain structure.

With the newer and widely available techniques, tumors can be better characterized on a molecular level and treatment can be individualized and risk adapted, so potentially no CNS irradiation therapy is needed or can be delayed as much as possible. As an example in ALL, intrathecal chemotherapy has replaced cranial irradiation for almost all risk groups. The newest radiation technique should be used whenever possible including proton beam therapy. Combination of neurotoxic chemotherapy and radiation therapy should be avoided if tumor biology permits this.

Neuroprotective agents are also under investigation with the idea to prevent neurotoxicity from healthy brain tissue by enhancing DNA repair and reducing cell death and neuroinflammation. Ideally, such an agent would be given prior to any irradiation or chemotherapy. Under discussion as neuroprotective agents are some vitamins or even erythropoietin which needs to be tested first in an animal model.

60.3 Psychosocial Issues

The diagnosis of childhood cancer has a major impact on the child, the family, and the social environment. Intense treatment often prevents patients from participating in ordinary daily life such as attending school and playing with friends. Later on, medical late effects can affect survivors' life and impact their emotional experience and their social life. We will therefore address four areas in which childhood cancer was shown to have a major impact on survivors' life:

- Psychological distress, such as depression, or anxiety
- Post-traumatic stress symptoms (PTSS) and post-traumatic stress disorder (PTSD)
- Fatigue
- Social problems, education and employment

Although we address these four topics separately, it is important to keep in mind that psychosocial health in childhood cancer survivors is often interrelated: psychological distress expressed as low mood, depression, and anxiety was found to be associated with insufficient sleep, poor sleep quality, and fatigue (Walter et al. 2015; Mulrooney et al. 2008), as well as with lack of employment and low income (Gurney et al. 2009).

60.3.1 Psychological Distress

60.3.1.1 Description of the Problem

Psychological distress can be described as emotional suffering covering symptoms such as depression, anxiety, somatization, and impaired emotional well-being. Psychological distress may start during or early after treatment. Diagnosis of cancer is a highly stressful event; patients and their family may experience anxiety about the diagnosis, treatment, and expected outcomes, and once treatment is completed fear of cancer recurrence and/or late effects may continue. Depressive symptoms might occur because of pain, physical changes, late effects, or problems occurring with family, friends, in school or later on in employment.

60.3.1.2 Who Is at Risk

In general, most childhood cancer survivors fare well and most do not suffer from significant psychological distress (Lund et al. 2011; Michel

et al. 2010). However, several studies found a considerable number of survivors reporting psychological distress. In a Swiss study of adult survivors of childhood cancer, around 25% of survivors reported psychological distress compared to 10% expected in the general population (Michel et al. 2010). Particularly, survivors who had been diagnosed with a CNS tumor were found to be at increased risk for psychological distress (Lown et al. 2015; Lund et al. 2011; Michel et al. 2010). Similarly, treatment with cranial radiation was found to be associated with poor emotional health in adult survivors (Zeltzer et al. 2008) and with higher likelihood for depression and anxiety in school-aged survivors of childhood cancer (Lund et al. 2011). In addition, more survivors of ALL reported low psychological well-being, anxiety, and depression (Lown et al. 2015; Lund et al. 2011).

Similar to the general population, female survivors of childhood cancer were at higher risk for psychological distress (Lund et al. 2011, Michel et al. 2010). Additionally, survivors who reported other psychological problems were unemployed, had low income, or an immigration background were more likely to suffer from psychological distress (Gurney et al. 2009; Michel et al. 2010).

60.3.1.3 Development Over Time

So far, longitudinal studies are rare in the field of psychological distress after childhood cancer. One study in survivors of childhood ALL found a higher proportion of children at risk for anxiety and depression compared to the expected proportion in the general population in the time between 1 month and 3 years after completion of chemotherapy treatment (Kunin-Batson et al. 2016). However, the prevalence for clinically relevant anxiety and depression was not increased. While the risk for anxiety decreased within the first year after treatment, and increased again after 3 years, the prevalence of elevated depression was fairly consistent over time. Because children with increased scores in anxiety or depression are at higher risk for later distress, early detection, and effective interventions are important and necessary (Kunin-Batson et al. 2016).

60.3.2 Post-traumatic Stress Symptoms (PTSS) and Post-traumatic Stress Disorder (PTSD)

60.3.2.1 Description of the Problem

PTSS and PTSD are another important problem occurring after childhood cancer. PTSD is characterized by avoidance of situations associated with the trauma (e.g., going back to the hospital for follow-up appointments), intrusive thoughts or re-experience of symptoms (e.g., nightmares or a sense of reliving cancer-related events), and heightened arousal (e.g., insomnia or hypervigilance). For childhood cancer survivors lifetime prevalence of post-traumatic stress disorder ranged from 20 to 35% (Bruce 2006). The lifetime prevalence in parents of childhood cancer survivors was even higher ranging from 27 to 54%.

60.3.2.2 Who Is at Risk

Similar to other forms of psychological distress, female survivors were found to be at higher risk for PTSD (Bruce 2006). No associations with objective diagnosis or treatment factors were found; however, subjective perceptions of these, as well as current perceptions of cancer or life threat were risk factors for PTSD and PTSS (Bruce 2006). Additionally reduced social support, impaired family functioning and number of other stressful life events increased the risk for PTSD and PTSS (Bruce 2006). Generally, recent research indicates that stressful life events only constitute one part of the necessary prerequisites for the development of PTSD; a genetic vulnerability appears to be the other major player.

60.3.3 Fatigue

60.3.3.1 Description of the Problem

Sleep and the quality of sleep play a fundamental role in psychological health. Fatigue can be defined as an overwhelming feeling of tiredness coming along with lack of energy and a feeling of exhaustion, which is associated with impaired

physical and/or cognitive functioning. Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or the treatment of cancer that interferes with the usual functioning. Although cancer-related fatigue and fatigue as late effects have been recognized as important problems in survivors of cancer in adulthood, the relevance has not yet been widely studied in survivors of childhood cancer.

Sleep problems are prevalent in cancer patients and include difficulties to fall asleep or staying asleep, poor sleep quality, and short sleep duration. In children with cancer, excessive daytime sleepiness is the most common symptom of sleep disorders and may lead to the manifestation of other sleep problems or anxiety or depression (Walter et al. 2015). Sleep problems during treatment have the potential to become chronic. They might continue and result in sleep problems and fatigue in adult survivors of childhood cancer (Walter et al. 2015); 15–30 years after diagnosis and treatment up to 19% of survivors suffer from fatigue (Mulrooney et al. 2008).

60.3.3.2 Who Is at Risk

Again, women were found to be more likely to suffer from fatigue, as were survivors who had been treated with radiotherapy (Mulrooney et al. 2008). Also survivors of ALL, CNS tumors, Hodgkin's lymphoma, soft tissue sarcoma, and bone tumors showed increased levels of fatigue (Mulrooney et al. 2008). Survivors who suffered from medical late effects such as lung fibrosis, congestive heart failure, who were depressed and those who were not married were also more likely to suffer from fatigue (Mulrooney et al. 2008). In turn, insufficient sleep or poor sleep quality was shown to impact mood and increase depression and anxiety (Walter et al. 2015).

60.3.4 Education and Employment

60.3.4.1 Description of the Problems

Many childhood cancer patients are confronted with the diagnosis during an important time of their education. Being away from school for repeated and sometimes longer periods of time may affect educational achievements later in life. Educational achievement but also cancer, treatment, and late effects might impact other social outcomes of survivors such as employment.

While finding employment appropriate to education and personal interest is an important goal for many, research has indicated that it might be even more important for survivors. Many survivors seek a career in health care in order to help others by using their own experiences (Brown et al. 2016). Others found that the self-image and sense of competence of survivors is often closely tied to their career and daily work experiences (de Boer et al. 2006). However, for many childhood cancer survivors it may be difficult obtaining a job if they suffer from late effects which limit their daily functioning.

Psychosocial late effects thus include lower educational attainment and higher use of special education programs compared to their siblings or the general population. Survivors are also less likely to reach high skilled, professional positions, or to work fulltime. They are at risk of receiving lower income and are also more likely to be unemployed (de Boer et al. 2006; Gurney et al. 2009; Lown et al. 2015).

60.3.4.2 Who Is at Risk

Most studies did not show lower educational outcomes for survivors of most cancer types. However, survivors of CNS tumors achieved significantly lower educational levels than other childhood cancer survivors and their siblings and peers (Lund et al. 2011). Many of these survivors were in need of special education programs (Gurney et al. 2009). They had a high risk to not graduate from college, remain unemployed, and have a lower income (Armstrong et al. 2009; de Boer et al. 2006). However, not all survivors of non-CNS tumors may easily and directly achieve a similar level of education and employment as their peers. Especially survivors of leukemia, non-Hodgkin's lymphoma, and neuroblastoma were found to be at greater risk for having educational problems (Gurney et al. 2009). However,

the use of special education programs mitigated the increased risk for not completing high school in most survivors (Gurney et al. 2009).

Cranial radiation therapy was most consistently found to be associated with poor psychosocial outcomes such as problems with education and employment; the risk was increased for being unemployed, repeating a school grade, not entering college, the attendance of special education programs and antisocial behavior, which may influence the course of education and employment as well (Gurney et al. 2009; Lund et al. 2011). Other risk factors related to the treatment include hematopoietic cell transplant (de Boer et al. 2006; Lown et al. 2015) and intrathecal therapy, which both were associated with poorer educational achievement and the attendance to special education programs (Gurney et al. 2009, Lund et al. 2011).

Female survivors were found to be less likely to achieve higher educational outcomes and being at higher risk for unemployment (de Boer et al. 2006; Lund et al. 2011). Younger age at diagnosis was found to be associated with lower intelligence, poorer educational achievement, and higher risk of unemployment; again this effect was especially pronounced in CNS tumor survivors (Gurney et al. 2009, Lund et al. 2011). Survivors with pre-morbid learning difficulties, emotional difficulties, low income or education, younger age at diagnosis (de Boer et al. 2006, Lown et al. 2015), and chronic medical conditions (Gurney et al. 2009) were at higher risk for low education and poor employment status.

Survivors suffering from more somatic health problems, including late effects due to cancer and its treatment, were found to be at risk for failing a grade, achieve lower educational levels, more likely to be unemployed, and report a lower income (Lund et al. 2011). Interestingly, the effects were smaller in Europe compared to the effects found in the United States and Canada (Lund et al. 2011). Also the risk for survivors of becoming unemployed was higher in the United States compared to Europe. Explanations may be higher job rejection rates for cancer survivors in the United States and Canada, and generally less discrimination regarding cancer and better access to medical care in Europe (de Boer et al. 2006, Lund et al. 2011).

Psychological distress such as depression and anxiety, as well as physical performance limitations were found to be associated with lack of employment and low income as well as other difficulties with expected adult social roles (Gurney et al. 2009).

60.4 Conclusions

Childhood cancer survivors are faced with a high risk of late effects, not only medical conditions but, as we have shown, also neurocognitive and psychosocial problems are common. To detect and treat these late adverse outcomes early regular follow-up is important. Follow-up care for childhood cancer survivors adapted to their age and including transition to adult care is still not established comprehensively. However, standards for follow-up care childhood cancer have been developed, including the recently published standards for psychosocial follow-up (Lown et al. 2015). In addition, guidelines are currently being developed within the International Guidelines Harmonization Group (www.ighg.org). These guidelines will provide specific recommendations on who needs what kind of screening and follow-up care, and in which frequency. These standards and guidelines will help to provide adequate care for patients and survivors in all phases of their cancer trajectory, starting at diagnosis and leading long into adulthood. In the future, neurocognitive and psychosocial problems in survivors should thus be reduced and quality of survivorship further improved.

References

Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, Hudson MM, Donaldson SS, King AA, Stovall M, Krull KR, Robison LL, Packer RJ. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the

Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101:946–58.
Brown MC, Pearce MS, Bailey S, Skinner R. The long-term psychosocial impact of cancer: the views of young adult survivors of childhood cancer. Eur J Cancer Care. 2016;25(3):428–39.
Bruce M. A systematic and conceptual review of posttraumatic stress in childhood cancer survivors and their parents. Clin Psychol Rev. 2006;26:233–56.
Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol. 2005;30:65–78.
Butler RW, Copeland DR, Fairclough DL, Mulhern RK, Katz ER, Kazak AE, Noll RB, Patel SK, Sahler OJ. A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. J Consult Clin Psychol. 2008a;76:367–78.
Butler RW, Sahler OJ, Askins MA, Alderfer MA, Katz ER, Phipps S, Noll RB. Interventions to improve neuropsychological functioning in childhood cancer survivors. Dev Disabil Res Rev. 2008b;14:251–8.
de Boer AG, Verbeek JH, van Dijk FJ. Adult survivors of childhood cancer and unemployment: a metaanalysis. Cancer. 2006;107:1–11.
Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, Tersak JM, Ness KK. Social outcomes in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009;27:2390–5.
Hardy KK, Willard VW, Allen TM, Bonner MJ. Working memory training in survivors of pediatric cancer: a randomized pilot study. Psychooncology. 2013;22:1856–65.
Janzen L, Mabbott D, Guger SL. Neuropsychological outcomes in pediatric brain tumor survivors. In: Scheinemann K, Bouffet E, editors. Pediatric neuro-oncology. New York: Springer; 2015.
Kunin-Batson AS, Lu X, Balsamo L, Graber K, Devidas M, Hunger SP, Carroll WL, Winick NJ, Mattano LA Jr, Maloney KW, Kadan-Lottick NS. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: a prospective longitudinal study. Cancer. 2016;122(10):1608–17.
Lown EA, Phillips F, Schwartz LA, Rosenberg AR, Jones B. Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. Pediatr Blood Cancer. 2015;62(Suppl 5):S531–601.
Lund LW, Schmiegelow K, Rechnitzer C, Johansen C. A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions. Pediatr Blood Cancer. 2011;56:532–43.
Michel G, Rebholz CE, von der Weid NX, Bergstraesser E, Kuehni CE. Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor Study. J Clin Oncol. 2010;28:1740–8.
Mulrooney DA, Ness KK, Neglia JP, Whitton JA, Green DM, Zeltzer LK, Robison LL, Mertens AC. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep. 2008;31:271–81.
Nathan PC, Patel SK, Dilley K, Goldsby R, Harvey J, Jacobsen C, Kadan-Lottick N, Mckinley K, Millham AK, Moore I, Okcu MF, Woodman CL, Brouwers P, Armstrong FD. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. Arch Pediatr Adolesc Med. 2007;161:798–806.
Noll RB, Patel SK, Embry L, Hardy KK, Pelletier W, Annett RD, Patenaude A, Lown EA, Sands SA, Barakat LP, Committee, C. O. G. B. S. Children's Oncology Group's 2013 blueprint for research: behavioral science. Pediatr Blood Cancer. 2013;60:1048–54.
Phillips SM, Padgett LS, Leisenring WM, Stratton KK, Bishop K, Krull KR, Alfano CM, Gibson TM, de Moor JS, Hartigan DB, Armstrong GT, Robison LL, Rowland JH, Oeffinger KC, Mariotto AB. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. Cancer Epidemiol Biomark Prev. 2015;24:653–63.
Ullrich NJ, Embry L. Neurocognitive dysfunction in survivors of childhood brain tumors. Semin Pediatr Neurol. 2012;19:35–42.
Walter LM, Nixon GM, Davey MJ, Downie PA, Horne RS. Sleep and fatigue in pediatric oncology: a review of the literature. Sleep Med Rev. 2015;24:71–82.
Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, Mertens AC, Robison LL, Ness KK. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 2008;17:435–46.
Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JC, Lu Q, Krull K. Psychological status in childhood cancer survivors: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27:2396–404.

Key Reading

1. Bruce M. A systematic and conceptual review of posttraumatic stress in childhood cancer survivors and their parents. Clin Psychol Rev. 2006;26(3):233–56.
2. Lown EA, et al. Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. Pediatr Blood Cancer. 2015;62(Suppl 5):S531–601.
3. Lund LW, et al. A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may

challenge the conclusions. Pediatr Blood Cancer. 2011;56(4):532–43.
4. Nathan PC, Patel SK, Dilley K, et al. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer. Arch Pediatric Adolesc Med. 2007;161(8):798–806.
5. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27(14):2396–404.

Part XI

Endocrine Emergencies

Philip Yeoh and Anne Marland

Management of Hyponatraemia in Adults and Children

61

Phillip Yeoh and Anne Marland

Contents

61.1 **Introduction** 1165

61.2 **Definition of Hyponatraemia** 1165
61.2.1 Based on Biochemical Severity 1165
61.2.2 Based on Duration of Hyponatraemia 1165
61.2.3 Based on Symptoms (Box 61.1) 1166

61.3 **Adult Hyponatraemia** 1166
61.3.1 Symptoms of Hyponatraemia 1166
61.3.2 Causes of Hyponatraemia 1166
61.3.3 Hyponatraemia Caused by Plasma Tonicity 1169
61.3.4 Mortality Rate and Volume Status of Hyponatraemia 1169
61.3.5 Management of Acute and Chronic Hyponatraemia 1170
61.3.6 Diagnosis of Hyponatraemia 1170
61.3.7 Investigations of Hyponatraemia 1171
61.3.8 Treatment of Hyponatraemia in Adult Patients 1172
61.3.9 Challenges with Hyponatraemia Management in Clinical Settings 1174
61.3.10 Identifying the Gaps for Endocrine Nurses to Develop in the Management of Adult Hyponatraemia 1175

61.4 **Hyponatraemia in Children** 1177
61.4.1 Symptoms of Hyponatraemia 1177
61.4.2 Causes of Hyponatraemia 1177
61.4.3 Assessment for Hyponatraemia 1178
61.4.4 Management of Hyponatraemia 1178
61.4.5 Symptomatic Hyponatraemia with Seizures and/or Neurological Deterioration 1178
61.4.6 Hyponatraemia with No Symptoms 1179
61.4.7 The Role of the Endocrine Nurse in Paediatric Hyponatraemia 1179

61.5 **Conclusions** 1179

References 1179

P. Yeoh (✉)
The London Clinic, London, UK
e-mail: p.yeoh@thelondonclinic.co.uk

A. Marland
Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Churchill Hospital, Oxford, UK
e-mail: Anne.Marland@ouh.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_61

Abstract

Hyponatraemia is common in the hospital settings. This is one of the endocrine emergencies where poor diagnosis, treatment and management can have profound outcomes for this group of patients. The mortality rate of this group of patients consistently show poorer outcomes compared to other disorders. The Endocrine Society and European Society of Endocrinology recently published comprehensive and complex recommendations to guide clinicians and healthcare professions to adopt more cohesive strategies to deal with the challenging nature of this medical emergency. Implementation of these recommendations will require a systematic approach and team-effort to ensure these guidelines are translated in day-to-day use. Endocrine nurses, who often work closely with endocrine colleagues, need to understand the implication of these guidelines in their roles and duties. The first step requires an understanding of the diagnosis and treatment process to treat this condition then to follow up the support within the team to ensure the clinical management plan is executed in line with clinical guidelines. The cycle of audit plays an important role to ensure the guidelines are robust so that further changes may bring about better outcomes for patients with hyponatraemia.

Keywords

Hyponatraemia · Adult · Children · Clinical guidelines · Severity · Symptoms · Outcomes

Abbreviations

ACE	Angiotensin-converting enzyme
ADH	Anti-diuretic hormone
ARBs	Angiotensin-II receptor blockers
AVP	Arginine vasopressin
AVPR2	Arginine vasopressin receptor 2
CNS	Central nervous system
CT	Computer tomography
CXR	Chest X ray
ECF	Extracellular fluid
GCS	Glasgow Coma Score
GFR	Glomerular filtration rate
ICF	Intracellular fluid
K	Potassium
MAOi	Monoamine oxidase inhibitors
MRI	Magnetic resonance imaging
Na^+	Sodium
NaCl	Sodium chloride
NSAIDs	Non-steroidal anti-inflammatory drugs
ODS	Osmotic demyelinating syndrome
SIAD	Syndrome of inappropriate anti-diuretic hormone
SSRIs	Serotonin-selective reuptake inhibitors

Key Terms

- **Hyponatraemia:** Low sodium in serum. The interpretation is based on biochemical severity, duration of hyponatraemia and symptoms. Assessing volume status is an important step in differentiating the diagnosis of hyponatraemia.
- **Tonicity:** Tonicity is a property of a solution which is equal to the sum of the concentrations of solutes that have the capacity to exert an osmotic force across a semi-permeable membrane.
- **Osmolality:** This is a measure of the number of particles present in a solution and is independent of the size or weight of the particles.
- **Volume status:** Usually refers to extracellular volume which indicates the solute status.
- **Clinical guidelines:** Set of recommendations on diagnostic approach and treatment to guide clinical treat certain condition.

Key Points

- Hyponatraemia is a common electrolyte imbalance in the clinical setting and has shown frequent poor outcomes and consequences.

- Hyponatraemia is an independent predictor of mortality for patients in the hospital setting.
- Focus should be placed on initial assessment, history taking and accurately performed investigations which lead to an accurate diagnosis before a specific treatment algorithm is initiated.
- Clinical guidelines for hyponatraemia provide a better structure and management for this high risk group.
- Endocrine nurses in adult or paediatric settings play a key role through direct patient care, working with other nursing colleagues, adopting an educational role to raise awareness and risk of hyponatraemia, and to conduct clinical audit so that better process can be implemented in the management of patients with hyponatraemia.

61.1 Introduction

Hyponatraemia is defined as a low sodium in blood. It is a very common medical condition which occurs up to 30% of hospital admission (Upadhyay et al. 2009). Hyponatraemia is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a spectrum of conditions (Spasovski et al. 2014; Verbalis et al. 2013; Tzoulis et al. 2014a). It is usually caused by disturbance in ADH secretion leading to serum electrolyte imbalance. It is a common incidental finding on routine blood tests often presenting asymptomatically.

Clinical guidelines (Spasovski et al. 2014; Verbalis et al. 2013) are often complex and difficult for non-specialists to understand. Therefore the application by inexperienced practitioners in the clinical setting may be problematic. This chapter aims to simplify and bring together the key points from these clinical guidelines and to bring some focus for endocrine nurses to apply in their day-to-day roles and responsibilities.

This chapter is going to focus on:

- Outline and definition of hyponatraemia
- Causes and diagnosis
- Investigation and treatments according to clinical guidelines
- Role of the endocrine nurse in inpatient and outpatient settings

61.2 Definition of Hyponatraemia

The European Society of Endocrinology (Spasovski et al. 2014) and the Endocrine Society (Verbalis et al. 2013) clinical guidelines on diagnosis and treatment of hyponatraemia defined it as a serum sodium (Na^+) of less than 135 mmol/L. However, it is important to exclude spurious hyponatremia due to high lipid levels which may produce apparent hyponatraemia in some assays.

Classification of hyponatraemia is based on three factors:

61.2.1 Based on Biochemical Severity

(a) Mild hyponatraemia when the serum sodium concentration is 130–135 mmol/L.
(b) Moderate hyponatraemia when the serum sodium concentration is 125–129 mmol/L.
(c) Severe hyponatraemia when the serum sodium concentration is less than 125 mmol/L.

61.2.2 Based on Duration of Hyponatraemia

(a) Acute—duration of less than 48 h
(b) Chronic—duration of 48 h or more

61.2.3 Based on Symptoms (Box 61.1)

Box 61.1 Classification of Hyponatraemia Based on Symptoms

Moderately severe	Nausea without vomiting Confusion Headache Muscle cramp Feeling weak Gait disturbance, ataxia and falls Concentration and cognitive deficits Unspecific symptoms
Severe	Vomiting Drowsiness Coma Cardiopulmonary dysfunction Raised intracranial pressure symptoms Deep somnolence of Glasgow Coma Scale ≤8 Seizures
Moderately severe to severe symptoms may suggest a degree of brain oedema. This list is not exhaustive, all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia	

61.3 Adult Hyponatraemia

61.3.1 Symptoms of Hyponatraemia

In a recent study, looking at 147 patients with severe hyponatraemia (Krummel et al. 2016), hyponatraemia symptoms were collated and the results are shown in Table 61.1. The majority of patients in the lowest serum sodium group had symptoms with the highest in severe neurological symptoms such as seizures, coma and confusion. Krummel et al. (2016) were unable to find association between the severity of neurological symptoms and the timing of hyponatraemia as the prior serum values were not available. However, they found that severe neurological symptoms were more likely to develop within 24 h in the very acute hyponatraemia patients, which is 24 h earlier than in the clinical guidelines (Spasovski et al. 2014; Verbalis et al. 2013).

61.3.2 Causes of Hyponatraemia

Common causes of hyponatraemia are dilution effects, dehydration or drug induced. This can be multifactorial due to:

- Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)
- Heart failure
- Liver failure
- Kidney disease
- Gastrointestinal sodium loss in severe diarrhoea and vomiting
- Adrenal insufficiency
- High water low solute intake—primary polydipsia
- Cerebral salt wasting
- Medication induced
- Hypothyroidism

Table 61.1 presents the frequency of symptoms in patients presenting with hyponatraemia (Krummel et al. 2016).

Arginine vasopressin (AVP), also called vasopressin or ADH (anti-diuretic hormone), is a peptide and neurohypophysial (posterior pituitary) hormone found in most mammals. Its two primary functions are to retain water in the body and to constrict blood vessels.

In the kidney, it retains water by increasing the water permeability of the kidney's collecting duct and distal convoluted tubules in inducing translocation of aquaporin water channels located in the plasma membrane of collecting duct cells to increase water absorption.

At high levels, it also increases peripheral vascular resistance by constricting blood vessels leading to an increase in arterial blood pressure. Most of vasopressin is stored in the posterior pituitary to be released into the bloodstream, and it has a very short half-life of 5–10 min (Baylis 2002).

Inappropriate elevation of arginine vasopressin (AVP) plays a key role in most states of hyponatraemia. Its secretion is stimulated by a rise in serum osmolality through the activation of osmoreceptors in hypothalamus and baroreceptors pressure changes in the carotid sinus, aortic arch, cardiac atria and pulmonary venous system.

Table 61.1 Hyponatraemia and associated symptoms

	All patients *N* = 147	Na < 110 mmol/L *N* = 20	Na 110–115 mmol/L *N* = 41	Na 116–120 mmol/L *N* = 86
With symptoms (%)	83 (56.5%)	19 (95%)	23 (56.1%)	41 (47.7%)
Severe neurological symptoms Seizures (%) Coma (%)	13 (8.8%) 9 (6.1%) 4 (15.0%)	7 (35%) 4 (20%) 3 (15%)	2 (4.9%) 1 (2.4%) 1 (2.4%)	4 (4.7%) 4 (4.7%) 0 (0%)
Confusion (%)	42 (28.6%)	10 (50%)	11 (26.8%)	21 (24.4%)
Nausea/vomiting (%)	17 (11.6%)	3 (15%)	6 (14.6%)	8 (9.3%)
Gait disturbance/fall (%)	20 (13.6%)	4 (20%)	7 (17.1%)	9 (10.5%)
Other symptoms (%)	7 (4.8%)	2 (10%)	2 (4.9%)	3 (3.5%)

Adapted from Krummel et al. (2016)

Failure to suppress AVP secretion in response to a low serum sodium and osmolality will result in water retention and hyponatraemia if one has sufficient hypotonic fluid intake.

61.3.2.1 Syndrome of Inappropriate Diuretic Hormone Secretion (SIADH)

SIADH is defined as:

- Clinically euvolaemic
- Serum osmolality <270 mOsm/kg
- Inappropriately concentrated urine >100 mOsm/kg, usually >300 mOsm/kg
- Increased urine Na^+ (> 20 mmol/L)
- Normal adrenal and thyroid function

In normal physiology, when the serum concentration increases, it drives thirst and leads to drinking behaviour. Once the body fluids reach a certain concentration, it suppresses vasopressin secretion allowing aquaresis to prevent over hydration. In SIADH, although the total water is increased, it is not clinically observed as the water is distributed within intracellular and extracellular tissues. General anaesthesia, nausea, pain, stress and a variety of non-specific drugs can be a potent stimulus for vasopressin secretion and can cause SIADH. However, there are four patterns of SIADH:

(a) Type I
This is caused by excessive and erratic vasopressin secretion that are independent of changes in serum osmolality.

(b) Type II
This is caused by an osmoregulatory defect where water excretion continues despite a lowered plasma osmolality.

(c) Type III
Normal and appropriate osmoregulation of the hormone, but when there is a decrease in serum osmotic pressure there is a constant non-suppressible vasopressin secretion cause by neurohypophysial damage, loss of inhibitory osmoregulatory neurons or persistent non-osmotic stimulation.

(d) Type IV
Normal osmoregulated vasopressin secretion but patients still fulfil SIADH criteria. The defect may lie within the kidney.

SIADH can be caused by other conditions small cell lung cancer, gastrointestinal tract malignancy, drugs such as desmopressin, carbamazepine, pulmonary conditions such as pneumonia, tuberculosis, intracranial pathology such as brain tumours, meningitis and other conditions such as HIV and multiple sclerosis (Hannon and Thompson 2010).

61.3.2.2 Heart Failure

Heart failure can cause hyponatraemia in several ways:

(a) Atrial pressure is increased but the complex atrial-renal reflexes that modulate renal sodium and water excretion are blunted.

(b) High-pressure baroreceptors in the left ventricle, carotid body, aortic arch and juxtaglomerular apparatus are less stretched, leading

to increase adrenergic activity, renin secretion and non-osmotic AVP release.

(c) Heart failure patients often has severe renal vasoconstriction with a decrease GFR and alteration in peritubular Starling forces leading to enhanced tubular sodium and water reabsorption.

61.3.2.3 Liver Disease

(a) Advanced liver cirrhosis can lead to portal hypertension which in turn causes arterial vasodilation and a decrease in stretch receptors in carotids and aortic arch. This eventually leads to decrease in adrenergic activity, renin secretion and non-osmotic AVP release as described in Sect. 61.3.2.2.

61.3.2.4 Kidney Diseases

(a) Severe renal vasoconstriction with a reduction in GFR in chronic kidney diseases leads to enhanced sodium and water reabsorption.

(b) Nephrogenic syndrome of inappropriate antidiuresis secondary to a mutation in the arginine vasopressin receptor AVPR2 in renal tubules presented with hyponatraemia has recently been reported (Powlson et al. 2016). This is caused by the inability of these mutated AVPR2 to achieve appropriate antidiuresis.

61.3.2.5 Gastrointestinal Sodium Loss in Severe Diarrhoea and Vomiting

(a) In diarrhoea and vomiting, the body loses sodium through the gastrointestinal tract.

(b) If a patient ingests low sodium such as water, tea or toast, this will dilute the serum further leading to hyponatraemia.

61.3.2.6 Adrenal Insufficiency

(a) Low aldosterone in primary insufficiency causes renal sodium loss and leads to hyponatraemia.

(b) In secondary adrenal insufficiency, reduction or an absence of ACTH leads to low cortisol and this persistent low cortisol leads to a rise in vasopressin, in part due to a loss of blood pressure.

61.3.2.7 High Water Low Solute Intake: Primary Polydipsia

(a) Excess water intake overtakes what the kidney can eliminate and leads to 'wash out' in the renal tubules. Patients with profound hyponatraemia due to primary polydipsia were found to have high prevalence of psychiatric, addictive and affective disorders (Sailer et al. 2017).

61.3.2.8 Cerebral Salt Wasting

(a) The term above is referred to the syndrome of sodium loss from renal observed following head injury, subarachnoid haemorrhage, neurosurgery or intracranial disorders. The hyponatraemia is caused by the initial intravascular volume loss trigger a baroreceptor pressure changes and leads to AVP secretion. Currently, it is thought to be extremely rare.

61.3.2.9 Hypothyroidism

(a) Hyponatraemia caused by hypothyroidism is extremely rare and this may be referred to myxoedema in severe hypothyroidism in which the cardiac output may be compromised leading to disturbances in AVP release. In a recent study, among 576 inpatient admissions with euvolaemic hyponatraemia, no cases of hyponatraemia were diagnosed (Cuesta et al. 2016), and this was supported by findings of an earlier larger analysis (Croal et al. 1997). In a large national survey (Holland-Bill et al. 2015) of first-time acute admission over a 5-year period, only 12.9% patients presented with hypothyroidism. However, the severity hypothyroidism was not explored in this study.

61.3.2.10 Medication-Induced

Drug-induced hyponatraemia is well recognised as also reflected in clinical guidelines (Spasovski et al. 2014; Verbalis et al. 2013) and is summarised in Table 61.2.

Table 61.2 Medications which can induce hyponatraemia

Diuretics	– Thiazides (can cause even after chronic use), e.g. bendroflumethiazide – Thiazide-like, e.g. indapamide – Potassium-sparing, e.g. spironolactone, amiloride – Loop diuretics (usually only a contributory factor), e.g. furosemide
Antihypertensive drugs	– ACE inhibitors, e.g. ramipril, lisinopril – ARBs, e.g. losartan, candesartan
Antidepressants	– Tricyclic, e.g. amitriptyline, dosulepin – SSRI, e.g. citalopram, paroxetine – MAOi, e.g. venlafaxine
Anti-epileptic drugs	– Carbamazepine – Oxcarbazepine – Sodium valproate
Anti-psychotic drugs	– Phenothiazines, e.g. chlorpromazine, prochlorperazine – Butyrophenones, e.g. haloperidol
Anti-cancer drugs	– Platinum agents, e.g. cisplatin, carboplatin – Alkylating agents, e.g. cyclophosphamide, melphalan, ifosfamide
Miscellaneous	– Desmopressin, oxytocin – NSAIDs – Amiodarone – Sulfonylurea—glipizide, glibenclamide
Proton pump inhibitors	– Omeprazole, Pantoprazole

ACE inhibitors angiotensin-converting enzyme inhibitor, *ARBs* angiotensin-II receptor blockers, *SSRIs* serotonin-selective reuptake inhibitors, *MAOi* monoamine oxidase inhibitors, *NSAIDs* non-steroidal anti-inflammatory drugs

61.3.3 Hyponatraemia Caused by Plasma Tonicity

Basal serum osmolality varies between individuals in the range 280–295 mOsm/kg. However, abnormally high concentration of lipids or proteins in plasma can interfere with the accurate measurement of sodium which leads to the term pseudo-hyponatraemia. These interfering factors can include unmeasured solutes such as mannitol, urea, maltose, alcohol, intravenous immunoglobulins or radiographic contrast agents, rendering the diagnosis of hyponatraemia extremely challenging in some clinical settings.

61.3.4 Mortality Rate and Volume Status of Hyponatraemia

In a study (Tzoulis et al. 2014a) looking at the mortality rate in a general hospital for 139 hospitalised patients with a serum sodium ≤128 mmol/L, patients with hyponatraemia had an inpatient mortality rate of 17.3% and were more than three times more likely to die during their hospital stay compared with controls. In a larger survey (Holland-Bill et al. 2015) involving first-time admissions in Denmark, the prevalence of admission with hyponatraemia was 15% (41,803 patients). Thirty-day mortality was 3.6% in normonatraemic patient, whereas patients with various degrees of hyponatraemia ranges had mortality rates between 7.3 and 10.4%. The mortality risk was increased across all clinical subgroups and remained increased by 30–40% over 1 year. These data are similar to another observational (Kuramatsu et al. 2014) study involving 464 patients conducted in a single US hospital over a 5-year period where the prevalence of hyponatremia on hospital admission was 15.6%. The inpatient mortality rate was 2.5-fold increase compared with non-hyponatraemia patients.

In an attempt to understand the mortality rate among SIADH, hypovolaemic and hypervolaemic hyponatraemia patients (Cuesta et al. 2017), 1323 admissions within these 3 groups were studied. Hyponatraemia groups had a higher mortality rate of 9.1% compared to a normal control group of 3.8%. In addition, hyponatraemic patients with SIADH had a lower mortality than patients with hypovolaemic and hypervolaemic hyponatraemia. The study also concluded that hypervolaemic hyponatraemia patient has the highest risk ratio of 4.9. Both hypovalaemic and hypervolaemic hyponatraemia patients had higher mean and SD scores in Charlson

Comorbidity Index which predicts 1 year mortality for a patient who may have a range of comorbid conditions. The study also reflects that mortality is likely linked to the severity of the underlying disease processes leading to the development of hyponatraemia.

61.3.5 Management of Acute and Chronic Hyponatraemia

The management of acute and chronic hyponatraemia is essayed in the European Society of Endocrinology clinical guidelines (Spasovski et al. 2014) and the Endocrine Society clinical guidelines (Verbalis et al. 2013). In acute hyponatraemia where brain cell swells too quickly, the brain's ability to adapt is impaired and this results in brain oedema with the risk of brain herniation. Conversely, in chronic hyponatraemia where the hyponatraemia develops over several days, brain cells have more time to extrude organic solutes allowing intracellular and extracellular osmolality to equalise without a large increase in cell water. Therefore, rapid overcorrection of chronic hyponatraemia can lead to neurological sequelae caused by the osmotic demyelination syndrome, previously known as pontine or extrapontine myelinolysis (Corona et al. 2014). The osmotic demyelination syndrome is the breakdown of myelin sheath which insulates individual neurons. Clinically, it can manifest with hypotonia, tremors and involuntary muscle spasm.

61.3.6 Diagnosis of Hyponatraemia

A group of experienced UK clinicians recommended (Grant et al. 2015) that a thorough clinical examination to access the patient's hydration status and some basic blood and urine tests are essential in elucidating the cause of hyponatraemia and guide its clinical management. They also recommended five key steps before commencing on treatment:

(a) Making the right diagnosis
This begins with a good clinical history and examination.

(b) Baseline investigations
It is important to consider the possible causes listed in Sect. 61.3.2. It has been reported that under-investigation is a common occurrence in clinical practice (Tzoulis et al. 2014b). Table 61.3 showed the gaps of investigation for hyponatraemia in three separate studies. Each of them shows the shortfalls addressed by clinical guidelines (Spasovski et al. 2014; Verbalis et al. 2013).

(c) Consider the context
Knowing certain conditions that may inform the diagnosis

(d) Assess hydration status
Clinical assessment to define if patient is hypovolaemic, hypervolaemic or euvolaemic has impact of the diagnosis and management of hyponatraemia (Table 61.4). However, in practice this is both challenging and inconsistent even with experienced clinicians as it has low sensitivity and specificity (Hoorn and Zietse 2017). A recent study found the clinical assessment of volume status was documented in 62/100 (62%) cases (Tzoulis et al. 2014b). Grant et al. (2015) suggested that if unsure of a patient's volume status one could infuse 0.9% normal saline 1 L over 12 h as a trial with a strict monitoring of serum sodium 6 hourly; hypovolaemic patients will respond well, whereas SIADH patient will usually not improve.

Table 61.3 Investigation and assessment of patients with hyponatraemia during admission

Investigation	Tzoulis et al. (2014b) (%)	Krummel et al. (2016) (%)	Cuesta et al. (2016) (%)
Volume status	62		
Serum osmolality	39	34	
Urine osmolality	33		86
Urine sodium	29		86
Paired osmolality—sodium	23		
Serum TSH	61	48.9	91
Serum cortisol	31	17.6	84
Full work-up	18		
Expert input	16		

(e) Acute severe hyponatraemia
This is a medical emergency and should be treated immediately without delay for the diagnosis of the cause of hyponatraemia.

61.3.7 Investigations of Hyponatraemia

Following the diagnosis of hyponatraemia, there are some important blood biochemistry screening and urine screening tests. Glucose, lipids, cortisol, thyroid function, liver function, serum osmolality, urine osmolality, urine sodium and potassium. This information can help to differentiate the underlying causes of hyponatraemia. It is essential to take into account all causes of hyponatraemia including the possible interference including volume status on examination (Hannon and Thompson 2010; Cuesta et al. 2017) as listed in Table 61.4 below.

Key Assessments and Tests for Hyponatraemia

- History taking: symptoms, underlying condition, common precipitants
- Examination: establishing the fluid status
- Screening panels: glucose, lipids, cortisol, thyroid function, liver function, plasma osmolality, urine osmolality, urine sodium and potassium
- Other investigations as indicated: CXR, Synacthen test (also called ACTH, cosyntropin or tetracosactide test), CT head

Further Tests That May Be Needed

- Check plasma ACTH if suspected of adrenal insufficiency
- May (rarely) require Glucagon test or Insulin Stress Test to diagnosis secondary adrenal insufficiency or hypopituitarism (Cuesta et al. 2016).
- Water deprivation or prolonged water deprivation if has mild hyponatraemia or suspect of primary polydipsia.
- Water load test has been described for patient with intermittent hyponatraemia with nephrogenic syndrome of inappropriate antidiuresis (Powlson et al. 2016).
- In the case of suspected osmotic demyelination syndrome, MRI of the brain may reveal the condition (Corona et al. 2014).

Table 61.4 Differential diagnosis by volume status

Hypovolaemic (hyponatraemia with decreased ECF volume)		Euvolaemic (hyponatraemia with normal ECF volume)		Hypervolaemic (hyponatraemia with increased ECF volume)	
Reduced skin turgor, dry membranes, tachycardia, low BP or postural hypotension		Underlying illness		Oedema, raised JVP, ascites, pulmonary oedema, underlying illness	
Urinary Na >20 mmol/L	Urinary Na <20 mmol/L	Urinary Na >20 mmol/L	Urinary Na <20 mmol/L	Urinary Na >20 mmol/L	Urinary Na <20 mmol/L
Renal losses – Osmotic diuresis – Diuretic therapy – Addison's disease – Salt-losing nephropathy – Cerebral salt wasting – Ketonuria	Extra-renal losses – Diarrhoea – Vomiting – Burns – Fistulae – Pancreatitis – Mucosal loss – Sodium depletion post-diuretics	– SIADH – Secondary adrenal insufficiency – Addison's disease (with secondary ADH response)—hypothyroidism – Diuretic therapy – Drugs	ECF loss with inappropriate fluid replacement	– Acute or chronic renal failure – Diuretic therapy for heart failure	– Nephrotic syndrome – Cirrhosis – Cardiac failure

Adapted from Hannon and Thompson (2010)

61.3.8 Treatment of Hyponatraemia in Adult Patients

Acute and severe symptoms at presentation, particularly when significant neurological symptoms listed are present, constitutes a medical emergency and treatment should be instigated immediately.

61.3.8.1 General Rules of Treatment for Hyponatraemia

The following general rules apply in the treatment of hyponatraemia (Spasovski et al. 2014; Verbalis et al. 2013; Grant et al. 2015).

Box 61.2 General Rules of Treatment for Hyponatraemia

Management is determined by:

- Severity of symptoms—GCS scores ≤8 is classified as severe.
- Acute or chronic: acute hyponatraemia <48 h; chronic hyponatraemia >48 h
- If unsure of status, follow severe hyponatraemia algorithm.
- Intravascular volume: Decide if patient is hypovolaemic, euvolaemic or hypervolaemic.

In all patients

- Determine the rates of correction.
- Stop any offending medications and recheck serum sodium.
- Treat underlying cause.
- Review volume status, see Table 61.2 and check urinary sodium.
  If patient is hypovolaemic, start 0.9% normal saline.
  If patient is hypervolaemic, treat underlying causes.
- If patient is euvolaemic, determine if hypotonic hyponatraemia by checking serum and urine osmolality.
  - If serum osmolality >275 mOsm/kg, consider causes of hypertonic hyponatraemia such as hyperglycaemia or mannitol infusion/hypertonic radiocontrast.
  - If urinary osmolality <100 mOsm/kg, consider primary polydipsia and other causes.
  - If serum osmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg, urinary sodium >20 mmol/L likely caused SIADH; please see section of SIADH below.
  - If plasma osmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg, urinary sodium <20 mmol/L, reconsider the volume status as this may reflect intravascular volume depletion.
- First-line treatment Free water fluid restriction (no water consumption and IV fluids unless hypovolaemic with acute hyponatraemia, then start with 0.9% saline).
- Specialist review.
- Transfer to high dependency unit.
- Check serum sodium 6 hourly and adjust trend.
- Safe limited no more than 10 mmol/L in first 24 h then 8 mmol/L in the subsequent 24 h (18 mmol/L in 48 h) aiming to achieve serum sodium of 130 mmol/L.

Exclude other possible aetiologies for a definitive diagnosis.

SIAD and Treatment

- First-line treatment free water fluid restriction.
- Second-line treatment with tolvaptan 7.5–15 mg as a single dose.
- Tolvaptan binds and blocks the V2 receptor to correct hyponatraemia in SIADH.
- Before tolvaptan is initiated to treat SIADH, it is essential that patients are allowed to drink in response to thirst. Check serum sodium 6 hourly to exclude rapid correction.
- Demeclocycline is used to treat hyponatraemia associated with SIAD secondary to malignant disease. It causes nephrogenic diabetes insipidus in 60% of patients and causes nephrotoxicity in patients with liver cirrhosis. The onset of action is unpredictable and normally takes 2–5 days. It is started at 150 mg thrice daily assessed in 3 days and increased if needed.

61.3.8.2 Management of Patients with Severe Symptomatic Hyponatraemia

Box 61.3 presents details on the management of hyponatraemia based on European and US/Canada guidelines (Spasovski et al. 2014; Tzoulis et al. 2014a).

Box 61.3 Management of Patients with Severe Symptomatic Hyponatraemia

If patient presents with CNS disturbance, confusion, headache, drowsiness, coma/altered GCS, seizure or encephalopathy, start the following treatment immediately.

- Secure airway
- Obtain intravenous access
- Draw baseline Na
- Instigate a close monitoring environment when starting hypertonic infusion

UK and EU guidelines for all acute or chronic severe symptomatic hyponatraemia:

- Within first hour, begin administration of 150 mL hypertonic 3% saline infusion intravenously over 20 min then check serum sodium.
- Repeat after 20 min if no clinical improvement while waiting for serum sodium.
- Repeat twice on the above regimen if no clinical improvement or until 5 mmol/L increase in serum sodium.
- Follow up management after 5 mmol/L rise in serum sodium and improvement in symptoms:
  Stop hypertonic saline infusion.
  Keep intravenous line open minimum volume 0.9% normal saline.
  Start diagnosis-specific treatment.
  Limit increase of serum sodium to 10 mmol/L first 24 h then no more than 8 mmol/L in subsequent 24 h thereafter until serum sodium reaches 130 mmol/L.
  Recheck serum sodium at 6 h, 12 h and daily until stable under stable treatment.
- Follow up management after 5 mmol/L rise in serum sodium and **NO** improvement in symptoms:
  Continue hypertonic 3% saline infusion or equivalent aim for additional 1 mmol/L increase in serum sodium.
  When symptoms improved, serum sodium concentration increases to 10 mmol/L in total or reaches 130 mmol/L (whichever is first), stop hypertonic 3% saline infusion.
  Explore other causes of symptoms.

Check serum sodium concentration every 4 h as long as an intravenous infusion hypertonic 3% saline or equivalent is continued.

UK and EU guidelines for over correction of hyponatraemia:

- Intervene for re-lowering the serum sodium concentration if it increases >10 mmol/L during the first 24 h or > 8 mmol/L in any 24 h thereafter.
- Discontinue ongoing active treatment.
- Consult an expert to discuss if it is appropriate to start an infusion of 10 mL/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance.
- Consult an expert to discuss if it is appropriate to add intravenous desmopressin 2 μg with the understanding that this should not be repeated more frequently than every 8 h.

US, Canada and Australia guideline for acute symptomatic hyponatraemia

- For severe symptoms:
- 100 mL of hypertonic 3% saline infused over 10 min, repeat three times as needed.
- For mild to moderate symptoms with a low risk of herniation:
- Hypertonic 3% saline infused at 0.5–2 mL/kg/h.
- The rate of correction need not be restricted in patients with true acute hyponatraemia nor in reducing the over correction. Follow the chronic hyponatraemia regimen if not certain if the hyponatraemia is acute or chronic.

US, Canada and Australia guideline for chronic symptomatic hyponatraemia in order to avoid ODS

- Determine high risk factors of putting patients of developing osmotic demyelinating syndrome:
- Serum sodium concentration of ≤105 mmol/L, hypokalaemia, alcoholism, malnutrition, and advanced liver disease.
- Determine if patient is in high risk group if has serum sodium concentration of ≤120 mmol/L over 48 h.
- Minimise correction of serum sodium by 4–8 mmol/L/day with a lower goal of 4–6 mmol/L/day if risk of ODS is high.
- High risk of ODS: 8 mmol/L in any 24 h period.
- Normal risk of ODS: 10–12 mmol/L in any 24 h period, 18 mmol/L in any 48 h period.

61.3.9 Challenges with Hyponatraemia Management in Clinical Settings

There are challenges in implementing the hyponatraemia clinical guidelines in real-world settings. Table 61.3 summarised the three prospective and retrospective studies looking at hyponatraemia patients' biochemical markers and assessment during their admissions.

From the Table, there are clear clinical shortfalls in the investigations and management of patients with hyponatraemia. Both studies by Krummel et al. (2016) and Tzoulis et al. (2014b) were retrospective studies, but Cuesta et al. (2016) was a prospective study involving a specific IT software to alert principle investigator when serum sodium decreased fall into the hyponatraemia inclusion criteria. Despite the extra effort by Cuesta et al. (2016), 17% of the criteria required for the study were not obtained despite requests. These frustrations and concerns were shared recently (Gleeson et al. 2016) that knowledge on how to manage diabetes insipidus in health is limited to endocrine outpatient settings, whereas inpatient care will expose these patients to a range of medical staff with no

expertise in this area. They highlighted that in a recent audit of 17 admissions for 8 patients with diabetes insipidus, 88% of these patients had 39 missed/delayed dose of desmopressin and concomitant administration of hydrocortisone was missed in 35.7% admission. Urinary sodium, one of the most important biochemical tests in investigation of hyponatraemia, was measured in less than one-third of cases (Tzoulis et al. 2014b). The data has also shown 63.1% of patients being discharged with persistent hyponatraemia. The complex hyponatraemia management hurdle is not going to be solved by an endocrine team. There is also the challenge of implementing fluids restriction regimen for these ward-based patients in concordance with clinical guidelines.

The Endocrine Society clinical guidelines make the following recommendation for fluid restriction:

- Restrict all fluid intake.
- Aim for a fluid restriction that is 500 mL/day below the 24 h urine volume.
- Do not restrict sodium or protein intake unless indicated.

They also make the following recommendation that could predict the likely failure of fluid restriction:

- High urine osmolality of over 500 mOsm/kg H_2O.
- Sum of the urine sodium and potassium concentration exceed the serum sodium concentration.
- 24 h urine volume of less than 1500 mL/day.
- Increase in serum sodium concentration of less than 2 mmol/L/day in 24–48 h on a fluid restriction of ≤1 L/day.

However, more data is needed to understand if these recommendations are transferable into clinical settings. More importantly, how these guidelines and recommendations are going to be executed, what processes need to put in place to ensure the guidelines are followed and how is it going to affect patient outcomes.

61.3.10 Identifying the Gaps for Endocrine Nurses to Develop in the Management of Adult Hyponatraemia

Clinical guidelines have made recommendations to improve clinical practice. In order to translate clinical guidelines into clinical setting, there should be a system in place in hospital to identify patients with hyponatraemia so that the right treatment plan can be instigated. Table 61.3 has shown when a group of patients with hyponatraemia are identified in clinical setting by an admission pathway (Cuesta et al. 2016) and seen by someone who has experience in hyponatraemia within 48 h of development of hyponatraemia, there is a higher rate of investigations and assessments conducted compared to the other two groups (Krummel et al. 2016; Tzoulis et al. 2014b) where hyponatraemia data was collected retrospectively.

Most of the endocrine services are outpatient based but still need to provide inpatient support for patients presented with endocrine issues, as in Table 61.5 patients with hyponatraemia are admitted in various inpatient areas (Tzoulis et al. 2014a). From the evidence presented in this chapter, there are several conclusions and recommendations that can be drawn from these data:

- The endocrine nurse can provide help and support to endocrine colleagues to make an accurate diagnosis and improve management of hyponatraemia through:
  <u>Immediate response during acute hyponatraemia phase:</u>
  (a) Collect relevant screening panels for glucose, lipids, cortisol, thyroid function, liver function, plasma osmolality, urine osmolality, urine sodium and potassium.
  (b) Liaise with the lab for urgent results turnaround.
  (c) Ensure observations including GSC scores are taken when the patient presents in the outpatient endocrine unit.
  (d) Admit patient as an emergency and refer the patient to an endocrine specialist for further investigation and management.

(e) Liaise with the ward staff to ensure clinical management plan is followed including a strict fluid restriction management.
(f) Work closely with inpatient colleagues to monitor patient progress.
(g) Ward-based teaching to educate ward-based staff the implications of hyponatraemia, how it is treated and outcomes of these patients.
(h) Support the patient and carer through patient education on hyponatraemia and support their clinical management plan before and after patient's discharge from hospital.

Post-acute phase:

(a) Carry out further endocrine test such as Synacthen test, water load test, water deprivation test, prolonged water deprivation or other diagnostic procedures such as Glucagon or Insulin Stress Test to check if patient has secondary adrenal insufficiency.
(b) If the patient is diagnosed with adrenal insufficiency, patient, carer and family member will require sick-day rule training on teaching patient, carers and family to manage adrenal insufficiency on day-to-day basis, as well as during sick-day management. More information on sick-day rules is covered in adrenal section in Part V and in adrenal crisis section of this chapter.
(c) If the patient requires a Synacthen test, water load test, water deprivation test or prolonged water deprivation test to further investigate the cause of hyponatraemia, this must be explained verbally and in writing to the patients. These clinical tests have clinical procedures to follow; however, this will not be addressed in this chapter as there are several versions of this procedure available online (Barts Endocrine Protocols 2009; Endocrinology handbook endocrine unit Imperial 2016).

Inpatient and outpatient support for patients with hyponatraemia

In a retrospective audit (Behan et al. 2015) looking at the frequency and impact of abnormal serum sodium among cranial diabetes insipidus patients with normal and abnormal thirst in an inpatient and outpatient setting, 77% of the neurosurgical inpatient admissions and 60% of the non-neurosurgical admission as well as 40% outpatient patients had hyponatraemia. This data shows that more efforts are needed to educate healthcare professionals in hospital settings, both in inpatient and outpatient, to be more aware of the risks exposed by patients with hyponatraemia. Endocrine nurses have educator role to address the risk of hyponatraemia in hospital setting, just like the diabetes nurse has education role in improving the care of diabetes patients in hospital. However, in practice, endocrine nurses have to cover for so many diseases within endocrine system in their patient care, getting the opportunity to address this shortfall requires imagination and careful thought. Cuesta et al. (2016) had shown if endocrine team can utilise an IT system to identify patients with hyponatraemia in hospital settings, it led to better screening and allowed an earlier interventions on these patients. There are several roles for endocrine nurses in neurosurgical and non-neurosurgical hospital setting:

(a) Support the patient who has surgery-induced hyponatraemia; this will include follow-up appointments for blood tests for electrolytes and assessment, liaise with primary care or General Practitioners to provide the necessary continuity of treatment and care.
(b) Patient and carers need to be aware of signs of hyponatraemia such as excessive drinking, polyuria and symptoms such as headache, feeling unwell or changes in neurological status. Patient and carers need to understand this requires emergency attentions and seek medical help immediately.
(c) Patients with abnormal thirst and cranial diabetes insipidus-treated desmopressin are also more likely to develop hypernatraemia when attending outpatient clinics

(Behan et al. 2015). Endocrine nurse clinic needs to be aware of these risks where patients can present with hypernatraemia and lethargy, irritability, ataxic, tremor, hyperreflexia, seizures and reduced GCS. Treatment must be instigated immediately with support from endocrine or emergency team.

Strategic role in safeguarding hyponatraemia patients in hospital through audits

This role includes conducting audits to look at the risks involved in patients with hyponatraemia, similar to various studies involving audits and retrospective methods looking at hyponatraemic patients' outcomes. However, in order to avoid replication, endocrine nurses can focus on areas such as policies, processes and procedures to see how to improve and build on this, to other endocrine emergencies such as adrenal crisis, thyroid storm or thyrotoxicosis and pituitary apoplexy. As health is dynamic, implementation of the audit findings need to be re-evaluated and re-audited as necessary and interventions as well as outcomes need to be captured and shared through publication so that endocrine communities can improve the outcomes for this rare endocrine condition.

All these service improvement initiatives require service investment, which means investing in more endocrine doctors and nurses. Clinical audit is a useful way to identify shortfalls in service and make a case for extra resources. This commitment must be part of the long-term organisational strategy to improve patients' outcomes and part of the continuous service improvement plan.

61.4 Hyponatraemia in Children

61.4.1 Symptoms of Hyponatraemia

Most children with mild to moderate hyponatraemia are asymptomatic, particularly when slow in onset. However, a child with hyponatraemia can present with nausea, vomiting, crying, headache, lethargy/irritability, hyporeflexia, an altered level consciousness and, in very severe cases, seizures and cardiopulmonary arrest. However, the early signs and symptoms of acute hyponatraemia are often non-specific. Healthcare professionals may attribute this to effects of surgery, anaesthetics, opioid medications or the underlying disease. Hyponatraemia with severe symptoms, or acute hyponatraemic encephalopathy, is a medical emergency and a child must be seen and managed immediately.

61.4.2 Causes of Hyponatraemia

Common causes of hyponatraemia in children are dilution effect, dehydration or drug induced. This can be multifactorial due to:

Iatrogenic:	Intravenous fluid administration such as hypotonic solutions
	Excessive water intake
	Diluted formula feeds
	Drug-induced
SIADH	Syndrome of inappropriate antidiuresis
GI loss	Gastrointestinal sodium loss in severe diarrhoea and vomiting
Extra-renal losses	Skin (sweating or burns)
Renal losses	Cerebral salt wasting, absence of aldosterone or lack of effect (e.g. 21-hydroxylase deficiency)
Other	Heart failure, liver failure, adrenal insufficiency, diabetic ketoacidosis

Table 61.5 Patient distribution for hyponatraemia was found in these specialties

Medical Specialty (77%)	Geriatrics 16.5% Oncology 8.6% Neurology 5% Haematology 2.2%	Hepatology 14.4% Cardiology 5.8% Gastroenterology 2.9% Infectious disease 0.7%	General medicine 13.7% Nephrology 5% Respiratory 2.2%
Surgical Specialty (19.4%)	Orthopaedics 5.8% Urology 2.9% Obstetrics 0.7%	General surgery 4.3% Vascular surgery 2.2%	Hepatobiliary 2.9% Plastic surgery 0.7%
ICU 2.2%	Accident and emergency 1.4%		

Adapted from Tzoulis et al. (2014a)

It has now been recognised that administering hypotonic solutions put children at a greater risk of developing life-threatening hyponatraemia than other types of fluid and should always be prescribed with caution (Medicines and Healthcare products Regulatory Agency 2012; Foster et al. 2014). Several national agencies have put up safety bulletin alerts (Foster et al. 2014; NPSA 2009; Koczmara et al. 2010), but this unnecessary death is still occurring. With hypotonic solution administration, the brain cells are unable to compensate for the rapid decrease in serum osmolality. The brain's ability to adapt is impaired and this results in brain oedema with the risk of brain herniation. Children exhibit symptoms more quickly than adults in response to abnormal sodium levels as there is less room for brain cells to swell.

Impaired free water excretion and high antidiuretic hormone levels caused by infections such as meningitis, encephalitis, sepsis, pneumonia, surgery, pain, nausea and vomiting are contributory factors to hyponatraemia. In children taking desmopressin for nocturnal enuresis, excess fluid intake can also lead to hyponatraemia.

61.4.3 Assessment for Hyponatraemia

Assessment of a child involves the points raised in the adult section of this chapter. This also includes full physical and biochemical assessment. Assessment of a child's hydration status is mandatory, as well as serum sodium, potassium, chloride, urea, glucose and osmolality, plus urinary sodium and osmolality.

61.4.4 Management of Hyponatraemia

There is no clinical guidelines for hyponatraemia specifically for a paediatric setting. However, the general principle from the clinical guidelines can be adapted. There are several important rules and precaution steps to be taken (NPSA 2009):

(a) Never routinely give any hypotonic solutions such as 0.18% sodium chloride (NaCl) with 4% glucose from stock level and general use to treat children. They must be removed and replaced with suitable alternative intravenous infusions. There should be restricted availability of these intravenous infusions to critical care and specialist areas such as renal, liver and cardiac units.
(b) Use 0.9% NaCl or 5% glucose as maintenance fluid.
(c) Prescribed fluids must be given the same considerations as other medicines with reference to dose, indications, contraindications, monitoring and most importantly volume.
(d) Whichever fluid is used, monitor serum sodium concentration regularly to avoid hypo- or hypernatraemia.
(e) Give enteral feeds where possible as fluid replacement, and the volume given should be included in fluid intake calculation.
(f) Put in place local clinical guidelines for the management of paediatric hyponatraemia including the fluid management protocol.
(g) Ensure guidelines are complied with by ensuring adequate training and supervision for all staff involved in the prescribing, administering and monitoring of intravenous infusions for children.
(h) Encourage hospital-acquired hyponatraemia incidents reporting via local reporting systems.

61.4.5 Symptomatic Hyponatraemia with Seizures and/or Neurological Deterioration

(a) Follow local emergency procedure to secure airway, breathing and circulation by involving the local emergency or resuscitation team. Hyponatraemia often responds poorly to standard anticonvulsants and do not delay sodium correction. Notify the intensive care unit and arrange for transfer as soon possible.

The golden rule is do not over treat hyponatraemia.

(b) Follow the local policy of NaCl replacement for hyponatraemia. Measure serum sodium at set intervals once correction has commenced.
(c) Investigate the cause of hyponatraemia and treat accordingly.

61.4.6 Hyponatraemia with No Symptoms

The management is influenced by a child's hydration status which can be influenced by underlying causes such as gastroenteritis, diarrhoea and vomiting. It is important to avoid over-rapid correction and allow plasma sodium concentration to rise no more than 8 mmol/L/day, aiming for correction to 135 mmol/L. This can be achieved by fluid restriction to increase the rise of serum sodium. If a child has moderate dehydration and serum sodium 130–135 mmol/L, try nasogastric rehydration. If a child has severe dehydration, give 0.9% NaCl until the child can take enteral feeds and measure electrolyte 4 hourly until stable. If hyponatraemia is caused by hyperglycaemia, correction of blood glucose should correct hyponatraemia. If hyponatraemia persists despite glucose correction, 0.9% NaCl should be used to correct hyponatraemia.

61.4.7 The Role of the Endocrine Nurse in Paediatric Hyponatraemia

The role of the endocrine nurse in paediatric setting for hyponatraemia is similar to the one listed in the adult section of this chapter. However, it has been recommended that clinical guidelines need to be put in place to ensure the safety of a child is maintained in hospital setting (NPSA 2009). This includes working closely with ward staff to ensure hypotonic solution is only made available to clinical areas such as intensive care, renal, liver and cardiac units. Endocrine specialist nurse in paediatric setting can also raise the awareness on the risk of hyponatraemia in paediatric setting by working closely with ward staff by providing them with training and support. Clinical audit is an effective way to assessment if the paediatric hyponatraemia clinical guideline is followed and well implemented.

61.5 Conclusions

The management of the patient with hyponatraemia is often a team approach, and the endocrine nurse must safeguard the well-being of the patient, by working closely with their endocrine colleagues. In paediatric setting, hyponatraemia can be minimised and in some cases avoided. Healthcare professionals need to be aware of this risk when caring for a child who can present with hyponatraemia due to surgical or medical interventions.

Most evidence suggests that over-enthusiastic treatment of hyponatraemia is considerably more dangerous than treatment that is slow or relatively ineffective in the case of mild or moderate hyponatremia. However, a collective team approach coupled with awareness of clinical guidelines and executing a clear clinical management plan will undoubtedly lead to more desirable patient outcomes.

References

Barts Endocrine Protocols. 2009. http://www.bartsendocrinology.co.uk/resources/PITUITARY_Barts_protocol_$5Bfinal$5D.pdf

Baylis PH. Posterior pituitary (Chapter 7). In: Besser GM, Thorner MO, editors. Comprehensive clinical endocrinology. 3rd ed. Philadelphia: Elsevier Science; 2002. p. 85–101.

Behan LA, Sherlock M, Moyles P, Renshaw O, Thompson CJT, Orr C, Holte K, Salehmohamed MR, Glynn N, Tormey W, Thompson CJ. Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study. Eur J Endocrinol. 2015;172:243–50.

Corona G, Simonetti L, Giuliani C, Sforza A, Peri A. A case of osmotic demyelination syndrome occurred after the correction of severe hyponatraemia in hyperemesis gravidarum. Endocr Disord. 2014;14:34. http://biomedcentral.com/1472-6823/14/34

Croal BL, Johnston AM, Glen ACA, O'Reilley DSJ. Absence of relation between hyponatraemia and hypothyroidism. Lancet. 1997;350:1402.

Cuesta M, Garrahy A, Slattery D, Gupta S, Hannon AM, Forde H, McGurren K, Sherlock M, Tormey W, Thompson CJ. The contribution of undiagnosed adrenal insufficiency to euvolaemic hyponatraemia: results of a large prospective singe-centre study. Clin Endocrinol. 2016;85:836–44.

Cuesta M, Garrahy A, Slattery D, Gupta S, Hannon AM, McGurren K, Sherlock M, Tormey W, Thompson CJ. Mortality rates are lower in SIAD, than in hypervolaemic or hypovolaemic hyponatraemia: results of a prospective observational study. Clin Endocrinol. 2017;5:1–7. https://doi.org/10.1111/cen.13388.

Endocrinology handbook endocrine unit Imperial. 2016. http://gim.org.uk/Bible2016.pdf

Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. J Pediatr. 2014;165(1):163–9.e2. https://doi.org/10.1016/j.jpeds.2014.01.040. Epub 2014 Feb 28.

Gleeson H, Bonfield A, Hackett E, Crasto W. Concerns about the safety of patients with diabetes insipidus admitted to hospital. Clin Endocrinol. 2016;84:946–51. https://doi.org/10.1111/cen.13028.

Grant P, Auk J, Bouloux PM, Cohen M, Cranston I, Murray RD, Rees A, Thatcher N, Grossman A. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015;45(8):888–94. https://doi.org/10.1111/eci.12465. Epub 2015 Jun 28.

Hannon MJ, Thompson CJ. The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences. Eur J Endocrinol. 2010;12:S5–S12.

Holland-Bill L, Christiansen CF, Heide-Jorgensen U, Ulrichen SP, Ring T, Jorgensen JOL, Sorensen HT. Hyponatremia and mortality risk: a Danish cohort study of 279508 acutely hospitalized patients. Eur J Endocrinol. 2015;173:71–81.

Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. J Am Soc Nephrol. 2017;28:1–10.

Koczmara C, Wade A, Skippen P, Campigotto MJ, Streitenberger K, Carr R, Wong E, Robertson K. Hospital-acquired acute hyponatremia and reports of pediatric deaths. Dynamics. 2010;21(1):21–6. https://www.researchgate.net/publication/42540087_Hospital-acquired_acute_hyponatremia_and_reports_of_pediatric_deaths

Krummel T, Prinz E, Metten MA, Borni-Duval C, Bazin-Kara D, Charlin E, Lessinger JM, Hannedouche T. Prognosis of patients with severe hyponatraemia is related not only to hyponatraemia but also to comorbidities and to medical management: results of an observational retrospective study. BMC Nephrol. 2016;17:159. https://doi.org/10.1186/s12882-016-0370-z.

Kuramatsu JB, Bobinger T, Volbers B, Staykov D, Lücking H, Kloska SP, Köhrmann M, Huttner HB. Hyponatremia is an independent predictor of in-hospital mortality in spontaneous intracerebral haemorrhage. Stroke. 2014;45:1285–91.

Medicines and Healthcare products Regulatory Agency. Intravenous 0.18% saline/4% glucose solution ('hypotonic saline') in children: reports of fatal hyponatraemia. 2012. https://www.gov.uk/drug-safety-update/intravenous-0-18-saline-4-glucose-solution-hypotonic-saline-in-children-reports-of-fatal-hyponatraemia

NPSA. National Patient Safety Agency hyponatraemia. 2009. http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59809

Powlson AS, Challis BG, Halsall DJ, Schoenmakers E, Gurnell M. Nephrogenic syndrome of inappropriate antidiuresis secondary to an activation mutation in the arginine vasopressin receptor AVPR2. Clin Endocrinol. 2016;85:306–12.

Sailer C, Winzeler B, Nigro N, Suter-Widmer I, Arici B, Bally M, Chuetz P, Mueller B, Christ-Crain M. Characteristics and outcomes of patients with profound hyponatraemia due to primary polydipsia. Clin Endocrinol. 2017;5:1–8.

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fensje W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, Van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1–G47.

Tzoulis P, Bagkeris E, Bouloux PM. A case-control study of hyponatraemia as an independent risk factor for inpatient mortality. Clin Endocrinol. 2014a;81:401–7.

Tzoulis P, Evans R, Falinska A, Barnard M, Tan T, Woolman E, Leyland R, Martin R, Edwards R, Scott R, Gurazada K, Parsons M, Nair D, Khoo B, Bouloux PM. Multicentre study of investigation and management of inpatient hyponatraemia in the UK. Postgrad Med J. 2014b;90:694–8. https://doi.org/10.1136/postgradmedj-2014-132885. http://pmj.bmj.com/content/90/1070/694

Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. Semin Nephrol. 2009;29:227–38.

Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126:S1–S42.

Key Reading

1. Baylis PH. Posterior pituitary (Chapter 7). In: Besser GM, Thorner MO, editors. Comprehensive clinical endocrinology. 3rd ed. Philadelphia: Elsevier Science; 2002. p. 85–101.
2. NICE National Institute of Clinical Excellence UK hyponatraemia guideline. 2015: https://cks.nice.org.uk/hyponatraemia

3. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fensje W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, Van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1–G47.

4. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126:S1–S42.

62 Prevention and Management of Adrenal Crisis in Children and Adults

Sofia Llahana, Kathrin Zopf, Irene Mitchelhill, and Ashley Grossman

Contents

62.1 **Introduction** 1185

62.2 **Clinical Presentation of Crisis in Adults** 1186
62.2.1 Presentation of Adrenal Crisis in Children 1188

62.3 **Prevalence and Mortality of Adrenal Crisis** 1188

62.4 **Prevention of Adrenal Crisis and GC Adjustment in Increased Stress** 1189
62.4.1 GC Replacement During Intercurrent Illness and "Sick Day Rules" 1189
62.4.2 Tools and Resources Important in the Prevention of AC 1192

62.5 **Treatment of AC in Adult Patients with AI** 1195
62.5.1 Prevention and Treatment of AC in Children with AI 1196
62.5.2 Management of AC in the Acute Setting 1198

62.6 **Patient Education for the Prevention and Management of Adrenal Crisis** 1199
62.6.1 Pitfalls in the Patient Education Process and Future Directions 1200

62.7 **The Importance of Collaboration with Patient Advocacy Groups** 1201
62.7.1 The Addison's Disease Self Help Group (ADSHG), UK 1202
62.7.2 Contact details for Addison's Disease Self-Help Group 1202

62.8 **Conclusions** 1202

References 1203

S. Llahana (✉)
School of Health Sciences, City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

K. Zopf
DGE (German Society of Endocrinology), Department of Medicine for Endocrinology, Diabetes and Nutrition Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany
e-mail: kathrin.zopf@charite.de

I. Mitchelhill
Department of Endocrinology, Sydney Children's Hospital (SCHN), Randwick, NSW, Australia
e-mail: Irene.mitchelhill@health.nsw.gov.au

A. Grossman
Royal Free Hospital, London, UK

Green Templeton College, University of Oxford, Oxford, UK

Barts and the London School of Medicine, London, UK
e-mail: ashley.grossman@ocdem.ox.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_62

Abstract

Adrenal crisis (AC) is a potentially life-threatening event in patients with adrenal insufficiency (AI). Patients with AI are at risk of developing AC if glucocorticoid replacement is reduced or stopped, or if the dose is not increased during periods of intercurrent illness or major emotional and physical stress. Infections and gastroenteritis are the main precipitating factors for AC which must be treated immediately with parenteral hydrocortisone administration. Mortality is twofold in patients with AI and 1 in 12 patients have at least one hospital admission per year due to AC. Most hospital admissions and deaths from AC can be prevented with prompt management. Education and support for self-management for patients and their families is of paramount importance to achieve optimal adherence with "sick day rules" and to prevent AC. Every patient should be provided with an emergency steroid card, a hydrocortisone injection pack and regular training on self-administration. Patients and families should be encouraged to access information and resources available via the patient advocacy groups. Moreover, raising awareness and training of healthcare professionals in the acute service and developing appropriate care pathways such as ambulance "red flag" protocols ensures that patients are treated immediately when presenting with AC. This chapter presents a comprehensive overview of the causes, clinical presentation, treatment, and prevention of AC. Specific sections in the chapter focus on the care and unique needs of the child presenting with AC and their families. A great emphasis is given on patient education with a focus on the key role of the endocrine nurse as an advanced practitioner in this aspect of patient care. This chapter follows on from Chap. 37 in the adrenal section and we strongly recommend the reader refers to it for a comprehensive overview of the diagnosis and management of adrenal insufficiency.

Keywords

Adrenal insufficiency · Adrenal crisis · Hydrocortisone · Glucocorticoids · Patient education · Steroid card · MedicAlert Hypoglycaemia

Abbreviations

AC	Adrenal crisis
AI	Adrenal insufficiency
GC	Glucocorticoid
HDC	Hydrocortisone
HRT	Hormone replacement therapy
IM	Intramuscular
IV	Intravenous
PAI	Primary adrenal insufficiency
SAI	Secondary adrenal insufficiency
SC	Subcutaneous

Key Terms

- **Adrenocorticotropic hormone (ACTH):** Is the hormone responsible for stimulating cortisol production from the adrenal glands, which is essential for life.
- **Adrenal insufficiency (AI):** Refers to the failure or impairment of the adrenal glands which can be primary adrenal insufficiency (PAI) most commonly autoimmune or Addison's disease, or secondary adrenal insufficiency (SAI) due to hypothalamic-pituitary diseases, resulting in cortisol deficiency.
- **ACTH stimulation test:** Is a diagnostic test to assess the adrenal steroid production after the administration of the synthetic ACTH analogue Tetracosactide
- **Adrenal crisis:** is life-threatening emergency caused by inadequate production of the adrenal hormone cortisol in situations of stress.

Key Points

- Adrenal crisis (AC) is a life-threatening event for patients with adrenal insufficiency (AI) and must be treated immediately with parenteral hydrocortisone to avoid hospitalisation and preventable death.

- Gastroenteritis with vomiting/diarrhoea and other infections are the main triggers for AC but other stressful events and illness can precipitate AC.
- The patient and their families should receive adequate education to follow "sick day rules" and to adjust medication appropriately during intercurrent illness and major stress.
- Education and treatment plans should be tailored to each patient's and family's individual needs.
- The endocrine nurse, through advanced practice skills and clinical expertise, plays a key role in the care and education of patients with AI and their families.

62.1 Introduction

Adrenal crisis (AC) or otherwise known as Addisonian crisis is a life-threatening emergency for people with adrenal insufficiency (AI). As we saw in Chap. 37, AI results from failure or impairment of the adrenal glands which can be primary (PAI), most commonly autoimmune or Addison's disease, or secondary (SAI) due to hypothalamic-pituitary disorders; it requires lifelong glucocorticoid (GC) replacement therapy and mineralocorticoid replacement for patients with PAI.

Patients with AI are at risk of developing AC if GCs are reduced or stopped, or if the dose is not increased during periods of intercurrent illness or other major psychological and physical stress such as surgical procedures or trauma to mimic the normal increase in physiological cortisol response to such situations (Johannsson et al. 2014). This is also referred to as "sick day rules" (Bornstein et al. 2016). Failure to do so can lead to an AC which presents with profoundly impaired well-being, nausea and vomiting, hypotension, hypovolaemic shock, and can be fatal without immediate administration of parenteral hydrocortisone (Allolio 2015). Risk of AC is also high in patients with long-term corticosteroids who may stop treatment abruptly or are unable to take tablets, e.g. vomiting/diarrhoea or surgical procedures (Schuetz et al. 2015; Broersen et al. 2015). The narrative in Box 62.1 illustrates the negative impact an AC can have on a patient's life. It also emphasises the crucial role the endocrine nurse plays in supporting and providing patients and their families with the right information at the right time to prepare them for prevention and management of an AC.

Box 62.1 A Patient Story Emphasising the Importance of the Role of the Endocrine Nurse

I was diagnosed with a large pituitary tumour in 2012. I had surgery shortly after diagnosis and straight after started levothyroxine, hydrocortisone, and HRT. I also saw a nurse the same day who gave me lots of information on hydrocortisone. She gave me leaflets too but I didn't quite get to read them. …I was devastated about my brain tumour [pituitary macroadenoma] diagnosis and that I have to take medication for the rest of my life so it didn't seem that important what she was saying.

Eight months later, I had norovirus with really bad vomiting and diarrhoea. I felt extremely weak and was losing consciousness, my husband called an ambulance. I don't remember much but a flashback from the nurse's voice came back to me saying "if you have vomiting, it can be life threatening…". As I was passing out, I saw my life flashing past. I was terrified that I was dying and that I will leave my children motherless without even having the chance to say "goodbye!". I woke up in hospital. Luckily for me the paramedic knew what an adrenal crisis was and gave me the hydrocortisone injection immediately. I did not die but will never get over the trauma from that experience.

When I was in hospital (different to where I had my surgery), the endocrine nurse came to see me. She gave me information on how I can manage an adrenal crisis and gave me an injection kit. This time of course I did take notice of what she was saying!... She saw me again in

(continued)

Box 62.1 (continued)

[outpatient's] clinic, it turns out I was taking too much hydrocortisone and too late in the day, that's why I was putting on so much weight and not sleeping well. She was very patient, explained everything in detail and simple language and showed me and my husband how to give the injection. I see her now every six months, my life has been transformed, and she started me on growth hormone too. I had another [adrenal] crisis from food poisoning when I was on holiday 6 months ago, but my husband gave me the [hydrocortisone] injection immediately, I felt better straight away and did not have to go to the hospital. I was fine after 2 days and we enjoyed our holiday. I am now always prepared and carry my injection kit with me all the time.

I wanted to share my story so all patients in my position DEMAND to see an endocrine specialist nurse! But most importantly to get information at the right time. It was pointless telling me how to take my medication at the time when I was devastated from such a dreadful diagnosis. It turns out the pituitary tumour is nothing compared to what comes next. I would not have the quality of life I have now without her [the endocrine nurse's] support and hope she will be at the hospital for many years to come. Thank you so much for all your help!...

Quote taken from anonymised patient responses from a Pituitary Nurse-led Clinic service evaluation project (from Llahana et al. 2018, unpublished data)

62.2 Clinical Presentation of Crisis in Adults

The most frequent precipitating factors for AC are gastrointestinal infections, vomiting, diarrhoea and fever for more than 50% of patients, but also other stressful events such as surgery, dental procedures, major pain, emotional distress, pregnancy, extreme temperatures and physical exertion (Hahner et al. 2010, 2015a; White and Arlt 2010; White and Wass 2015; Smans et al. 2016; Rushworth and Torpy 2014). Table 62.1 lists the most common triggering factors for AC as reported by patients in six studies.

AC is the first presentation of AI for up to 50% of patients with Addison's disease. Patients developing an AC have major impairment of general health and present with the following clinical signs and symptoms requiring immediate parenteral hydrocortisone administration (Bornstein et al. 2016; Allolio 2015; Bancos et al. 2015; Arlt and Society for Endocrinology Clinical Committee 2016).

- Fatigue, profound lack of energy, and general weakness
- History of weight loss
- Generalised skin hyper-pigmentation in patients with PAI
- Nausea and/or vomiting
- Abdominal pain, tenderness, and guarding
- Fever >38 °C
- Hypotension (systolic blood pressure < 100 mmHg), postural dizziness and hypotension (≥20 mmHg drop in blood pressure from supine to standing position)
- Hyponatraemia (≤132 nmol/L), hyperkalaemia (in PAI), hypoglycaemia (more common in children)
- Confusion, somnolence, delirium, and impaired cognition
- At a later stage, symptoms accelerate to hypovolaemic shock, pre-renal failure (increased serum creatinine due to hypovolaemia), loss of consciousness, and coma leading to cardiovascular failure and death

Improvement in clinical signs and symptoms should be expected within 24 h (Allolio 2015). This improvement of clinical conditions after parenteral administration of hydrocortisone is important as it differentiates an adrenal crisis from other severe medical conditions which require relevant treatment. Development of an AC usually takes several hours; however some

Table 62.1 Common triggering factors for AC and frequency by percent

	Hahner et al. (2010) (N = 291)		Hahner et al. (2015a)	White and Arlt (2010)	White and Wass (2015)	Rushworth and Torpy (2014)	Smans et al. (2016)
Triggering factor for AC	PAI (*N* = 181) %	SAI (*N* = 110) %	*N* = 46[a] %	*N* = 767 %	*N* = 598 %	*N* = 824 %	*N* = 149[a] %
Gastroenteritis, diarrhoea	32.6	21.8	23	23	55.2	15.2	32
Vomiting				33	79.4		
Other infectious diseases/fever	24.3	17.3	22	6	20.9	15.9	
Surgery, surgical recovery	7.2	45.5	16	6	18.9		
Strenuous physical activity/stress	7.7	7.3	9		24.7		0.7
Cessation of GC by patient	5.0	6.4	1.9				11.4
Nonadherence to/ inadequate GC	5.0	3.6	4.3				
Psychic distress/ mental disorder	2.8	2.7					2
Accident, injury	1.1	3.6	3.1	4	8.7		
Cessation of GC by physician			1.7				
Emotional stress, anxiety, bereavement			16	1	15.7		
Urinary tract infections			3			10	11
Flu-like illness				11	26.8		
Blackout/ unconsciousness				6	11.9		
Dental procedure					8.0		2
Labour, post-delivery					2.5		
Viral infections						7.4	28
Pneumonia						10.3	29
Unknown	6.6	12.7	9.9	1	2.7		
Other causes	4.4	5.4	8.7	3	8.5		

N number of respondents, *AC* number of adrenal crises episodes, % percentage of cases
[a]Multiple responses were possible for patients who experienced more than one AC

patients, especially children, can deteriorate very rapidly even within 1 h (Allolio 2015). This makes it difficult for patients to take preventative measures and be fit to self-administer hydrocortisone injection.

Allolio also graded the severity of AC from 1 to 4 as follows depending on the setting required for treatment and outcome (Allolio 2015):

- Grade 1: Outpatient care only [this may also be home setting or general practice and includes administration of parenteral hydrocortisone 100 mg by the patient, family member, or healthcare professional]
- Grade 2: In hospital care [includes hospital admission on a general ward due to signs and symptoms of an adrenal crisis]
- Grade 3: Admission to intensive care unit resulting from AC
- Grade 4: Death from adrenal crisis (with or without parenteral glucocorticoid administration)

62.2.1 Presentation of Adrenal Crisis in Children

The possibility of AI should be considered as a provisional diagnosis in any severely unwell neonate or child presenting to an emergency department (Miller et al. 2008; Brook and Dattani 2012). For Emergency Department staff, a neonate or child presenting in a severe state of systemic collapse with hypoglycaemia, hypotension, and fluid and electrolyte disturbance should trigger a provisional diagnostic path to rule out the possibility of life-threatening AC. Both hypoglycaemia and AI are inter-related conditions as cortisol is a counter-regulatory hormone important for systemic support, balancing blood sugar via hepatic gluconeogenesis and maintaining blood pressure and electrolyte levels (Kwok et al. 2005). Depending on the significance of the presentation, resuscitative procedures may be required before critical blood samples can be adequately obtained. Once the neonate or child is stabilised, further evaluation will be required to ascertain the cause of the event, with a comprehensive history and consultation by an endocrinologist if hormone deficiencies are detected or suspected (Brook and Dattani 2012; Linder et al. 1990).

An AC can be a result of a seriously unwell neonate or child as a new presentation or a child with a known diagnosis where an AC can be precipitated by a significant illness, trauma, or stress if left untreated can be fatal (Miller et al. 2008; Brook and Dattani 2012; Webb and Krone 2015). Precipitating factors for AC which need parenteral hydrocortisone administration are similar to the adult patients but nonadherence to medication can affect children more severely leading to:

- Cortisol insufficiency/hypoglycaemia
- Postural hypotension/pallor
- Impaired growth and weight
- Lethargy and tiredness
- Lack of energy and exercise tolerance

The management of an acute adrenal crisis involves an immediate triage and history of the presenting issues and symptoms whilst emergency management procedures are instigated. An infant or child presenting in a state of systemic collapse may exhibit any of the following (Miller et al. 2008; Brook and Dattani 2012; Webb and Krone 2015):

Presentation

- Drowsy and difficult to rouse
- Pale and mottled in appearance
- A neonate with persistent jaundice or a bronzed appearance of the skin
- A male infant with signs of mild–moderate pigmented genitalia, umbilicus, nipples, and crease lines

Observations

- Hypothermic, tachycardic, laboured and rapid breathing, hypotensive, delayed capillary return, hypoglycaemia

History

Neonate/infant: poor and difficult feeding, excessively sleepy and lethargic, not waking for feeds, vomiting, poor urine output, significant weight loss >10%.

Child: lethargy, muscle weakness with a lack of energy, poor appetite, failure to thrive with evident growth failure and poor weight gain. Presentation may follow a period of prolonged fasting and or inadequate oral intake exacerbated by an inter-current illness. There is often a history of slow and prolonged recovery from illness.

62.3 Prevalence and Mortality of Adrenal Crisis

The prevalence of primary AI is 93–140 patients/million population and secondary AI is 150–280/per million (Arlt and Allolio 2003) with an estimated population between 110,000 and 213,000 patients with AI in the European Union (Allolio 2015). The standard mortality rate (SMR) for patients with AI is more than twofold compared to the average population (Bergthorsdottir et al. 2006; Tomlinson et al. 2001). AC is a factor that increases the mortality rate in patients with AI. Erichsen et al. (2009) found that SMR was significantly elevated in patients diagnosed before the age of 40 years; this was more pronounced in males with SMR 2.03 (CI 1.19–2.86) and younger patients were at higher risk of sudden death from

AC. Four patients died from AC during a 2-year prospective study of 364 patients with AI (767.5 patient years) leading to a mortality rate from AC of 0.5/100 patient years (Hahner et al. 2015a). Similar findings were reported by another study from Australia which looked at hospital admissions for patients with AI and found that four patients ($N = 467$) had died with a principal diagnosis of AC (Rushworth and Torpy 2014). Hospitalisations and deaths from AC are potentially preventable and if treated promptly can save patients' lives. The late Professor Bruno Allolio estimated that, at the current mortality rate for AC, between 5526 and 10,647 patients with AI, in an average population of 507 million people in the European Union, will die from a potentially preventable AC (Allolio 2015).

Studies from Europe show an incidence of AC between 5 and 10 AC per 100 patient years (Hahner et al. 2010, 2015a; White and Arlt 2010; Smans et al. 2016). An earlier study from Japan showed a much higher incidence and 29% of patients ($N = 137$) had experienced at least one AC episode (Omori et al. 2003). The incidence of AC is somewhat higher in patients with PAI who have combined GC and mineralocorticoid deficiency compared to those with SAI (Hahner et al. 2010; Smans et al. 2016). Comorbidities, such as diabetes, asthma, premature ovarian failure, and coeliac disease, are added risk factors for AC for more than 50% of patients with PAI (White and Arlt 2010; White and Wass 2015), and diabetes insipidus and growth hormone deficiency for approx. 70% of patients with SAI (White and Wass 2015).

The prevalence of hospitalisation due to AC is also very high for this patient population, even though most hospital admissions could be prevented with prompt parenteral administration of hydrocortisone (Allolio 2015; Wass and Arlt 2012). An international study found that 38% of participants ($N = 977$) had been hospitalised at least once during the past 12 months and of these hospital admissions, 17% were due to an AC, i.e. 1 in 6 patients with a hospital admission (Forss et al. 2012). One in 12 patients report at least one hospital admission per year related to an AC (Hahner et al. 2015a; White and Arlt 2010), and 10.6% of patients with PAI, and 7.4% with SAI who reported AC had this on four or more occasions (Hahner et al. 2010). This suggests that there is a subgroup of patients at high risk and we need to identify and support them with relevant individualised treatment planning and education. In addition to health burden and risk to patient's lives, AC has significant cost implications for the health service despite the low prevalence of AI. In 2015, 2052 AC-related hospital admissions were recorded in National Health Service (NHS) hospitals in England (HSCIS 2015), which incurs a minimum cost to the NHS of £3.2 million/year (€3.6 million or $4.2) based on a daily inpatient rate of £1565 (DoH 2015).

62.4 Prevention of Adrenal Crisis and GC Adjustment in Increased Stress

Patients with AI need to increase the dose of their GC replacement to mirror the physiological increase in serum cortisol levels during major stress and illness. In the cases where oral tablet intake is not possible, immediate parenteral hydrocortisone administration is crucial to prevent life-threatening AC. This is normally referred to as "sick day rules". Professors John Wass and Wiebke Arlt, leading experts in AI, emphasise that "*prevention of adrenal crisis is better than cure*" (Wass and Arlt 2012). Endocrine nurses should be leading on this aspect of care for patients with AI and ensure that all patients and their families are provided with the necessary information and resources to minimise the risk of hospitalisations and to eliminate preventable deaths from AC. They should also strive for strategic involvement in improving care services for patients with AI, including the development of nurse-led services and clinics in specialist centres and coordination of seamless care pathways for acute services and primary care. Close collaboration with patient advocacy groups is also essential (see next section).

62.4.1 GC Replacement During Intercurrent Illness and "Sick Day Rules"

A number of cross-sectional studies found that 26–38% of patients with AI did not adjust the GRT dose during stressful events or intercurrent

Table 62.2 Glucocorticoid dose adjustment in stressful events and intercurrent illness (adapted from Allolio (2015) and Bornstein et al. (2016))

Increased stress situations or events	**Hydrocortisone (HDC) dose adjustment**
Strenuous physical activity (e.g. marathon running, hiking, moving house, gardening)	Take 5–10 mg HDC 30–60 min before activity
Long-haul flights (e.g. trans-Atlantic)	Take 5–10 mg HDC 30–60 min before flight take off
Major emotional/mental stress (major end of year exams, job interview, death of close relative/family member)	Add 10–20 mg HDC to standards replacement dose
Long days (e.g. Saturday night out, wedding parties, working late)	Take an additional 5–10 mg HDC before going out or late evening
Shift working	Adjust HDC to take during the awake times
Ramadan fasting	Switch to long acting GC, take dose before dawn
Intercurrent illness/procedures	**Able to take GC orally**
Illness with or without fever (unable to work or go by with daily routine)	Double (fever >38 °C) or triple (fever >39 °C) dose of HDC until recovery, **take at least three times daily**, return to standard dose within 1–2 days by tapering down
Minor painful procedures (e.g. skin mole removal, tattooing, body piercing)	Take 10 mg HDC 60 min before procedure, if infection develops, additional HDC needed as per above
Major dental work with local anaesthetic (e.g. root canal, implant)	Take an extra 20 mg HDC 60 min before procedure, double dose for 24 h
Minor dental procedure (filling, scale and polish, hygienist)	Take 10 mg HDC 60 min before procedure, take an extra dose later in the day if pain or discomfort
If taking dual-release hydrocortisone (Plenadren®) or prednisolone once daily	
Febrile intercurrent illness	Increase dose to twice or thrice daily with 6–10-h intervals between tablets
For short stressful events (as above)	Take a single dose of HDC of 5–10 mg or 20 mg for more severe stress 30–60 mg prior to event
More severe intercurrent illness	**Requires parenteral hydrocortisone**
Gastroenteritis with vomiting and/or diarrhoea, trauma (unable to take tablets)	Immediate hydrocortisone 100 mg IM or SC administration, to be repeated after 6–12 h; seek medical help if symptoms don't improve
Severe infection (e.g. pneumonia)	As above

NOTE: This table provides general guidance but each patient's needs should be assessed individually.

illness (Llahana 2013; Flemming and Kristensen 1999; van Eck et al. 2016; Peacey et al. 1993). All patients and their families should receive detailed patient education in face-to-face consultations to advise them on "sick day rules" based on their individual needs for GC replacement. It is advised that patients should add 5–10 mg of hydrocortisone to their normal dose about 30–60 min before any events of excessive/major physical, emotional, or mental stress (Allolio 2015), such as exams, job interviews, extreme physical exercise, and bereavement (Table 62.2). However, it is important to remember that the degree to which patients are affected by similar stressful situations varies from patient to patient (please read the case scenarios in Box 62.2).

Box 62.2 Case Scenario of GC Dose Adjustment in Stressful Events

Two students take end of year exams. The first student who has Addison's disease tells you he experiences severe perspiration, hot flushes, tachycardia, dizziness, and anxiety when entering the classroom and finds it impossible to focus. The second student has hypopituitarism following surgery for non-functioning pituitary adenoma; he feels slightly anxious, but he is still able to focus on his exam and performs well. None of them were previously advised on what to do in stressful events such as an exam. They are both on a daily dose of hydrocortisone 10 + 5 + 5 mg. What do you advise them?

The endocrine nurse should take a detailed history of events that affect the patient's well-being or that may have triggered AC episodes in the past and should educate them on recognising and managing these situations through appropriate adjustment of GC therapy. In the case scenarios in Box 62.2, the first patient should be advised to take an extra 10 mg of hydrocortisone before the exam, but the second patient does not necessarily need to increase the dose, assuming he adheres to his daily dose of hydrocortisone. The dose of GC also needs to be adjusted accordingly with concomitant use of certain drugs such as mitotane or foods (please see table in Chap. 37 for food and drug interactions with GC).

For intercurrent illness such as infections, injuries, flu, and fever, the dose of GC should be doubled or tripled (Table 62.2). It should be maintained for the duration of illness and reduced back to the standard dose within 1–2 days after recovery (Bornstein et al. 2016; Allolio 2015). It is also important to advise patients to take hydrocortisone in three divided doses daily with 5–7 h between tablets; some patients with SAI for example may only take hydrocortisone once or twice daily for their maintenance dose.

For patients who take long acting GC, such as prednisolone or dual-release hydrocortisone (Plenadren®), the total daily dose should be increased by administering the maintenance dose twice or thrice daily with 6–10-h intervals, i.e. increase in the number of administrations, not increase in the morning dose (EMA 2018; Nilsson et al. 2017). For short periods of increased stress, e.g. extreme sports, a single dose of immediate-release hydrocortisone of 5–10 mg should be taken prior to the stressful event.

For more severe illness, vomiting, diarrhoea, and when the patient is unable to take tablets orally in situations such as elective procedures or surgery, hydrocortisone must be administered immediately intramuscularly (IM) or intravenously (IV) at 50–100 mg followed by 100 mg every 6 h. For patients who are not comfortable with self-administering IM injections, subcutaneous (SC) administration of hydrocortisone is a good alternative, with only an 11 min delay in reaching desired cortisol levels compared to the IM injection, (Hahner et al. 2013). In the absence

Table 62.3 Glucocorticoid replacement during surgical and other invasive procedures (adapted from Allolio (2015), Bornstein et al. (2016), Husebye et al. (2014), and Wass et al. (2017))

Surgical or other procedures	Pre-operative needs for hydrocortisone (HDC)	Post-operative needs for hydrocortisone (HDC)
Long major surgery with long recovery time (e.g. open-heart surgery, major bowel surgery, transplant surgery)	100 mg hydrocortisone IM or IV just before anaesthesia	100 mg IM or IV every 6 h or continuous IV infusion 200 mg/24 h or until able to eat and drink normally *(discharged from ITU)* If well, then double oral dose for 48+ h, then taper the return to normal dose
Major surgery with rapid recovery (caesarean section, laparoscopic surgery)	100 mg hydrocortisone IM or IV just before anaesthesia	100 mg IM or IV or continuous infusion 200 mg/24 h for 24–48 h for 24–48 h *(or until able to eat and drink normally)* If well, then double oral dose for 24–48 h, then return to normal dose
Labour and vaginal birth	100 mg hydrocortisone IM or IV at onset of active labour, immediately followed by continuous IV infusion 200 mg/24 h or 100 mg IM or IV 6 hourly until delivery	Double oral dose for 24–48 h after delivery If well, then return to normal dose
Minor surgery (e.g. cataracts, laparoscopic surgery with local anaesthetic, IVF egg collection surgery)	100 mg hydrocortisone IM just before anaesthesia	Double oral dose for 24 h, then return to normal dose

(continued)

Table 62.3 (continued)

Surgical or other procedures	Pre-operative needs for hydrocortisone (HDC)	Post-operative needs for hydrocortisone (HDC)
Major dental surgery (e.g. tooth extraction, orthodontic surgery)	100 mg hydrocortisone IM just before anaesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives (e.g. colonoscopy)	Hospital admission overnight with IV fluids and 100 mg hydrocortisone IM during preparation period (bowel cleaning), 100 mg hydrocortisone IM before start of procedure	Double oral dose for 24 h, then return to normal dose
Other invasive procedures (e.g. endoscopy)	100 mg hydrocortisone IM just before start of procedure	Double oral dose for 24 h, then return to normal dose

Download Pdf guidelines from the UK Addison's Disease Self Help Group (https://www.addisons.org.uk/files/file/4-adshg-surgical-guidelines/)

of diarrhoea, rectal suppositories of prednisolone 100 mg are also easy to administer if parenteral hydrocortisone is not possible (Bornstein et al. 2016; Quinkler and Hahner 2012) although these are not available in every country. Table 62.3 presents details on need for GC replacement during elective surgical or nil by mouth procedures and other investigations (adapted from Bornstein et al. (2016), Allolio (2015), Arlt and Allolio (2003), Husebye et al. (2014), and Wass et al. (2017)).

The two-step process for "sick day rules" can simplify patient education regarding symptom awareness and the correct adjustment of GC replacement dose and it is easier for healthcare professionals and patients to understand and follow (Bornstein et al. 2016; Arlt and Society for Endocrinology Clinical Committee 2016) (Box 62.3).

Box 62.3 The Simple Two-Step Process of "Sick Day Rules" for GC Replacement

Sick Day Rule 1: the need to double or triple daily oral GC dose during intercurrent illness often accompanied by fever that requires bed rest and/or antibiotics**.**

Sick Day Rule 2: the need to administer hydrocortisone per IV, IM, or SC injection during prolonged vomiting or diarrhoea, during preparation for colonoscopy or in case of acute trauma or surgery.

62.4.2 Tools and Resources Important in the Prevention of AC

Additional measures are important to ensure patients and their families are prepared to manage and prevent AC. Patients should have sufficient supply of GC tablets to account for dose increase during intercurrent illness and should be advised to always carry medication with them, especially when travelling. It is our responsibility to provide all patients with AI with a Steroid Emergency Card, such as should they require urgent care or be rendered unconscious, the attending paramedical staff or the triaging team in the Emergency Department knows that the emergency hydrocortisone administration is a life-saving treatment which must not be delayed (Grossman 2010). This can be strengthened by the patient wearing a MedicAlert bracelet, necklace, or anklet (Bornstein et al. 2016; Allolio 2015; Bancos et al. 2015; Husebye et al. 2014; Grossman 2010) indicating their need for hydrocortisone injection for AC (a patient attending our clinic has tattooed this below his neckline).

The development and rollout of the highly standardised European Steroid Emergency Card (Quinkler et al. 2015) has made a significant contribution to raising awareness of the risk associated with AC risks and provides precise instructions for healthcare professionals in the acute service on the treatment of AC. The credit-card-sized card (Fig. 62.1) is endorsed by the European Society of Endocrinology (https://www.ese-hormones.org/). It has so far been

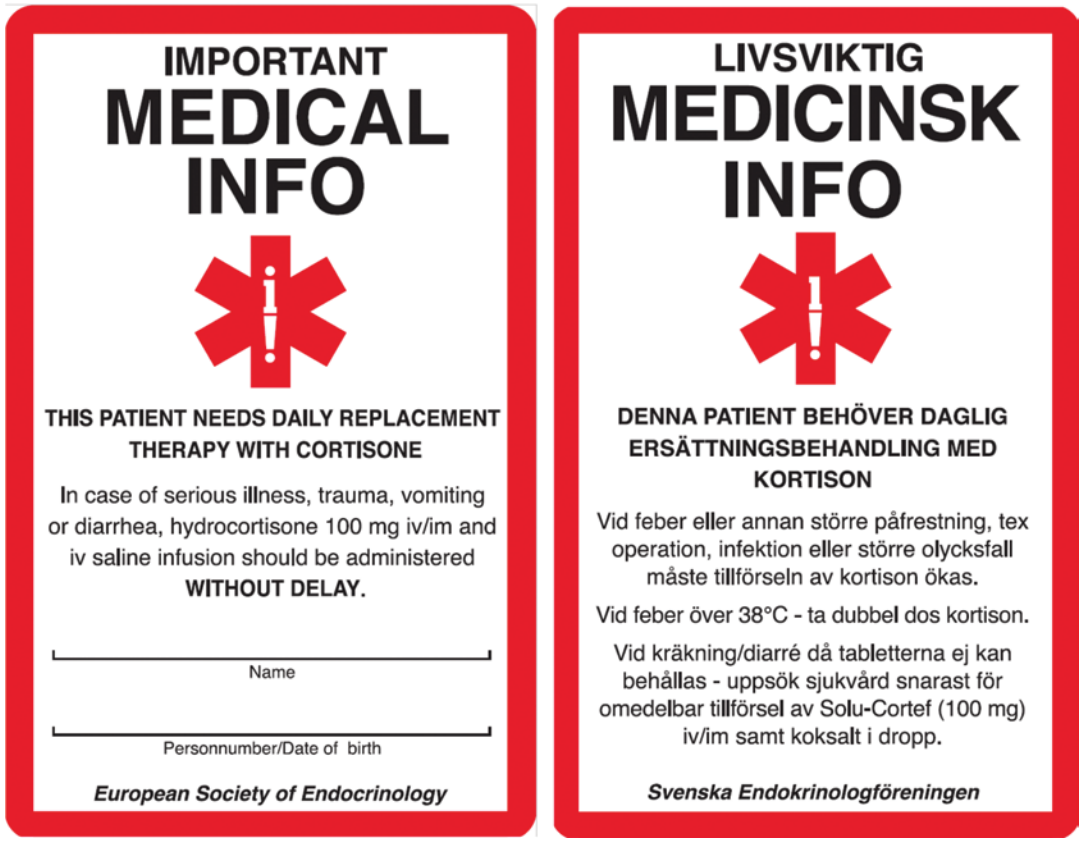


Fig. 62.1 The standardised European Emergency Steroid Card. Translated in 25 languages (two-sided English and Swedish here) and available to download from AdrenalNet (https://adrenals.eu/emergency-card/), used with permission

translated in 25 languages (double-sided card with English as the international side) and more than 110,000 cards have been distributed across Europe by AdrenalNet, a non-profit organisation aiming to promote knowledge and improve quality of care in AI (https://adrenals.eu/).

All patients should be provided with a specially designed "hydrocortisone emergency pack" (Grossman 2010) which should include the following: the hydrocortisone 100 mg injection for IM or SC administration, 2 syringes, 2 needles, at least 10 extra hydrocortisone tablets, 2 rectal suppositories of prednisolone 100 mg (where available), the emergency steroid card (Fig. 62.1) or a medical letter with the patient details (name, address, diagnosis, and treatment), brief guidelines for the treatment of AC (e.g. the credit card concertina wallet with printed guidelines developed by the Addison's Disease Self Help Group, Fig. 62.2). The case study in Box 62.4 emphasises the value of these resources for patients with AI.

Fig. 62.2 Guidelines for treatment of AC in a credit card concertina wallet. Used with permission from Addison's Disease Self Help Group (translated in 10 languages and available to download from https://www.addisons.org.uk/files/file/71-adshg-adrenal-crisis-guidelines/)

Box 62.4 A Case Study Elucidating the Importance of the Preventative Measures for AC

I am 51 years old and have had Addison's since 1995. We travel to Lanzarote regularly; it is our second home. We are very familiar with the surroundings and climate; I always take adequate supplies of all my medications, a medical letter for travelling, plus a couple of emergency injection kits. In the last 10 years we have been visiting, we have never had to make use of any of the medical facilities—until now.

We had a nice relaxing afternoon in the sun. My first mistake of the day was to remove my medical emblem from my neck—I didn't want it to affect my suntan.

As we were driving back, life took a sudden turn when we were involved in a road traffic accident… a car did not give way and crashed into the passenger side where I was sitting. I was immediately aware of pain in my arm and shoulder and a large gash on my chest. Fortunately, my husband suffered minimal injuries. The accident involved the police attending, the fire brigade cutting me out of the car and an ambulance, with none of the crew able to speak English.

We didn't have an emergency injection in the car with us, but we did have a large supply of hydrocortisone tablets. …I was not allowed to have anything orally, and then I vomited. I was taken to a private hospital and when we got there the situation was quickly brought under control by English-speaking doctors. They quickly gave me IV fluids and steroids whilst they sorted out my injuries. I was very well cared for.

So here are my lessons learned, that I now have to remember to put into practice:

When you travel, take a copy of the ADSHG adrenal crisis guidelines, stating you have Addison's, in the language of the country you are visiting.

Don't ever remove your medical jewellery—you wear it for a reason, even if you are sun bathing.

Take your emergency injection kit with you everywhere you go.

Always take more medication on your holiday than you will ever think you will need—and don't keep it all in one place.

Make sure your insurance covers all your pre-existing conditions.

NOTE: Patient case study published in the Addison's Disease Self Help Group (ADSHG) newsletter, used with permission from ADSHG (https://www.addisons.org.uk).

A third of patients experienced AC away from home and relied on emergency-care clinicians for the management of AC (White and Arlt 2010). Interestingly, 62–68% of patients with AI held an up-to-date emergency injection kit (White and Arlt 2010; Hahner et al. 2015b) but only 12% managed to self-administer the injection when they experienced an AC (White and Arlt 2010) and only 19% were trained to self-inject (Hahner et al. 2015b). Two other studies found that only 60% of patients carry an emergency medical-alert card even though they were all provided with a card and verbal/written information at their consultation (Flemming and Kristensen 1999; van Eck et al. 2016).

At every consultation, the endocrine nurse should emphasise the need for patients to wear a MedicAlert and to always carry a steroid emergency card and the emergency injection pack, particularly when travelling to places with limited access to medical services. Patients should also be encouraged to inform friends, family, or work colleagues of their risk of AC and how to use the emergency pack. Endocrinology clinics should make these resources available for their patients, and it should be the responsibility of the endocrine nurse to check that patients have an up-to-date emergency injection.

The use of digital health technology, online resources, and electronic patient records provide the patient and healthcare professional with timely access to information where and when needed. Information leaflets and online videos on administering the hydrocortisone injection available from websites of the patient advocacy groups can be exceptionally useful and membership in these organisations should be encouraged for all patients. The AdrenalNet (https://adrenals.eu/) has developed a free smartphone multilingual app which offers essential information on all aspects of management of AI and AC and has the possibil-

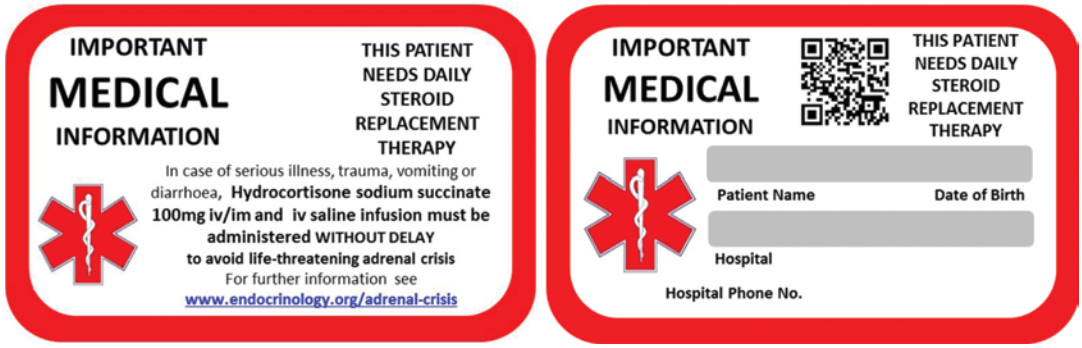


Fig. 62.3 Using the QR code of the Emergency Steroid Card to access guidance on treatment for AC. Card translated in 14 languages and available to download from the Society for Endocrinology, UK (https://www.endocrinology.org/adrenal-crisis)

ity to link up with the patient's hospital records where hospital system allows. In our hospital (London, UK), we have incorporated "alert messages" in the patients' electronic records advising of the risk and treatment for AC. Similarly, the new Emergency Steroid Card from the Society for Endocrinology in the UK includes a QR code (Fig. 62.3) which links to the website with the emergency guidance for treatment of AC. Patients with access to a smart phone can be encouraged to add this card as a wallpaper on their phone.

62.5 Treatment of AC in Adult Patients with AI

Patients with known or suspected AI presenting with AC must be treated immediately as failure to do so can be life-threatening (Box 62.5).

Box 62.5 Urgent Treatment for Adrenal Crisis Can Save Patients' Lives

TREAT FIRST, DIAGNOSE LATER!
Patients with suspected adrenal crisis should be treated immediately with intramuscular or intravenous hydrocortisone and prompt rehydration with isotonic saline of 1000 mL within the first hour. Diagnostic measures should never delay treatment.

Treatment of AC includes the following steps (Bornstein et al. 2016; Allolio 2015; Bancos et al. 2015; Arlt and Society for Endocrinology Clinical Committee 2016; Arlt and Allolio 2003; Husebye et al. 2014).

- **Immediate bolus IV or IM injection of hydrocortisone 100 mg** (hydrocortisone sodium succinate or hydrocortisone sodium phosphate) followed by continuous IV infusion of 200 mg hydrocortisone for 24 h (alternatively 50 mg every 6 h IM or IV bolus), reduced to hydrocortisone 100 mg/day the following day. Hydrocortisone acetate must not be used to treat AC due to its slow release, microcrystalline formulation (Wass et al. 2017).
- **Rehydration to correct hypovolaemia with rapid intravenous of 1000 mL isotonic saline** infusion (or 5% glucose in isotonic saline) within the first hour and, 500 mL in the second hour, followed by continuous fluid administration (usually 4–6 L in 24 h). Fluid overload should be monitored in case of renal impairment and elderly patients. Continuous cardiac monitoring, regular assessment of patients' electrolytes, and vital signs to monitor clinical recovery.
- **Relevant treatment of the precipitating factor of AC**, e.g. infection, trauma, other hormone deficiencies in SAI. Treatment for AC should result in clinical recovery within 24 h. If improvement does not occur, alternative causes for the profound impairment of health need to be considered again. Depending on the severity of the intercurrent illness, admission to the intensive care or high-dependency unit may be necessary (Allolio 2015; Husebye et al. 2014).

- **When the patient is clinically stable** and able to return to oral GC intake, "sick day rules" should be followed until full recovery and the GC dose should be tapered down to usual maintenance dose within 24–72 h.
- **Urgent endocrinology review** is necessary, especially for patients with a new diagnosis of AI. A nursing review is also crucial to review and advise the patient and their families on "sick day rules" and assess the need for further education and outpatient input.

62.5.1 Prevention and Treatment of AC in Children with AI

Children can develop AC quicker and more severely than adults with hypoglycaemia, very common presenting symptom of AC in children, and which can lead to severe brain damage. To prevent AC, "sick day rules" must be followed immediately after the onset of symptoms occur and GC dose should be increased for any significant illness (Speiser et al. 2010). Table 62.4 presents the

Table 62.4 A practical guide to plan, predict and manage illness events in children to prevent an AC

Patients with adrenal insufficiency (AI) are at risk of an adrenal crisis when unwell: e.g. significant illness or injury or procedures requiring anaesthesia. In these situations increased "**stress**" **doses** of hydrocortisone (HDC) are required. This condition can be life threatening if treatment is withheld

Managed care plans are critical in ensuring parents and patients understand the importance of compliance with their medication and to follow "sick day rules" when illness occurs

Minor illness:	**Moderate illness:**
Stress HDC doses are not required for incidental/minor illnesses, such as cough, sniffles, runny nose or regular school exams • Monitor and encourage fluids and oral intake • Observe and monitor for any symptoms indicating a more significant illness (possible respiratory, middle ear, urinary tract infections or abdominal upset) • Seek medical advice • *Refer to emergency letter* **Immunisations:** monitor for symptoms/fevers • Oral stress dose for 24 h **Vomiting of medications:** if within 1 h: • Repeat the dose and observe for further episodes • Refer to emergency letter	Not their usual self, labile demeanor, cranky, irritable, off their food, fever above 38 °C Inter-current illness—upper respiratory, flu-like symptoms, headache with or without fever Mild episode of diarrhoea and/or vomiting (D&V) • Oral stress HC doses with a sweet drink for 24 h or until well again • Encourage oral fluids and a light diet • Glucose/electrolyte solution for D&V • Monitor for deterioration • Give IM HDC if deterioration and go to the Emergency department *Follow instructions in your emergency letter* *If in doubt, seek medical advice* **Medical and dental Procedures**: prolonged fasting, anaesthesia and surgery require stress HDC dosing • Procedure plan required

Major illness/crisis (critical) immediate medical attention required

Symptoms:

- Persistent diarrhoea and/or vomiting, significant injury (fracture, head injury)
- Significant systemic illness requiring admission to hospital
- Lethargy, drowsiness, dizziness and confusion and reduced conscious level
- Pale and mottled appearance, poor capillary return

Interim Management:

- Urgent injection of intramuscular HDC injection required
- *Parents should administer IMI HDC immediately and take child to hospital*
- *Carers/teachers should call an ambulance and state child with AI needs cortisone injection urgently*
- *All parents/carers should be trained in IM injection of HDC administration*

Critical observations:

- Hypoglycaemia and hypotension, tachycardia, dyspnea, hypothermia with circulatory collapse with poor capillary return, deterioration to coma, shock and impending death

Triage assessment: immediate—without delay—noting medical alert—adrenal Insufficiency

- Instigate emergency management noted in emergency letter
  - IM HDC stat: prevent an adrenal crisis—first PRIORITY
- IM Glucagon: hypoglycaemia <2.6 nmol/L, buccal glucose gel if needed
- IV access and fluid resuscitation as per standard hospital protocols (intra-osseous if need) and ongoing IV/oral stress HDC is needed until well again
- Oxygen, ECG monitor, thermal blanket, BGL, electrolytes and hormone profile are needed

Clinical Practice Guideline developed by Irene Mitchelhill, Endocrine Clinical Nurse Consultant, Sydney Children's Hospital Randwick NSW Australia. Document available via: http://www.schn.health.nsw.gov.au/policies/pdf/2014-9017.pdf

clinical guidance developed by the paediatric nurse consultant and her team to support parents and healthcare professionals with identifying and applying "sick day rules" to various situations which can precipitate AC in a child with AI.

Hydrocortisone should be used in the treatment of AC in children for its GC and mineralocorticoid action and rapid bioavailability. The calculation of a "stress dose" of hydrocortisone for children is determined between 3 and 10 times the normal physiological secretion of cortisone of 6–9 mg/m^2/day up to 15 mg/m^2/day (Migeon and Lanes 2009). Tripling the upper limit in this range is often used as a starting point for such calculating sick day doses. The actual dose given for sick day events is determined on the severity of the stressful event and is prescribed between 50 and 100 mg/m^2 (Bornstein et al. 2016).

A child with a suspected AC must be treated immediately with parenteral hydrocortisone (IM as priority pending IV access) and diagnostic measures must not delay administration. As a general guide, the following steps should be followed (Bornstein et al. 2016; Lecahwg 2002) although it is advisable to refer to hospital emergency management guidelines if available.

Step 1: Give Hydrocortisone IM/IV as a stat dose using a suggested aged-based dosing guide of: 25 mg <3 years, 50 mg 3–12 years, 100 mg >12 years of age (Bornstein et al. 2016).

NB: Such doses should be repeated if there is an inadequate response.

If IV access is difficult, this is given as an IM injection as a priority for systemic support which can aid IV access.

IM Glucagon follows hydrocortisone for any hypoglycaemia.

Step 2: Start immediate rehydration with isotonic saline infusion according to protocols for age: 10–20 mL/kg 0.9% saline, with ongoing maintenance plus deficit for dehydration given as 0.9% saline and 5% glucose and adjusted according to electrolytes and blood glucose (SCHN 2017; RCHM 2016).

Step 3: Correct hypoglycaemia which is often evident with AC in children. If blood glucose (BG) level <3.5 mmol/L, give 2 mL/kg IV of 10% glucose and recheck BG in 30 min. IM Glucagon should be given if IV access is delayed. (SCHN 2017; RCHM 2016).

Step 4: Start continuous IV infusion of hydrocortisone after bolus injection at 45 mg/m^2, or in divided doses 6 hourly using the following age-related dosage guide: ≤3 years—20–30 mg per 24 h, 3–12 years—50–60 mg per 24 h; >12 years—100 mg per 24 h (Webb and Krone 2015).

Omeprazole should be considered to prevent gastritis if stress hydrocortisone treatment is prolonged.

Step 5: Treat the precipitating factor (infection or trauma) and manage fevers for comfort.

Step 6: Contact an endocrinologist for urgent review of the child and further management of hydrocortisone dosing.

Step 7: Patient education about "sick day rules" by the endocrine nurse.

Step 8: Stress cover is required for any significant procedures requiring anaesthesia or surgery. Children should have an emergency management plan with medical alerts on both hospital and ambulance systems.

Education and regular review of knowledge is critical for a positive outcome for the child and normal growth and development. Parents of children with known adrenal insufficiency are required to understand the need for additional "stress doses" of glucocorticoids during any significant intercurrent illness, injury, or procedures surgery requiring anaesthesia.

An education review regarding emergency management plans should occur on a regular basis with emergency letters updated yearly. All families should be supplied with a hydrocortisone injection kit for emergencies and trained in its use. Many parents find it difficult to make the "judgement call" regarding the severity of their child's illness and often delay giving an injection of hydrocortisone. A Canadian study of 136 children with AI conducted between 1973 and 2007 found that the use of GC stress doses and administration of hydrocortisone injection increased significantly after 1997 ($p < 0.05$) with improvement in patient education and access to the emergency hydrocortisone injection kit at home (Leblicq et al. 2011).

Nursing management of the critically ill neonate, infant, or child commences with the initial presentation at triage and emergency rescue procedures, the subsequent diagnosis and continues through the treatment and recovery phase until the infant/child is back to full health and lifelong. The most critical component of this process is in providing support for the parents, who will be in a state of shock and disbelief, with their child presenting with a life-threatening condition. Providing clear and simple explanations for the parent initially will help them understand the emergency management procedures and what has led to the cause of the presentation.

Preventing delays at the triage desk in an emergency department is essential (Hahner et al. 2015b). It is important for all parents and adolescents to practice the preparation and administration of an injection on a regular basis to be able to administer the injection before going to the emergency department. Endocrine on-call services are provided by most tertiary healthcare facilities, which can provide important advice and guidance for any concerns.

62.5.2 Management of AC in the Acute Setting

Many ACs occur by the slow reaction time of clinicians involved in the acute care of patients presenting with an AC as they do not understand the urgency of treatment for acute AC or fail to heed the request of well-informed patients for urgent administration of hydrocortisone injection. (Wass and Arlt 2012).

Severe delays in the administration of the emergency hydrocortisone injection have been reported with 15% of patients having to wait between 6 and 12 h (Ibrahim et al. 2015); this led to lengthy hospitalisations for 41% of patients in another study (Hahner et al. 2015b). About one in five patients encountered clinicians who had ignored presentation of their medical-alert identification when presenting with an AC (Hahner et al. 2015b). Many patients felt averse to seeking medical help in an AC due to such delays (Ibrahim et al. 2015).

The use of hydrocortisone injection and training for paramedical staff on management of AC and the establishment of a "flagging" system for paramedics to have warning when attending the patient with AI has been successfully adopted by most ambulance services across Great Britain (Box 62.6). This service was initiated in the South of England and led by an endocrinology clinical nurse specialist (CNS) (Cox 2006). Patients feel safer when they ring the ambulance service, and paramedics are more prepared and competent at managing an AC successfully without delays (Quinkler and Hahner 2012).

Box 62.6 Good Clinical Practice Example: Development of a Care Pathway for Management of AC by Ambulance Service

Sue Cox, a Clinical Nurse Specialist from Torbay in the South of England, UK, initiated and led the development of a training programme and treatment pathway on the management of AC for the local ambulance crew in 2005. A few weeks later, Kevin, one of the paramedics who attended the training, was able to respond promptly to an emergency call to a 63-year-old man at his home who had collapsed and was not breathing following an AC. Hydrocortisone 100 mg was administered immediately and the patient regained consciousness on the journey to hospital. Response time was 20–30 min and the patient made a complete recovery and was discharged from hospital 2 days later.

Since then, endocrinology specialists led by Professor John Wass in collaboration with the national patient advocacy groups, the Addison's Disease Self Help Group (https://

www.addisons.org.uk) and the Pituitary Foundation (https://www.pituitary.org.uk), and the Joint Royal Colleges Ambulance Liaison Committee, have developed a national pathway and guidance on the treatment of AC which is adopted by most ambulance services in the UK. This results in improved awareness among paramedical staff regarding the treatment of AC and can avoid unnecessary hospital admissions and eliminate preventable deaths.

The "**Get Red Flagged**" campaign by the Pituitary Foundation has also been a significant development in the UK as it empowers patients with AI to register with their local ambulance, so they can be "flagged" for priority attendance by a vehicle carrying emergency hydrocortisone.

NOTE: The case study, used with permission from the Addison's Disease Self Help Group, was published in their newsletter, ***issue 83, March 2006.***

The endocrine nurse has a crucial role in ensuring that patients and their families know how to contact acute services and, where available, to register with the ambulance service. Involvement or leading on training and teaching sessions for acute care healthcare professionals should also form an important component of the endocrine nurses' role. Until the time comes when all paramedical staff and acute care healthcare professionals are fully trained on treatment protocols for AC, it is important that we prepare our patients to act based on the principle of:

> "*The well-informed patient (or his/her relative) guides the poorly informed health-care professional!*" (Allolio 2015: R121).

62.6 Patient Education for the Prevention and Management of Adrenal Crisis

Patient education is of paramount importance in the prevention and management of AC and the endocrine nurse is a key player in this aspect.

All patients with AI, their families, partners, and/or friends should be involved in the education process to support patients' self-management and prevention of AC. This helps to act adequately in critical situations in a self-care setting and to communicate with healthcare professionals who are not familiar with AC. Patient education should cover the following aspects:

- Daily maintenance of GC replacement to avoid over- or under-replacement
- "Sick day rules" and adjustment of GC replacement during intercurrent illness
- Prevention and management of AC and training on self-administration for hydrocortisone injection

Nursing-led education programmes for patients with AI have been documented since the early 1960s (Shea et al. 1965) and recent evidence suggests that patient education interventions improve satisfaction and knowledge with GC replacement and prevention of AC. Group education programmes for patients with AI are now standard practice in many centres across the world and have shown improvement in the patients' satisfaction, confidence, and knowledge of adjusting GC replacement during "sick days" and self-administration of hydrocortisone injection to prevent AC (Repping-Wuts et al. 2013; Saeed et al. 2011; van der Meij et al. 2016). Patient education however does not translate to improved adherence to GC replacement (Llahana 2013; van Eck et al. 2016) or reduction in the prevalence of AC and hospital admissions (Hahner et al. 2010; 2015a; van der Meij et al. 2016), even though

patients attended highly experienced units in AI with skilled staff and good patient education standards.

Omori et al. found that duration from diagnosis of AI longer than 4 years was the largest single contributor to the relative risk factor for AC as patients' ability to recognise and prevent AC had declined over the years. Although they could not elucidate on reasons for this, they postulated that patients had forgotten their "sick day rules" and suggested that patient education is provided in every consultation (Omori et al. 2003). In another study of 338 patients with AI, less than 42% could recall information on GC dose adjustment and use of emergency steroid card, following face-to-face teaching during clinic consultations (Harsch et al. 2010). It is therefore recommended that patient education is provided at every consultation and at least annually (Bornstein et al. 2016; Allolio 2015).

62.6.1 Pitfalls in the Patient Education Process and Future Directions

The goal for patient education is to achieve long-lasting changes in health behaviour and for this a robust research methodology is needed to develop and deliver structured educational programmes (Llahana and Thomas 2016). Patient education programmes in AI have so far lacked theoretical underpinning and a research methodology which can explain the likely influences of the programme on behaviour change; details of the interventions are not fully reported, and more importantly outcome measures are not clearly articulated.

To this end, a standardised structured education programme in AI was developed and established in Germany in 2014 (Box 62.7); preliminary data from 212 patients show significant improvement in self-management and prevention of AC post intervention (Eff et al. 2016).

Box 62.7 The Structured Group Education Programme for Patients with AI in Germany

The Adrenal Section of the German Society for Endocrinology initiated in 2014 a structured patient group education programme in AI which has now been adopted by 77 endocrinology centres across Germany; endocrinology nurses have played a crucial role in the development of this programme and are at the core of its delivery. An 8-h training session every year is required to attain certification to deliver this programme, ensuring thus standardisation of the programme and transferability across the centres; 186 nurses and physicians completed the certification training at the time of writing this chapter.

After successful participation of the teaching course, the centres are qualified for the use of the teaching programme. Standardised training materials (and the teaching program) are available to all qualified teaching teams via an internet-based platform. The programme consists of multiple elements, topics, and learning points to tailor the teaching individually to the needs of the patients attending. The teaching is delivered in 2 sessions of 90–120 min each and takes place in small groups of 3–5 patients with accompanying relatives or spouses. The patients learn general information on adrenal insufficiency, signs and symptoms of hypocortisolism, the steroid adjustment in special situations and critical situations, and learn self-administration of parenteral hydrocortisone.

Good practice example provided by and used with permission from Marcus Quinkler, Professor of Endocrinology, Berlin, Germany.

Despite advantages of group educational programmes, one should not assume that this approach is suitable for all patients. Geographical dispersion, time/date restrictions when educational programmes are delivered, literacy levels, and patients' comfort levels of learning and interacting within a group may often influence low uptake and attendance rates in these programmes (Repping-Wuts et al. 2013; Martinez-Momblan et al. 2016). Group educational programmes generally adopt a "one fits all" approach which lacks the ability to individualise the intervention to each patient's needs. "Real-time" access to information and continuous reinforcement of existing knowledge is important and support should continue beyond the duration of a formal educational programme.

Specific individualised education and a person-based plan (Yardley et al. 2015) of "sick day rules" should be provided to patients with AI and this can only be achieved with one-to-one consultations. This however can be time consuming and, with current financial pressures in the health service, resources may not always allow detailed cover of all aspects of patient education. With recent advances in digital technology, we need to be creative and eHealth educational programmes may present many opportunities to provide patients with "real-time" structured and individualised education to complement face-to-face care away from the traditional hospital setting (Llahana and Thomas 2016; Yardley et al. 2015).

Moreover, education programmes should not only aim to improve patient's knowledge and self-management but should also adopt psychosocial approaches to address patient motivations, beliefs, and perceptions of their condition and treatment. Evidence shows a clear association between patient beliefs, concerns, and attitudes regarding their GC treatment, nonadherence, and increase in the incidence of AC (Allolio 2015; Smans et al. 2016; Chapman et al. 2016; Rushworth et al. 2015; Tiemensma et al. 2014). A pragmatic approach should be provided for patients to understand the necessity for the adjustment of GC replacement during sick days and that this but could potentially save their lives.

Education should not be directed only to patients and their families, but should include healthcare professionals such as general practitioners, paramedical staff, and emergency services clinicians. A wider awareness is needed to inform the public, school teachers, employers, and most importantly to influence the political agenda in addressing the seriousness of the AC and to eliminate preventable hospitalisations and deaths from AC. The current "emergency pack" is very complex for an already compromised patient to be able to self-administer when having an AC, and hence patients must rely on family, friends, and acute medical services. As Allolio stated, only the availability of a hydrocortisone autoinjector will bypass the current barriers of self-administration and as industry are reluctant to develop such a device, public funding is needed (Allolio 2015). More robust evidence is needed, and endocrine nurses are strategically placed to collect research and clinical data regarding patients' and families' needs to support the need for this change in the management of AC. This requires them to practise at an advanced level with clinical expertise, expert coaching, consultation skills, and research competence (Hamric et al. 2013) (please read Chaps. 67–69 for more details).

62.7 The Importance of Collaboration with Patient Advocacy Groups

The value of resources and importance of collaboration with patient support groups in AI has already been highlighted throughout this chapter; below we describe the resources available via the Addison's Disease Self Help Group (ADSHG) to illustrate this further. Endocrine nurses should encourage membership as it can be helpful in allowing patients with AI to associate with others with the same conditions and similar experiences. This can encourage a more active and independent role in self-management.

62.7.1 The Addison's Disease Self Help Group (ADSHG), UK

ADSHG is supported by an independent panel of endocrinologists with an interest in adrenal medicine, known as the Addison's Clinical Advisory Panel. They have authored a series of valuable medical guidelines on the management of Addison's disease and adrenal crisis, which the charity makes available to the public on its website, free of charge. ADSHG literature, available as open access publications on its website, may be copied by medical practitioners for use as an educational resource with their patients, or by individuals for personal use.

The growth of social media over the past decade has profoundly changed the dynamic of voluntary groups and peer support for medical conditions. In addition to print literature, ADSHG today offers its community of interest a series of open access educational videos, also published on You Tube, illustrating intramuscular injection method for prevention of adrenal crisis. The charity makes print copies of its literature available, at cost, through its online Shop, along with practical documentation to support emergency medical treatment or elective surgery, such as the hospital folder. Subscribers to the charity also benefit from access to a confidential (closed) discussion forum where they can share day-to-day experiences with others. There is also a privately published newsletter for members available to the charity's registered subscribers, who numbered nearly 2000 in the summer of 2018. ADSHG members arrange local social meetings around the UK, and the charity's annual medical lecture and AGM usually takes place in London in early summer.

Peer learning and support is increasingly recognised as a useful tool to facilitate effective self-management by patients with long-term conditions. Hearing from others that self-injection was easier than they had thought and hurt less than they feared will often provide more reassurance to the newly diagnosed patient than anything a clinician could say. Peer learning can literally help to save lives. In the 2 years since it was launched online, ADSHG's Personal stories video about self-injection has been viewed more than 8600 times.

Personal stories conveyed via ADSHG's web discussion forum, about how people who are steroid dependent adjust their medication for infectious illness, can often offer practical guidance to those newly diagnosed more speedily and concretely than the same "sick day rules" instruction could be relayed from their GP or endocrine team.

62.7.2 Contact details for Addison's Disease Self-Help Group

Website: https://www.addisons.org.uk
Email: enquiries@addisons.org.uk
Twitter: https://twitter.com/addisonsuk
Facebook: https://www.facebook.com/addisons.org.uk

62.8 Conclusions

This chapter provided a comprehensive overview of the causes, prevalence, and clinical presentation of adrenal crisis in adults and children with adrenal insufficiency. It is a life-threatening condition, and although easily treatable, many patients still experience devastating hospital admissions and fatalities which are preventable with immediate treatment with parenteral hydrocortisone. Patient education and supportive infrastructure and care services are the key to improving the prevalence of AC. The endocrine nurse is a key member in the multidisciplinary team to support patients and their families with day-to-day self-management and prevention of AC. Endocrine nurses however should also strive for strategic involvement in the care services and driving the political agenda to emphasise the need for improvement and change to minimise the preventable hospitalisations and to eliminate the devastating deaths from AC. Involvement in research is necessary as the endocrine nurse is best placed to identify and address research questions that can provide the evidence needed to change practice.

Acknowledgments With special thanks to the following organisations that provided us with

permission to use case studies, patient resources, and information on their Patient Advocacy Groups:

Addison's Disease Self Help Group, United Kingdom, https://www.addisons.org

AdrenalNet (European Adrenal Network), https://www.adrenals.eu

The Pituitary Foundation, United Kingdom, https://www.pituitary.org.uk

Australian Addison's Disease Association, Australia, http://www.addisons.org.au

References

Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015;172(3):R115–24.

Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361(9372):1881–93.

Arlt W, Society for Endocrinology Clinical Committee. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect. 2016;5(5):G1–3.

Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216–26.

Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab. 2006;91(12):4849–53.

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.

Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metabol. 2015;100(6):2171–80.

Brook CGD, Dattani MT. Handbook of clinical endocrinology, 2nd ed. In: Blackwell W, editor; 2012.

Chapman SC, Llahana S, Carroll P, Horne R. Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. Clin Endocrinol. 2016;84(5):664–71.

Cox S, editor. Torbay adrenal and pituitary project, poster 187. In: 8th European Congress of Endocrinology, Glasgow, 1–5 April 2006; 2006.

DoH. Reference costs 2014–15. London: Department of Health; 2015. https://www.gov.uk/government/. Accessed 7 Mar 2016.

Eff A, Burger-Stritt S, Quinkler M, editors. Evaluation of a German-wide education programme for patients with adrenal insufficiency—first interim analysis DACH-symposium of the DGE, ÖGES and SGED, 26–28 May 2016, München, Germany; 2016.

EMA. Prescribing information and summary of product characteristics for modified release hodrocortisone, Plenadren®. EMA (European Medicines Agency); 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002185/WC500117637pdf

Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol. 2009;160(2):233–7.

Flemming TG, Kristensen LO. Quality of self-care in patients on replacement therapy with hydrocortisone. J Intern Med. 1999;246(5):497–501.

Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency—a worldwide patient survey. BMC Endocr Disord. 2012;12:8.

Grossman AB. Clinical review: the diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab. 2010;95(11):4855–63.

Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010;162(3):597–602.

Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. Eur J Endocrinol. 2013;169(2):147–54.

Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015a;100(2):407–16.

Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the management of adrenal crisis—targets, limits and reality. Clin Endocrinol. 2015b;82(4):497–502.

Hamric AB, Hanson CM, Tracy MF, O'Grady ET. Advanced practice nursing: an integrative approach. St Louis: Elsevier Health Sciences; 2013.

Harsch IA, Schuller A, Hahn EG, Hensen J. Cortisone replacement therapy in endocrine disorders—quality of self-care. J Eval Clin Pract. 2010;16(3):492–8.

HSCIS. Hospital episode statistics, admitted patient care—England, 2014–15 [NS]: diagnosis. In: Centre HSCI, editor. London: Health & Social Care Information Centre; 2015. http://www.hscic.gov.uk/. Accessed 7 Mar 2016.

Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104–15.

Ibrahim C, Mahon JL, Fraser L-A, Uum SV, editors. Adrenal insufficiency, quality of life, and treatment in the emergency room [Adequate study]. In: Endocrine Society's 97th annual meeting and expo, 5–8 March 2015, San Diego, USA; 2015.

Johannsson G, Skrtic S, Lennernas H, Quinkler M, Stewart PM. Improving outcomes in patients with adrenal insufficiency: a review of current and future treatments. Curr Med Res Opin. 2014;30(9):1833–47.

Kwok MY, Scanlon MC, Slyper AH. Atypical presentation of shock from acute adrenal insufficiency in an adolescent male. Pediatr Emerg Care. 2005;21(6):380–3.

Leblicq C, Rottembourg D, Deladoey J, Van Vliet G, Deal C. Are guidelines for glucocorticoid coverage in adrenal insufficiency currently followed? J Pediatr. 2011;158(3):492–8.e1.

Lecahwg J. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. J Clin Endocrinol Metab. 2002;87(9):4048–53. https://doi.org/10.1210/jc.2002-020611.

Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. J Pediatr. 1990;117(6):892–6.

Llahana S, editor. Assessing treatment satisfaction, knowledge and adherence of patients attending a pituitary Nurse-led Clinic. European Congress of Endocrinology; Copenhagen, Denmark: Endocrine Abstracts (2013) 32 N5; 2013.

Llahana S, Thomas N. Structured nursing educational programs improve quality of life outcomes in patients with Cushing's syndrome. Endocrine. 2016;53(1):1–3. https://doi.org/10.1007/s12020-016-0934-5.

Martinez-Momblan MA, Gomez C, Santos A, Porta N, Esteve J, Ubeda I, et al. A specific nursing educational program in patients with Cushing's syndrome. Endocrine. 2016;53(1):199–209.

Migeon CJ, Lanes R. Adrenal cortex: hypofunction and hyperfunction (Chpater 8). In: Lifshitz F, editor. Pediatric endocrinology. Growth, adrenal, sexual, thyroid, calcium and fluid balance disorders, vol. 2. 5th ed. New York: Informa Healthcare; 2009.

Miller W, Achermann JC, Fluck CE. The adrenal cortex and its disorders (Chapter 12). In: Sperling MA, editor. Pediatric endocrinology. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2008. p. 444–512.

Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engstrom BE, et al. Long-term safety of once-daily, dual-release hydrocortisone in patients with adrenal insufficiency: a phase 3b, open-label, extension study. Eur J Endocrinol. 2017;176(6):715–25.

Omori K, Nomura K, Shimizu S, Omori N, Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. Endocr J. 2003;50(6):745–52.

Peacey SR, Pope RM, Naik KS, Hardern RD, Page MD, Belchetz PE. Corticosteroid therapy and intercurrent illness: the need for continuing patient education. Postgrad Med J. 1993;69(810):282.

Quinkler M, Hahner S. What is the best long-term management strategy for patients with primary adrenal insufficiency? Clin Endocrinol. 2012;76(1):21–5.

Quinkler M, Dahlqvist P, Husebye ES, Kampe O. A European Emergency Card for adrenal insufficiency can save lives. Eur J Intern Med. 2015;26(1):75–6.

RCHM. Adrenal crisis and acute adrenal insufficiency. The Royal Children's Hospital Melbourne. 2016. https://www.rch.org.au/clinicalguide/guideline_index/Adrenal_crisis_and_acute_adrenal_insufficiency/.

Repping-Wuts HJWJ, Stikkelbroeck NMML, Noordzij A, Kerstens M, Hermus ARMM. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. Eur J Endocrinol. 2013;169(1):17–22.

Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. BMC Endocr Disord. 2014;14:79.

Rushworth LR, Slobodian P, Torpy DJ. Interruptions to supply of high-dose hydrocortisone tablets and the incidence of adrenal crises. Clin Endocrinol. 2015;83(6):999–1000.

Saeed M, Aung T, MacDonald J, Wass J, Karavitaki N, editors. Steroid replacement education: impact on patients and their carers, poster 286. In: Society for Endocrinology BES 2011, 11–14 April 2011, Birmingham, UK; 2011.

SCHN. RCH clinical practice guideline: adrenal insufficiency—emergency management practice guideline. The Sydney Children's Hospitals Network. 2017. http://www.schn.health.nsw.gov.au/_policies/pdf/2014-9017.pdf.

Schuetz P, Leuppi JD, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Prospective analysis of adrenal function in patients with acute exacerbations of COPD: the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial. Eur J Endocrinol. 2015;173(1):19–27.

Shea KM, O'Connor CP, Karafelis EG, Thorn GW, Kozak GP. Teaching a patient to live with adrenal insufficiency. Am J Nurs. 1965;65(12):80.

Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. Clin Endocrinol. 2016;84(1):17–22.

Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(9):4133–60.

Tiemensma J, Andela CD, Pereira AM, Biermasz NR, Kaptein AA, Romijn JA. Patients with adrenal insufficiency hate their medication: the relation between medication beliefs and illness perceptions. Endocr Rev. 2014;35.

Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. 2001;357(9254):425–31.

van der Meij N, van Leeuwaarde RS, Vervoort SCJM, Zelissen PMJ. Self-management support in patients with adrenal insufficiency. Clin Endocrinol. 2016;85(4):652–9. https://doi.org/10.1111/cen.13083.

van Eck JP, Gobbens RJ, Beukers J, Geilvoet W, van der Lely AJ, Neggers SJ. Much to be desired in self-management of patients with adrenal insufficiency. Int J Nurs Pract. 2016;22(1):61–9.

Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. BMJ. 2012;345:e6333.

Wass J, Howlett T, Arlt W, Pearce S, Drake W, Swords F, et al. Surgical guidelines for Addison's disease and other forms of adrenal insufficiency. London: Addison's Self Help Group; 2017.. www.addisons.org.uk/surgery

Webb EA, Krone N. Current and novel approaches to children and young people with congenital adrenal hyperplasia and adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2015;29(3):449–68.

White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol. 2010;162(1):115–20.

White K, Wass J, editors. Steroid-dependent patients with multiple co-morbidities are more vulnerable to adrenal crisis. Edinburgh: Society for Endocrinology BES; 2015.

Yardley L, Morrison L, Bradbury K, Muller I. The person-based approach to intervention development: application to digital health-related behavior change interventions. J Med Internet Res. 2015;17(1):e30.

Key Reading

1. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol 2015;172(3):R115–24.
2. Arlt W, Society for Endocrinology Clinical Committee. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect. 2016;5(5):G1–3.
3. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216–26.
4. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.
5. Grossman AB. Clinical review: the diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab. 2010;95(11):4855–63.
6. SCHN. RCH clinical practice guideline: adrenal insufficiency—emergency management practice guideline. The Sydney Children's Hospitals Network. 2017. http://www.schn.health.nsw.gov.au/_policies/pdf/2014-9017.pdf.

Thyroid Emergency: Thyroid Storm and Myxoedema Coma

63

Paul V. Carroll

Contents

63.1 **Thyroid Emergency: Thyroid Storm and Myxoedema Coma** 1208

63.2 **Thyroid Storm** 1208
63.2.1 Clinical Presentation of Thyroid Storm 1209
63.2.2 Diagnosis of Thyroid (Thyrotoxic) Storm 1209
63.2.3 Priorities in the Assessment and Management of Severe Thyrotoxicosis 1209
63.2.4 Outcome of Thyroid Storm 1212
63.2.5 Severe Hypothyroidism/Myxoedema Coma 1212
63.2.6 Outcome of Patients Presenting with Myxoedema Coma 1214

63.3 **The Role of Endocrine Nurse in Thyroid Emergency** 1214

63.4 **Conclusions** 1215

References 1215

Abstract

This chapter outlines the presentation, assessment, and management of patients presenting with acute thyroid-related illness including thyroid storm and myxoedema coma. Thyroid storm is a clinical diagnosis describing severe thyrotoxicosis, often with multi-organ dysfunction. Patients need intensive care, and treatment to reduce the metabolic effects of thyrotoxicosis and lower circulating thyroid hormones. Thyrotoxicosis is the term for the clinical syndrome that results from exposure to excessive levels of circulating thyroid hormones. Hyperthyroidism is used to describe thyrotoxicosis resulting from overproduction of thyroid hormones by thyroid cells and there are several possible aetiologies. Thyrotoxicosis also occurs in the absence of hyperthyroidism, for example, when stored hormones are released in a destructive thyroiditis. The common causes of hyperthyroidism (Graves' disease, toxic nodular goitre, Hashimoto's thyroiditis, and others) are comprehensively covered in Chapter 28. Myxoedema coma is a rare presentation of severe hypothyroidism. It is most commonly seen in the elderly. Management is supportive and includes thyroid hormone replacement; there is often hypothermia and cardiac dysfunction. Mortality in myxoedema coma remains high.

P. V. Carroll (✉)
Department of Endocrinology, Guy's & St. Thomas' NHS Foundation Trust, DEDC 3rd Floor Lambeth Wing, St. Thomas' Hospital, London, UK
e-mail: paul.carroll@gstt.nhs.uk

Keywords

Thyrotoxicosis · Hyperthyroidism · Hypothyroidism · Thyroid crisis · Thyroid storm · Myxoedema · Coma

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_63

Abbreviations

AF	Atrial fibrillation
ATDs	Anti-thyroid drugs
BP	Blood pressure
BWPS	Burch-Wartofsky Point Scale
CNS	Central nervous system
CVA	Cerebrovascular accident
CVP	Central venous pressure
ECG	Electro-cardiogram
HDU	High dependency unit
ITU	Intensive therapy unit
IV	Intravenous
NG	Nasogastric
PO	Per oral
PTU	Propylthiouracil
SSKI	Saturated solution of potassium iodide
T3	Tri-iodothyronine, liothyronine
T4	Thyroxine, levothyroxine
TSH	Thyroid stimulating hormone

Key Terms

- **Hyperthyroid:** Conditions that cause increased secretion of thyroid hormones from the thyroid gland that leads to thyrotoxicosis.
- **Thyrotoxicosis:** Clinical syndrome results from exposure to excessive levels of circulating thyroid hormones.
- **Thyroid (thyrotoxic) storm:** A clinical diagnosis describing severe thyrotoxicosis, often with multi-organ dysfunction.
- **Myxoedema coma:** An emergency hypothyroid condition presented with hypothermia, reduced conscious level, bradycardia, bradycapnoea, hypoxaemia, hyponatraemia, hypercapnia, hypercalcaemia, hypoglycaemia, and elevated creatine kinase.

Key Points

- Thyroid storm is a rare endocrine emergency and occurs in patients with untreated or undertreated thyrotoxicosis. The most common aetiology is Graves' disease. (Refer to thyroid chapter for explanation of Graves' disease).
- The diagnosis is a clinical one.
- Clinical symptoms are caused by elevated circulating levels of free thyroid hormones, causing severe features of thyrotoxicosis and multi-organ dysfunction.
- Prompt recognition and urgent management are required to improve outcome. Patients should be managed in the HDU or ITU.
- Myxoedema coma is a rare endocrine emergency. The condition most commonly occurs in the elderly and is associated with high mortality.
- Management involves supportive care and replacement of thyroid hormone deficiency.

63.1 Thyroid Emergency: Thyroid Storm and Myxoedema Coma

There are two types of endocrine emergencies related to thyroid conditions: (1) thyroid storm which is a clinical diagnosis describing severe thyrotoxicosis and (2) myxoedema coma describing severe hypothyroidism. It is most commonly seen in the elderly.

63.2 Thyroid Storm

This potentially life-threatening condition can be an initial presentation of an undiagnosed patient or an acute exacerbation of thyrotoxicosis. It is characterised by marked hyper-metabolism and an exaggerated adrenergic response. As well as being an initial presentation, thyroid storm may be precipitated by specific thyroid treatments (surgery or radioiodine) in a patient with inadequately controlled thyrotoxicosis, or in a patient with thyrotoxicosis following parturition or during a severe illness (including uncontrolled diabetes, severe infection, or myocardial infarction (Bahn et al. 2011)). Hyperpyrexia is the striking feature but tachycardia, atrial fibrillation (AF), heart failure, agitation, confusion, vomiting, diarrhoea, coma,

Table 63.1 Systemic effects of thyrotoxicosis

System	Effects
General	Weight reduction, nervousness, irritability, heat intolerance, fatigue, poor sleep
Skin	Warm, moist palms, hyperhidrosis, urticaria, itching, exacerbation of eczema
Eye	Periorbital oedema, lid lag and retraction, chemosis, exophthalmos, opthalmoplegia, redness, loss of vision
CNS	Irritability, worsening of psychiatric conditions, stupor, coma
CVS	Tachycardia, cardiomegaly, heart failure, rhythm disturbance
Respiratory	Dyspnoea
Bone	Reduced bone mineral density
Fertility/reproduction	Gynaecomastia, infertility, light or absent menstrual periods
Metabolic	Hyperglycaemia, hypercalcaemia
Gastrointestinal	Diarrhoea/hyperdefecation
Neuromuscular	Tremor, myopathy, paralysis

and shock can variably occur. Patients are best managed in an intensive care/therapy environment (ITU). Treatment is aimed at reducing thyroid hormone secretion, supportive therapy, and treatment of the precipitating underlying cause.

63.2.1 Clinical Presentation of Thyroid Storm

The clinical features of thyrotoxicosis depend on the severity and duration of the condition, age of the patient, extra-thyroidal manifestations, and the specific cause of the thyrotoxicosis. Thyroid hormone excess affects all organ systems and the symptoms and signs of thyrotoxicosis are similar regardless of aetiology. Widespread effects occur due to the stimulation of metabolic processes and sensitisation of the sympathetic nervous system (Table 63.1). In the elderly, the symptoms may be less marked than in younger patients. Graves' disease has additional features, in particular thyroid eye disease and diffuse goitre with bruit, indicative of increased vascularity.

Both Graves' disease and toxic nodular goitre are commonly associated with enlargement of the thyroid gland. Toxic adenoma and multinodular goitre commonly result in an asymmetric thyroid gland. The goitre of Graves' disease is typically visible, diffusely enlarged, smooth, and in more severe presentations associated with a bruit or thrill.

Thyroid storm is a rare but important presentation of untreated or undertreated thyrotoxicosis. Also known as thyroid crisis this is a life-threatening condition, with features of thyrotoxicosis and acute multisystem involvement with dysfunction.

63.2.2 Diagnosis of Thyroid (Thyrotoxic) Storm

The diagnosis is a clinical one and should be considered in the patient with fever, abnormal mental state, rapid sinus tachycardia, or atrial fibrillation, who also has signs of thyrotoxicosis (Burch and Wartofsky 1993). Thyrotoxic storm is an acute life-threatening metabolic emergency. If the diagnosis is suspected, anti-thyroid medical treatment should be started without delay (e.g. when suspected even if not biochemically confirmed). Maintenance of the circulation with tissue oxygenation is a key requirement, often with a combination of fluids for volume expansion and beta-blockade to reduce the associated autonomic overdrive .

63.2.3 Priorities in the Assessment and Management of Severe Thyrotoxicosis

63.2.3.1 Assessment: Is This Thyrotoxic Storm?

- The diagnosis of thyrotoxic storm is a clinical one and is based on the identification of actual or impending decompensation of organ function due to thyrotoxicosis (Table 63.2).
- The diagnosis is difficult as thyroid storm represents the end of a spectrum of severity and

Table 63.2 Diagnosis and assessment of severity of thyroid storm (Burch-Wartofsky Point Scale)

Criteria	Points
Thermoregulatory dysfunction	
Temperature	
Less than 37.2 °C (99.0 °F)	0
37.2–37.7 °C (99.0–99.9 °F)	5
37.8–38.2 °C (100.0–100.9 °F)	10
38.3–38.8 °C (101.0–101.9 °F)	15
38.9–39.3 °C (102.0–102.9 °F)	20
39.4–39.9 °C (103.0–103.9 °F)	25
40.0 °C or higher (104 °F or higher)	30
Cardiovascular	
Heart rate	
Less than 100	0
100–109	5
110–119	10
120–129	15
130–139	20
140 or higher	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	20
Gastrointestinal/hepatic dysfunction	
Manifestation	
Absent	0
Moderate (diarrhoea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	20
Central nervous system disturbance	
Manifestation	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure/coma)	30
Precipitant history	
Status	
Present	0
Absent	10
Interpretation	
Total score	**Interpretation**
<25	Thyrotoxic storm unlikely
25–45	Impending thyrotoxic storm
>45	Thyrotoxic storm confirmed

Used with permission from Burch HB, Wartofsky L. Life-threatening hyperthyroidism: thyroid storm. Endocrinol Metab Clin North Am (1993): **22**:263–277

due to inter-patient differences in the tipping point between compensated organ stress and decompensated organ failure.

- Although no universally accepted criteria currently exist, the Burch-Wartofsky Point Scale (BWPS; see Table 63.2) can be used to assess disease severity and guide the extent of treatment and monitoring.

63.2.3.2 Assessment: What Has Triggered the Thyrotoxic Storm?

- Thyrotoxic storm may occur in the course of the natural history of an underlying thyrotoxic process, particularly Graves' disease. It is more often related to decompensation caused by an intercurrent precipitant. This is most frequently an infective illness, but may also be surgery (particularly thyroid surgery or occasionally non-thyroid surgery), other critical illness, and childbirth (Carroll and Matfin 2010).
- Other iatrogenic causes include radioactive iodine therapy in patients with insufficiently controlled hyperthyroidism, abrupt cessation of anti-thyroid medications (or non-adherence to these), administration of iodine-containing pharmaceuticals (e.g. amiodarone) or contrast agents (e.g. for CT imaging), induction of anaesthesia, or neck stimulation in Graves' disease with large goitre (Migneco et al. 2005).

63.2.3.3 Immediate Management

Thyroid storm is an acutely life-threatening condition and must be managed in a level 2 or 3 (resuscitation area/HDU/ITU) setting. Often patients present to the Emergency Department and the condition requires prompt recognition, stabilisation, and initiation of management prior to transfer to an inpatient HDU or ITU (Akamizu et al. 2012). Figure 63.1 outlines an algorithm for the management of thyroid storm (Fig. 63.1). The immediate management priorities (golden hour) are:

- Rapid assessment of airway, breathing, circulation, and conscious level. Establish continuous monitoring of blood pressure, heart rate, and ECG.

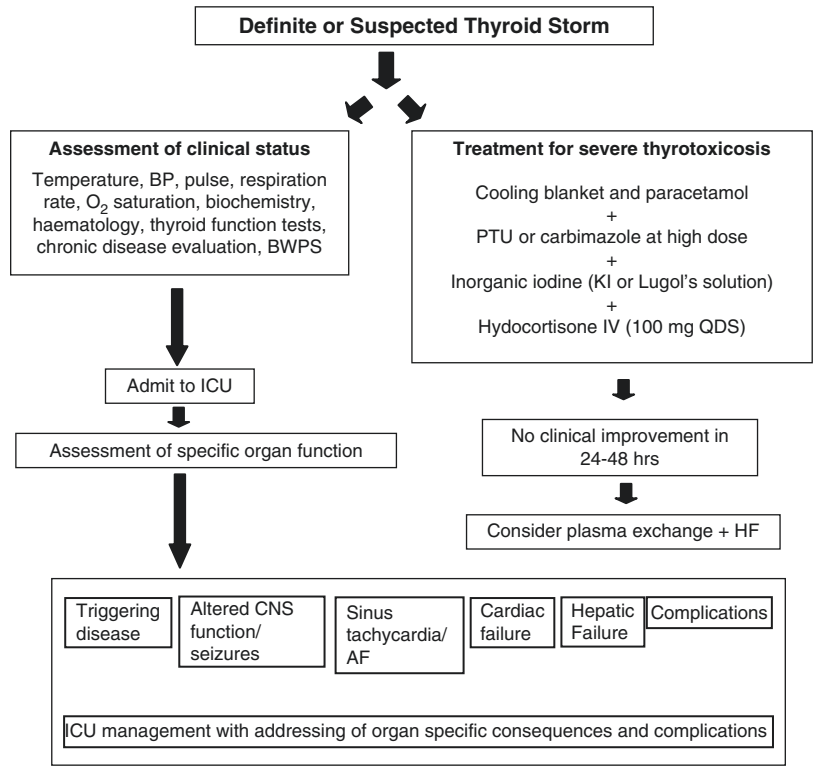


Fig. 63.1 Algorithm for the management of suspected thyroid storm. *BP* blood pressure, *APACHE* acute physiology and chronic health evaluation, *CNS* central nervous system, *ICU* intensive care/ therapy unit, *HF* haemofiltration, *KI* potassium iodide, *AF* atrial fibrillation

- Airway management by competent staff if the airway is compromised or the Glasgow Coma Scale score is less than 8/15.
- Supplemental oxygen if needed to maintain arterial oxygen saturation >95%.
- Haemodynamic stabilisation. Hypotension may be due to high output cardiac failure or a compromising tachyarrhythmia (usually supraventricular). Direct current cardioversion is usually unsuccessful for AF in a severely hyperthyroid patient. Unless there is clinical suspicion of underlying cardiomyopathy, rate-related failure may be managed with a short-acting beta-blocker (e.g. IV esmolol) with prompt withdrawal if clinical state worsens. Patients with thyrotoxic storm and heart failure must be managed in a level 3 environment with continuous BP and CVP monitoring.
- Assessment for common precipitants of thyrotoxic storm: sepsis, diabetic ketoacidosis, or myocardial infarction (see above). If identified, appropriate management initiated. When no precipitating factor is apparent, broad-spectrum antibiotics are warranted until intercurrent infection has been excluded. Cooling measures should be employed to correct fever, initially with paracetamol 1000 mg PO/IV.
- Administer a non-cardioselective beta-blocker, e.g. propranolol 40–80 mg PO. If rapid onset of action needed or if oral route unavailable due to reduced conscious level, intravenous esmolol 50–100 μg/kg/min may be used. Consider an arterial line for continuous blood pressure monitoring if IV beta-blockers initiated.
- Administer a thionamide to prevent further thyroid hormone production, e.g. propylthiouracil 500–1000 mg loading dose PO (followed by 250 mg 4-hourly). Carbimazole may also be used (20–30 mg every 4–6 h PO). There are no intravenous preparations but they may be given via nasogastric tube or rectally if there are concerns about absorption.
- Transfer to HDU/ITU for continuing management.

63.2.3.4 Further Management

- The ongoing management of thyroid storm is directed at reducing further production of thyroid hormone, blocking its release, inhibiting conversion of T4 to active T3, and limiting the adrenergic effects of high thyroid hormone activity. Thionamide treatment should be continued. Propylthiouracil at a dose of 250 mg every 4–6 h has been the preferred agent due to its potential additional benefit in reducing conversion of T4 to active T3. Concerns regarding an association between propylthiouracil and hepatitis should be taken into account and in patients with known liver disease or if liver function tests become abnormal, carbimazole 60–80 mg daily is an alternative. "Cold" iodine (i.e. non-radioactive iodine) can be administered in the form of 3–5 drops of Lugol's solution (5% elemental iodine, 10% potassium iodide in distilled water) or a saturated solution of potassium iodide (SSKI), diluted in water three times daily, making use of the Wolff-Chaikoff effect in which high doses of iodine result in blockade of the incorporation of iodine into thyroglobulin. Effectiveness of iodine solutions is time-limited to approximately 10 days, after which the thyroid escapes this effect by downregulating iodine transporters.
- A beta-blocker should be administered to negate the catecholaminergic effects of thyrotoxicosis. Oral propranolol is most frequently used due to its additional capacity to block peripheral T4 to T3 conversion. The dose is titrated according to cardiovascular variables. In thyrotoxic storm, 60–120 mg 6-hourly PO may be required. Glucocorticoids also reduce peripheral conversion of T4 to T3: hydrocortisone 100 mg 6-hourly IV is a suitable dose.
- In extreme, treatment refractory thyrotoxicosis, plasmapheresis has been used to clear circulating thyroid hormones to allow a window for emergency thyroidectomy to be performed safely.

63.2.4 Outcome of Thyroid Storm

Thyroid storm is a medical emergency with a high mortality rate. Until recently, there has been little published material on the management and outcome of thyroid storm. A taskforce from the Japan Thyroid Association and Japan Endocrine Society have reported data from nationwide surveys, contributing significantly to our knowledge base (Isozaki et al. 2016). This information has helped inform guidance on the assessment and management of the patient with thyroid storm. A recent study (2016) including 356 cases reported an overall mortality rate of 10.7%. In this group of patients, methimazole was the most commonly used anti-thyroid drug, and it has been suggested that there is little difference in outcome and survival, between methimazole and PTU. Most of the patients in this report had multi-modal therapy with ATDs, cold iodine, and corticosteroids, reflecting the severe nature of the presentations. One-hundred percent of thyroid storm patients required admission to ICU and approximately 50% were intubated with positive pressure ventilation. The median length of stay for this group of patients was 10 days. Angell et al. recently highlighted alterations in CNS function (altered mentation) as a risk factor in addition to the BWPS for poor outcome and need for intensive support (Angell et al. 2015). Therapeutic plasma exchange to remove excessive circulating free thyroid hormones has been reported in a small number of patients. This technique appears safe and effective but has a transient effect and other modalities of treatment should continue (Muller et al. 2011).

Early recognition with clinical suspicion, prompt structured management, and intensive support are each an essential requirement for the management of the adult with thyroid storm.

63.2.5 Severe Hypothyroidism/ Myxoedema Coma

At the extreme end of the hypothyroid spectrum is the rare endocrine emergency of myxoedema coma. This condition is thought to have a

prevalence of less than 1 per million per year and is mostly a disease of the elderly. The physical signs of hypothermia closely resemble those of myxoedema coma; however, if there is other evidence of hypothyroidism thyroid hormone and hydrocortisone (as there may be co-existing autoimmune adrenal insufficiency) should be given. Even with treatment, the mortality from myxoedema coma is high (Pangtey et al. 2017).

63.2.5.1 Assessment: Is This Myxoedema Coma?

- Myxoedema coma is a clinical diagnosis and requires an index of suspicion. Known thyroid disease and hypothermia with altered consciousness should prompt consideration of the diagnosis.
- Hypothermia and reduced conscious level are the cardinal features (although most patients are not actually comatose, i.e. Glasgow Coma Scale <8).
- Bradycardia, bradypnoea, and hypoxaemia are common.
- Hyponatraemia, hypercapnia, hypercalcaemia, hypoglycaemia and elevated creatinine kinase are often present.

63.2.5.2 Assessment: What Has Caused the Myxoedema Coma?

- Myxoedema coma is most commonly precipitated by an event causing an increased metabolic demand which exceeds the adaptive mechanisms compensating for chronic hypothyroidism, such as infection or trauma.
- Other triggers include cold weather, long-lie in a cold environment, sedative agents, general anaesthesia, acute coronary syndrome, and CVA.
- Hashimoto's thyroiditis, amiodarone, and lithium use has each resulted in presentation of myxoedema coma.

63.2.5.3 Immediate Management

- ABCDE assessment
  - Airway—may be compromised by oedema of the upper respiratory tract structures. Airway adjuncts or intubation may be required, especially if airway not considered safe.
  - Breathing—ventilatory failure is usual and should be confirmed with arterial blood gas analysis. Assisted ventilation is often necessary for the first 24–48 h.
  - Circulation—careful fluid resuscitation, recognising the likely impairment of cardiac contractility, can be employed. Glucocorticoids should be administered (50–100 mg 6-hourly IV). The possibility of undiagnosed autoimmune adrenal insufficiency as a comorbidity should be considered.
- Correct hypoglycaemia using intravenous glucose.
- If possible avoid using a warming blanket. Instead gently and slowly, increase temperature naturally if hypothermic.
- Identify the precipitant and initiate treatment.
  - Infection may be occult and sepsis is unlikely to be accompanied by an elevated temperature. If in doubt, take blood for culture and administer broad-spectrum antibiotics.
  - The ECG will be abnormal and usually shows bradycardia, small voltage QRS complexes, and flattened or inverted T-waves. Varying degrees of heart block may be present. Measure the QTc interval which may be prolonged bringing a risk of polymorphic ventricular tachycardia (torsades des pointes). Assess for evidence of myocardial ischaemia or infarction.
  - Cerebellar signs may be the result of severe hypothyroidism but assess for evidence of an acute stroke.
  - Assess for evidence of an upper gastrointestinal bleed.
  - Obtain a collateral history—there will most commonly be a history of hypothyroidism, thyroid surgery, or radioiodine ablation.
  - Review the drug history for new medications which may have precipitated the acute presentation.

Alert the critical care team and transfer to an appropriate ITU or HDU bed when resuscitation effective.

63.2.5.4 Further Management

Thyroid Hormone Replacement

- Restoration of thyroid hormone activity is essential. There is no high-grade evidence to suggest how this is best achieved. Replacement may be enteral or parenteral; with T4, T3, or both. In the UK IV liothyronine (T3) is available and commonly used.
- Restoring normal target tissue thyroid hormone activity as soon as possible to reverse life-threatening disturbance of body systems must be weighed against the possibility of inducing fatal tachyarrhythmia with rapid correction. The enteral route should lead to a less abrupt increase in circulating thyroid hormone levels and allows for the use of T4 (levothyroxine) which, by virtue of requiring peripheral conversion to T3 for maximal activity, a smoother tissue response. However, absorption may be impaired by oedema, slow transit, or ileus. The intravenous route limits one to using T3 since intravenous preparations of T4 are not commonly available. The associated rapid increase in thyroid hormone receptor activity may induce adverse cardiac events.
- The choice of treatment should be made on a patient-specific basis. The options are:
  - NG T4 alone:
  - NG T4 plus T3
  - IV T3: typically 20 μg/24 h

– T3 and T4 replacement should be carefully titrated against free thyroid hormone levels which may be measured daily. Over-replacement risks tachyarrhythmia in what is likely to be at least temporarily a myopathic heart. Commonly T3 is commenced at escalating doses with subsequent introduction of T4 provided there is no precipitation of myocardial ischaemia or tachyarrhythmia.

63.2.5.5 Supportive Care

- Hypothermia should not be treated with external rewarming since this will induce peripheral vasodilatation negating the compensatory diversion of blood flow to the vital organs.
- Glucocorticoids should be continued until co-existing adrenal insufficiency has been excluded by a short synacthen (co-syntropin) test.
- Ongoing supportive management of organ failure (e.g. mechanical ventilation or vasopressors) while awaiting response to thyroid hormone replacement is a key determinant of outcome. The time to recovery may be variable depending on the duration of severe hypothyroidism.
- Patients should be managed in the ICU, and many will need organ support including inotropic treatment.

63.2.6 Outcome of Patients Presenting with Myxoedema Coma

Myxoedema coma typically occurs in the elderly, often with co-existing chronic health issues. Until recently, there was a paucity of outcome data. A nationwide inpatient database study from Japan recently reported the mortality in myxoedema coma to be ~30% (Ono et al. 2017). Cardiovascular disease was the most common comorbidity and many patients presented during winter months. Older age and need for inotropic support were risk factors for mortality. Although rare, myxoedema coma is associated with significant morbidity and mortality (Murthy et al. 2015; Mathew et al. 2011).

63.3 The Role of Endocrine Nurse in Thyroid Emergency

The majority of patients experiencing a severe thyroid emergency will be admitted to an accident and emergency department. Therefore, an outpatient-based endocrine nurse will rarely be involved in this scenario. However for an endocrine nurse who is involved in thyroid clinics, seeing thyroid patients for blood tests or providing education and supportive care for patients, family, and carers with thyroid conditions, raising awareness on the risk and consequences of thyrotoxicosis, thyroid storm, or myxoedema coma should be part of the patient education for thyroid conditions.

This patient education awareness is important and is as important as the education of adrenal insufficiency patients with steroids replacement therapy, in order to prevent the risk of adrenal crisis or the over treatment with steroids.

An assessment tool for severe thyroid storm (Table 63.2) can be used to determine if a patient is at risk or has developed thyroid storm when assessed in a thyroid clinic. This tool requires the assessor to have the relevant clinical skills in order to make the diagnosis. If the risk of thyroid storm is suspected or identified, an endocrine nurse will need to escalate this emergency to colleagues to seek help and support.

Myxoedema coma is a critical situation. The role of the endocrine nurse is to support ward base colleagues in the management of this group of rare patients and the patients next of kin by utilising their endocrine expertise.

Thyroid storm and myxoedema coma each has complex multi-professional treatment algorithms. Clinical guidelines may be drafted in order to maximise the management of these rare and high-risk patients. The endocrine nurse has an essential role to ensure patient management is followed, patient outcomes measured and support is given to patient, family, and carers. The nurse should follow the guidelines appropriate for their individual clinical setting. Following recovery from severe thyroid-related illness, close follow-up care, and often thyroidectomy for Graves' disease is best managed by the multidisciplinary endocrine team.

63.4 Conclusions

Emergency thyroid presentations including thyroid storm and myxoedema coma are rare but serious consequences of thyroid disease. The mortality and morbidity from these conditions is significant. Endocrine nurse specialists involved in thyroid management must be aware of these complications and recognise presentations at the severe end of the thyroid disease spectrum. Co-ordination of care for the patient with severe thyroid disease is best provided by an experienced endocrine nurse specialist as part of a comprehensive multi-disciplinary team.

References

Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M, Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012;22(7):661–79.

Angell TE, Lechner MG, Nguyen CT, Salvato VL, Nicoloff JT, LoPresti JS. Clinical features and hospital outcomes in thyroid storm: a retrospective cohort study. J Clin Endocrinol Metab. 2015;100(2):451–9.

Bahn R, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN, American Thyroid Association, American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21(6):593–646.

Burch HB, Wartofsky L. Life-threatening hyperthyroidism: thyroid storm. Endocrinol Metab Clin North Am. 1993;22:263–77.

Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. Ther Adv Endocrinol Metab. 2010;1(3):139–45.

Isozaki O, Satoh T, Wakino S, Suzuki A, Iburi T, Tsuboi K, Kanamoto N, Otani H, Furukawa Y, Teramukai S, Akamizu T. Treatment and management of thyroid storm: analysis of the nationwide surveys: the task-force committee of the Japan Thyroid Association and Japan Endocrine Society for the establishment of diagnostic criteria and nationwide surveys for thyroid storm. Clin Endocrinol. 2016;84(6):912–8.

Mathew V, Misgar RA, Ghosh S, Mukhopadhyay P, Roychowdhury P, Pandit K, Mukhopadhyay S, Chowdhury S. Myxedema coma: a new look into an old crisis. J Thyroid Res. 2011;2011:493462.

Migneco A, Ojetti V, Testa A, De Lorenzo A, Gentiloni Silveri N. Management of thyrotoxic crisis. Eur Rev Med Pharmacol Sci. 2005;9(1):69–74.

Muller C, Perrin P, Faller B, Richter S, Chantrel F. Role of plasma exchange in the thyroid storm. Ther Apher Dial. 2011;15:522–31.

Murthy TA, Rangappa P, Jacob I, Janakiraman R, Rao K. Myxoedema coma in adults: experience from a tertiary referral hospital intensive care unit. Indian J Anaesth. 2015;59(5):315–7.

Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical characteristics and outcomes of myxedema coma: analysis of a national inpatient database in Japan. J Epidemiol. 2017;27(3):117–22.

Pangtey GS, Baruah U, Baruah MP, Bhagat S. Thyroid emergencies: new insight into old problems. J Assoc Physicians India. 2017;65(8):68–76.

64 Diagnosis and Management of Pituitary Apoplexy in Adult Patients

Stephanie E. Baldeweg

Contents

64.1 **Introduction** 1218

64.2 **Definition of Pituitary Apoplexy** 1219

64.3 **Pathophysiology of the Clinical Manifestations** 1219

64.4 **Precipitating Factors** 1219

64.5 **Assessments** 1219
64.5.1 Clinical Assessments 1219
64.5.2 Endocrine Assessments 1220
64.5.3 Radiological Assessments 1221

64.6 **Clinical Managements of Pituitary Apoplexy** 1221
64.6.1 Steroid Therapy in Pituitary Apoplexy 1221
64.6.2 Surgery or Conservative Management 1221
64.6.3 Visual Assessment 1223

64.7 **Long-Term Follow-up and Outcomes** 1223
64.7.1 Endocrine Outcomes 1223
64.7.2 Visual Outcomes 1223
64.7.3 Long-Term Monitoring and Surveillance 1223

64.8 **The Role of the Endocrine Specialist Nurse in the Management of Patients with Pituitary Apoplexy** 1224

64.9 **Conclusions** 1224

References 1225

Abstract

Pituitary apoplexy is a rare medical emergency in patients with pituitary tumours. Patients may present at emergency departments or at different medical services and this can lead to diagnostic difficulties and delays. Pituitary apoplexy is caused by a rapid increase in the size of the intrasellar contents leading to increase in the intrasellar pressure. This increased pressure may lead to loss of blood supply to the pituitary gland causing infarction, tumour cell death, bleeding, and tumour swelling. Patient can present with sudden

S. E. Baldeweg (✉)
Department of Diabetes and Endocrinology, University College London Hospitals, London, UK

Department of Medicine, University College London, London, UK
e-mail: Stephanie.baldeweg@nhs.net

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_64

onset of headache, vomiting, visual impairment, and decreased consciousness.

Assessment of suspected pituitary apoplexy includes a mixture of clinical, endocrine, and radiological assessments. Clinical management includes immediate steroid therapy followed by the decision to manage conservatively or surgically. The long-term follow-up includes endocrine and visual assessment and imaging surveillance. The endocrine specialist nurse has an important role in acute management of the patient with apoplexy including performing endocrine testing, steroid replacement therapy education and long term monitoring and outcome measurement.

Keywords
Pituitary emergency · Pituitary apoplexy
Pituitary haemorrhage · Pituitary infarction

Abbreviations

ACTH	Adrenocorticotropic hormone
CRH	Corticotropin-releasing hormone
CT	Computerized tomographic
FBC	Full blood count
FSH	Follicle-stimulating hormone
FT4	Free thyroxine
GH	Growth hormone
GNRH	Gonadotropin-releasing hormone
IGF-1	Insulin-like growth factor 1
ITT	Insulin tolerance test
LFT	Liver function tests
LH	Luteinizing hormone
µg	Microgram
MRI	Magnetic resonance imaging
mu/L	Milliunits per litre
nmol/L	Nanomoles per litre
pmol/L	Picomoles per litre
PRL	Prolactin
T4	Thyroxine, levothyroxine
TFT	Thyroid function tests
TRH	Thyrotropin-releasing hormone
TRH	Thyroid-stimulating hormone, thyrotropin
U&E	Urea, creatinine & electrolytes

Key Terms

- **Apoplexy:** clinical syndrome caused by haemorrhage and/or infarction of the pituitary gland.
- **Decompressive surgery:** pituitary surgery to relieve new or deteriorating visual deficit or neurological deterioration.

Key Points

- Pituitary apoplexy is a rare endocrine emergency and occurs in patients with existing pituitary tumours.
- Clinical symptoms are caused by rapid increase in size of the intrasellar contents, leading to increase in the intrasellar pressure.
- Clinical guidelines provide evidence based and expert consensus data for more effective management of this clinical emergency.
- The endocrine nurse has a vital role to play in the management of this group of patients in both the acute and chronic phases of treatment.

64.1 Introduction

Pituitary apoplexy is a rare medical emergency. The incidence of pituitary apoplexy is between 2 and 7% when defined on the basis of clinical signs with surgical or histopathological evidence. It occurs in a small number of patients with a pituitary tumour, most often a non-functioning macroadenoma. In over 80% of patients, pituitary apoplexy is the first presentation of an underlying pituitary tumour (Rajasekaran et al. 2011).

Apoplexy usually occurs in patients with pre-existing pituitary adenomas and evolves within hours or days. Diagnosing pituitary apoplexy can be difficult and delayed due to clinical unawareness of the presence of a pre-existing pituitary tumour. Patients may present as an emergency to emergency units or to different specialties. This can lead to diagnostic difficulties and delays with significant morbidity and possible mortality.

There are uncertainties about the management of pituitary apoplexy. It is not clear whether immediate neurosurgical intervention is essential to improve outcomes, or if a more conservative approach provides similar outcomes. UK National guidelines have therefore been developed and published with wide consultation of stakeholders in 2011 (Rajasekaran et al. 2011; Baldeweg et al. 2016).

64.2 Definition of Pituitary Apoplexy

Classical pituitary apoplexy refers to a clinical syndrome caused by haemorrhage and/or infarction of the pituitary gland. Patients can present with

- Sudden onset of headache
- Vomiting
- Visual impairment and
- Decreased consciousness

64.3 Pathophysiology of the Clinical Manifestations

The clinical manifestations of pituitary apoplexy are due to a rapid increase in the size of the intrasellar contents, leading to increase in the intrasellar pressure. This sudden increase in size of a pituitary adenoma may compress the following:

- Normal pituitary gland
- Optic nerves
- Nerves that control eye movements

The compression may also lead to a loss of blood supply (pituitary infarct), which can cause tumour cell death, bleeding, and sudden tumour swelling (Rajasekaran et al. 2011).

The earliest most common symptom of pituitary apoplexy is sudden severe headache which may be accompanied by nausea and vomiting. Lateral compression can affect the contents of the cavernous sinus leading to ocular palsies in nearly 70% of the patients (Rajasekaran et al. 2011).

The third (oculomotor) nerve is the most common cranial nerve affected. Decreased visual acuity and visual field defects, specifically bitemporal hemianopia are seen in nearly 75% of the patients and are caused by optic chiasmal compression. Extravasation of blood or necrotic tissue into the subarachnoid space can cause meningism resulting in fever, photophobia, and altered consciousness level.

64.4 Precipitating Factors

Precipitating factors have been identified in nearly half of cases of pituitary apoplexy. The commonest precipitating factor was hypertension. Major surgery, especially coronary artery bypass grafting, can also precipitate apoplexy (Rajasekaran et al. 2011; Baldeweg et al. 2016).

For the specialist nurse, it is especially important to know that dynamic testing of the pituitary gland, using gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and insulin tolerance test (ITT) have all been reported to trigger pituitary apoplexy. In the reported cases of pituitary apoplexy after pituitary tests apoplexy occurred within 2 h in 83% and within 88 h in all patients (Rajasekaran et al. 2011).

Patients known to have a pituitary tumour must therefore be observed for signs and symptoms of pituitary apoplexy when performing pituitary stimulation tests, commencing anticoagulation therapy, or undertaking coronary artery bypass or other major surgery.

64.5 Assessments

64.5.1 Clinical Assessments

A diagnosis of pituitary apoplexy should be considered in all patients presenting with acute severe headache with or without neuro-ophthalmic signs. Figure 64.1 presents the algorithm for the emergency management of pituitary apoplexy in adult patients published by the Society for Endocrinology in the UK (Baldeweg et al. 2016).

Pituitary apoplexy most frequently occurs in a patient with an undiagnosed pituitary tumour. Initial assessment of the patients presenting with

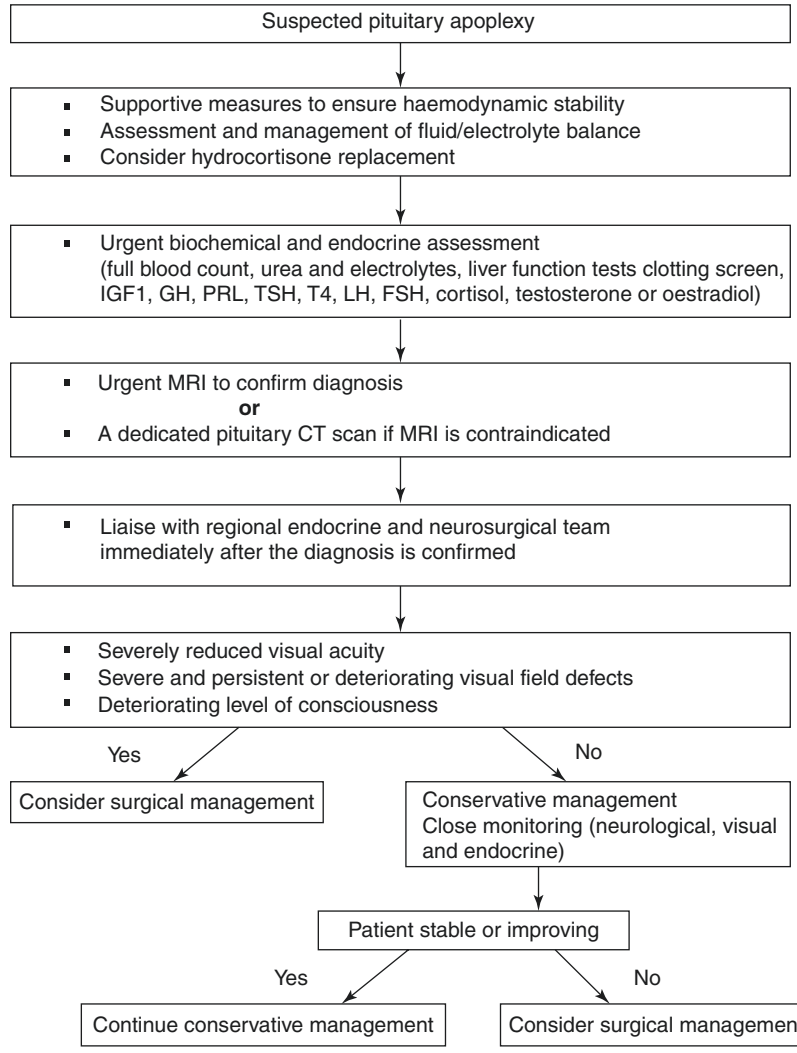


Fig. 64.1 Algorithm for the management of pituitary apoplexy. Baldeweg SE, et al. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of pituitary apoplexy in adult patients. Endocr Connect. 2016;5 (5):G12-g5. Open access no copyright permission required: Free via Creative Commons: CC

symptoms consistent with pituitary apoplexy should include a detailed history followed by a thorough physical examination including cranial nerves and visual fields to confrontation. The clinical symptoms mimic other common neurological emergencies such as subarachnoid haemorrhage, bacterial meningitis, or stroke. Clinical presentation can be either acute or subacute, with slow development of symptoms and signs and this is largely determined by the extent of haemorrhage, oedema, and necrosis. Formal visual fields assessment must be undertaken when the patient is clinically stable, preferably within 24 h of the suspected diagnosis (Rajasekaran et al. 2011; Baldeweg et al. 2016; Randeva et al. 1999).

In haemodynamically unstable patients, intravenous hydrocortisone should be administered after taking blood samples for baseline endocrine function tests (Rajasekaran et al. 2011).

Patients who have been diagnosed with a pituitary tumour should be given clear information regarding the signs and symptoms of pituitary apoplexy and the precipitating factors.

64.5.2 Endocrine Assessments

Nearly 80% of patients will have deficiency of one or more anterior pituitary hormones at presentation. Clinically, the most crucial deficit is that of adrenocorticotroph hormone (ACTH) and

has been reported in up to 70% of the patients. Thyrotropin and gonadotropin deficiencies are observed in 50 and 75% of the patients, respectively. Hyponatremia has been reported in up to 40% of the patients due either to the syndrome of inappropriate antidiuretic hormone secretion or hypocortisolism (Randeva et al. 1999; Sibal et al. 2004; Ayuk et al. 2004).

Patients with suspected pituitary apoplexy should have urgent blood samples taken for electrolytes, renal function, liver function, clotting screen, full blood count, and random cortisol, prolactin, free thyroxine (FT4), thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1), growth hormone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone in men and oestradiol in women.

64.5.3 Radiological Assessments

Computerized tomography (CT) is the most commonly used imaging modality in an acute clinical setting if a patient presents with severer headache and/or ophthalmoplegia or altered consciousness level. CT scan is diagnostic in approx. 25% of cases but this rises to 80% for those with extrasellar mass (Baldeweg et al. 2016).

Urgent MRI scan must be done in all patients with suspected pituitary apoplexy to confirm the diagnosis. Magnetic resonance imaging (MRI) is the radiological investigation of choice for a suspected diagnosis of pituitary apoplexy. A dedicated pituitary CT scan is indicated if the MRI scan is either contraindicated or not possible. The results of the MRI or CT scan should be clearly explained to the patient as soon as possible after the investigation.

64.6 Clinical Managements of Pituitary Apoplexy

64.6.1 Steroid Therapy in Pituitary Apoplexy

Acute secondary adrenal insufficiency is the major source of mortality associated with pituitary apoplexy. It is seen in approximately two-thirds of patients with pituitary tumour apoplexy. Before the results of confirmatory tests are available, prompt intramuscular or intravenous corticosteroid replacement should be started in patients who are haemodynamically unstable, or for patients who have other symptoms or signs suggestive of hypoadrenalism. Patients with pituitary apoplexy frequently present with nausea and vomiting; hence, oral corticosteroids are not recommended in the acute setting.

Hydrocortisone 100–200 mg as an intravenous bolus is recommended followed either by 2–4 mg per hour by continuous intravenous infusion or 50–100 mg six hourly by intramuscular injection. Once the patient has recovered from the acute episode, the hydrocortisone dose should be quickly tapered to a standard maintenance dose of 20–30 mg per day, orally usually in three divided doses. The immediate medical management of patients with pituitary apoplexy should include careful assessment of fluid and electrolyte balance, replacement of corticosteroids, and supportive measures to ensure haemodynamic stability (Baldeweg et al. 2016).

Indications for empirical steroid therapy in patients with pituitary apoplexy are haemodynamic instability, altered consciousness level, reduced visual acuity, and severe visual field defects. Patients who do not fulfil the criteria for urgent empirical steroid therapy should be considered for treatment with steroids, if their 09.00 serum cortisol is less than 550 nmol/L.(19 ng/dL) ACTH reserve should be reassessed 2–3 months after the episode of acute pituitary tumour apoplexy has resolved (Rajasekaran et al. 2011).

64.6.2 Surgery or Conservative Management

Patients with pituitary apoplexy should first be stabilized medically with steroid replacement as required. The decision to manage conservatively or with surgical intervention should be made carefully by a multidisciplinary team, including experts in neurosurgery, endocrinology, and ophthalmology (Rajasekaran et al. 2011). Semi-elective trans-

sphenoidal surgery should be considered for patients who are clinically stable, but show no improvement or deterioration in the neuro-ophthalmic signs. Such an approach would enable the surgery to be performed by the pituitary surgeon, rather than by the on call neurosurgical team. If no pituitary surgeon is available, consideration should be given to transfer to the nearest available neurosurgical unit. The rationale behind the clinical decisions should be fully explained to the patient and when possible their informed consent should be obtained. The presence of a new or deteriorating visual deficit or neurological deterioration should prompt further urgent imaging with a view to decompressive surgery (Rajasekaran et al. 2011; Baldeweg et al. 2016).

Renal functions and electrolytes should be checked daily. Further endocrine specialist evaluation to assess possible under or over secretion of pituitary hormones should be undertaken in stable patients.

Once a diagnosis has been confirmed and the patient is medically stabilized, it is recommended that all patients be transferred to a speciality neurosurgical/pituitary facility/unit (neurosurgical high dependency unit (HDU). Liaison and consultation with specialist neurosurgical/endocrine teams at the receiving location is strongly recommended. This team must also have access to specialist endocrine and ophthalmological expertise (Baldeweg et al. 2016).

64.6.2.1 Immediate Post-Operative Care

The post-operative management of patients following surgery for pituitary apoplexy is similar to that of elective pituitary surgery for pituitary tumour. However, as most patients with pituitary apoplexy may not have had a full endocrine work-up prior to the operation, it is essential to monitor them more closely perioperatively.

It is important to watch out for transient diabetes insipidus. This is noted post-operatively in up to 16% of the patients with pituitary apoplexy during their hospital stay (Arafah et al. 1990). Plasma and urine osmolality should be checked immediately if diabetes insipidus is suspected. Other potential post-operative complications include cortisol deficiency, visual loss, cerebrospinal fluid leakage, and meningitis. These should be proactively considered.

Patients should be reviewed hourly to assess the fluid balance and as appropriate serum urea, serum creatinine, and serum electrolytes.

64.6.2.2 Post-Operative Endocrine Assessment

Evaluation of steroid reserve and thyroid functions should be undertaken carefully during the post-operative period. The 09.00 serum cortisol is initially used to assess the steroid status. Cortisol values should be interpreted with caution in women, who have stopped oestrogen replacement therapy less than 6 weeks before surgery because of the confounding effect of raised cortisol binding globulin levels (Rajasekaran et al. 2011; Randeva et al. 1999).

Thyroid function (FT4 and TSH) should be tested on day 3 or day 4 after surgery. Thyroid function can be normal in the immediate post-operative period, and hence it is important to test again at 4–8 weeks post-operatively. Sick euthyroid syndrome can sometimes complicate the biochemical picture and affect the interpretation of thyroid function test results (Rajasekaran et al. 2011; Randeva et al. 1999).

If pre-operative steroid reserve adequate or unknown:

Check 9 am serum cortisol on day 2 and day 3 post-operatively in patients with no evidence of cortisol deficiency before operation. If the patient is already taking hydrocortisone replacement, omit the evening dose for the previous day before checking.

If pre-operative steroid reserve deficient:

In patients with proven cortisol deficiency before surgery, continue hydrocortisone and consider changing over to maintenance dosage when

stable. These patients will need further assessment at 4–8 weeks to determine whether they will need long-term steroids.

64.6.3 Visual Assessment

Visual acuity, eye movements, and visual fields should be examined at the bedside preferably within 48 h, and this should be followed by formal visual field assessment. Patients who develop unexpected visual loss or significant deterioration in the visual fields should have an urgent MRI scan and a review by the neurosurgical team (Rajasekaran et al. 2011).

64.7 Long-Term Follow-up and Outcomes

64.7.1 Endocrine Outcomes

All patients with pituitary apoplexy should have an endocrine review at 4–8 weeks following the event. They should undergo full biochemical assessment of pituitary function.

Studies have shown partial or complete recovery of pituitary function in up to 50% of patients (Arafah et al. 1990). Nearly 80% of the patients will need some form of hormone replacement after apoplexy (Randeva et al. 1999; Ayuk et al. 2004).

Growth hormone deficiency is the most commonly observed deficit after apoplexy and is present in almost all patients. The data suggest that long-term hormone replacement therapy following pituitary apoplexy is corticosteroids in 60–80%, thyroid hormone in 50–60%, desmopressin in 10–25% of patients, and testosterone in 60–80% of men (Baldeweg et al. 2016; Randeva et al. 1999; Ayuk et al. 2004).

Patients treated for apoplexy should have an annual biochemical assessment of pituitary function which should include FT4, TSH, LH, FSH, testosterone in men, oestradiol in women, prolactin, IGF-1, and dynamic tests of cortisol and growth hormone secretion if clinically appropriate (Rajasekaran et al. 2011).

64.7.2 Visual Outcomes

Visual acuity, visual field defects, and ophthalmoplegia have been reported to improve in the majority of the patients after surgical decompression. Such improvement can be observed early in the immediate post-operative period and often continues for several weeks after surgery. Patients should undergo formal assessment of their visual acuity, eye movements, and visual fields about 6–8 weeks after diagnosis of pituitary apoplexy (Rajasekaran et al. 2011).

64.7.3 Long-Term Monitoring and Surveillance

Recurrent apoplexy and tumour regrowth has been documented both in surgically and conservatively managed group of patients. Therefore, all patients who have been treated for apoplexy need long-term follow-up imaging to detect recurrent growth. Additional long-term management depends on the nature of the underlying pituitary tumour (Rajasekaran et al. 2011; Arafah et al. 1990).

Both conservatively and surgically treated patients need close radiological follow-up and if residual tumour or recurrence is detected, additional modalities such as radiotherapy or redo-surgery should be considered:

(a) MRI scan is recommended at 3–6 months after apoplexy and thereafter an annual MRI scan should be considered for the next 5 years, then two yearly.
(b) All patients require at least an annual clinical review preferably in a joint endocrine/neurosurgical clinic. It is recommended that all patients be discussed within the pituitary multidisciplinary team.

(c) There should be recognition of the psychological aspects of pituitary disease and support from endocrine specialist nurse and patient support organizations like The Pituitary Foundation should be provided where appropriate (www.pituitary.org.uk).

64.8 The Role of the Endocrine Specialist Nurse in the Management of Patients with Pituitary Apoplexy

The role of the endocrine specialist nurse in the management of the patient with pituitary apoplexy spans from the moment of diagnosis to the lifelong long-term management including education, psychological support, dynamic endocrine testing, and multidisciplinary team discussions as well as nurse-led clinic consultations.

In the acute settings, endocrine nurses who perform endocrine testing need to be aware of the risk involved in endocrine testing. In some endocrine centres, the task of performing endocrine testing is separated from the role of endocrine specialist nurse hence awareness of the risk involved needs to be communicated to all health care professionals involved in dynamic testing. If a patient presents acutely with signs or symptoms of pituitary apoplexy in the endocrine nurse led clinics, an endocrine nurse will need to have some knowledge or skills to recognize this emergency situation. A working group of endocrine specialist nurses supported by The Society for Endocrinology (UK) published a framework of competencies for endocrine specialist nurses, which provides guidance in the nursing management of different endocrine conditions. It also supports role development and performance at different levels of competence and expertise (Kieffer et al. 2015). In the "dynamic function testing" competency of the framework, an expert endocrine nurse will need to have the skills and knowledge as well as the ability to integrate clinical guideline of pituitary apoplexy into clinical setting to ensure the safety of their patients is upheld (Kieffer et al. 2015).

Whilst there is no specific competency framework for pituitary apoplexy, the competencies on "dynamic function testing", steroid replacement therapy", and "hypopituitarism" can be directly related to management of patients with pituitary apoplexy.

Especially, the "hypopituitarism" competency includes a number of skills and roles for endocrine specialist nurses which are very useful and relevant for patients with pituitary apoplexy (Kieffer et al. 2015):

- To display a comprehensive knowledge of the disease process and evaluate biochemical results and scans
- To demonstrate advanced communication skills to share complex information with patients regarding the risks/benefits of surgical vs medical treatment options
- To analyse dynamic testing results and prescribe when appropriate, recognizing when medical input is needed
- To interpret monitoring results, advising on treatment changes or adjustment
- To actively take part in MDTs discussing complex patients and their management
- To identify patients at increased risk and develops robust strategies to achieve safety and concordance with prescribed replacements
- To liaise with relevant patient support groups, sharing expertise and collaborating with the wider community
- To support junior staff

64.9 Conclusions

Pituitary apoplexy is a medical emergency requiring close multidisciplinary working between the acute medical team, the endocrinologists, ophthalmologists, and neurosurgeons.

There is currently uncertainty whether conservative or surgical treatment is most appropriate and treatment decisions must be individualized for each patient.

The main acute endocrine issue is steroid replacement and it here as well as in the long-term management of these patients that the endocrine specialist nurse plays an important role to optimize the outcome for each patient.

References

Arafah BM, Harrington JF, Madhoun ZT, Selman WR. Improvement of pituitary function after surgical decompression for pituitary tumor apoplexy. J Clin Endocrinol Metab. 1990;71(2):323–8.

Ayuk J, McGregor EJ, Mitchell RD, Gittoes NJ. Acute management of pituitary apoplexy—surgery or conservative management? Clin Endocrinol. 2004;61(6):747–52.

Baldeweg SE, Vanderpump M, Drake W, Reddy N, Markey A, Plant GT, et al. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: emergency management of pituitary apoplexy in adult patients. Endocr Connect. 2016;5(5):G12–g5.

Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, et al. Society for Endocrinology competency framework for adult endocrine nursing: 2nd edition. Endocr Connect. 2015;4(1):W1–W17.

Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, et al. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol. 2011;74(1):9–20.

Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol. 1999;51(2):181–8.

Sibal L, Ball SG, Connolly V, James RA, Kane P, Kelly WF, et al. Pituitary apoplexy: a review of clinical presentation, management and outcome in 45 cases. Pituitary. 2004;7(3):157–63.

Part XII

Neuroendocrine Tumours and Multiple Endocrine Neoplasia

Mike Tadman

Neuroendocrine Tumours

65

Mike Tadman, Philippa Davies, Tara Whyand, and Lee Martin

Contents

65.1 **Neuroendocrine Cells and Their Function** 1232

65.2 **Incidence and Risk Factors** 1233
65.2.1 Incidence and Prevalence 1233
65.2.2 Risk Factors for Neuroendocrine Tumours 1233
65.2.3 Genetics 1233

65.3 **Classification of NETs** 1234
65.3.1 Site of Origin 1234
65.3.2 Grading 1234
65.3.3 Staging 1235
65.3.4 Metastatic Spread 1235

65.4 **Survival** 1236

65.5 **Diagnosis** 1236
65.5.1 Introduction 1236
65.5.2 Presenting Signs and Symptoms 1236
65.5.3 Investigations 1237

M. Tadman (✉)
Oxford University Hospitals NHS Foundation Trust, Oxford, UK
e-mail: Michael.Tadman@ouh.nhs.uk

P. Davies
Royal Free London NHS Foundation Trust, London, UK
e-mail: philippadavies@nhs.net

T. Whyand
8 South: NET Unit, Royal Free London NHS Foundation Trust, London, UK
e-mail: tara.whyand@nhs.net

L. Martin
Barts Health NHS Trust, The Royal London Hospital, London, UK
e-mail: lee.martin@bartshealth.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_65

65.6 **Treatment of NETs** 1239
65.6.1 Surgery 1240
65.6.2 Liver-Directed Treatments 1241
65.6.3 Drug Therapies 1242
65.6.4 Peptide Receptor Radionuclide Therapy (PRRT) 1244
65.6.5 Treatment Decision-Making and NETs 1245

65.7 **Nursing Support of Patients with NETs** 1246
65.7.1 Health-Related Quality of Life and NETs 1246
65.7.2 Gastrointestinal Symptoms in NETs 1249
65.7.3 Dietary Management of Neuroendocrine Tumours 1252

65.8 **Conclusions** 1254

References 1255

Abstract

Neuroendocrine tumours (NETs) are a heterogenous group of cancers that can cause characteristic hormonal syndromes, such as carcinoid syndrome. The incidence and prevalence of NETs is increasing and though many are slow growing, others are aggressive high grade cancers.

Surgery is the only possible curative approach, but since the majority of NETS present only once they have metastasised, treatment is more often directed at control of disease, management of symptoms, and improvement in the quality of life.

Commonly used treatments include palliative resections and drug therapy with somatostatin analogues (SSAs), as well as targeted therapies such as everolimus. SSAs have been shown to improve the symptoms of carcinoid syndrome and stabilise tumour growth in many patients. Liver-directed therapies are also commonly used, e.g. ablation or hepatic artery embolisation, to improve symptoms control in patients with worsening syndromes. More recently, peptide receptor radionuclide therapy (PRRT) has been shown to be effective in treating patients with somatostatin receptor positive disease. However, there is lack of evidence as to the best approach to managing many patients, and overall response rates to treatment are often low.

Caring for individual with NETs is therefore complex and challenging. Effective care and support requires the cooperation of a multidisciplinary team covering a broad range of specialities with the patient actively involved in decision-making. Patients may live with advanced disease for many years. They face a roller-coaster ride of multiple treatments, often with different teams, ongoing symptoms, and the psychological and social burden of living with a life-limiting illness. As gastrointestinal symptoms are commonplace, the use of gastroenterologists interested in NETs and the involvement of a specialist NET dietitian are essential in managing patients' symptoms.

Specialist nurses are well-placed within the MDT to take on a key worker role, supporting patients through a complex illness trajectory, providing a consistent single point of contact.

Key aspects of the role include liaising with the MDT, support with treatment decision-making, holistic assessment of need, management of symptoms, and ongoing informational and psychological support.

Keywords

Neuroendocrine tumours (NETs) · Carcinoid syndrome · Somatostatin analogues (SSAs) Peptide receptor radionuclide therapy (PRRT) Liver-directed therapies · Health-related quality of life · Dietary management Gastrointestinal symptoms

Abbreviations

BAM	Bile acid malabsorption
EPI	Exocrine pancreatic insufficiency
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans
GEP	Gastroenteropancreatic
MDTs	Multidisciplinary teams
MEN	Multiple endocrine neoplasia
NECs	Neuroendocrine carcinomas
NETs	Neuroendocrine tumours
NF	Neurofibromatosis
OS	Overall survival
PERT	Pancreatic enzyme replacement therapy
PRRT	Peptide receptor radionuclide therapy
RE	Radioembolisation
RFA	Radio frequency ablation
SACTs	Systemic anti-cancer treatments
SeHCAT	23-Seleno-25-homotaurocholic acid, selenium homocholic acid taurine, or tauroselcholic acid to test to diagnose bile acid malabsorption
SIBO	Small intestinal bacterial overgrowth
SSAs	Somatostatin analogues
SSTRs	Somatostatin receptors
TAE	Transarterial embolisation
TACE	Transarterial chemoembolisation
TNM	Tumour node metastases
VIP	Vasoactive intestinal peptide
VHL	Von Hippel-Lindau disease
WHO	World Health Organisation

Key Terms

- **Cell differentiation:** differentiated cancers are mature cells look like cells in the tissue it arose from. Differentiated cancers tend to be decidedly less aggressive than undifferentiated cancers composed of immature cells.
- **Tumour grading:** assessment of markers of tumor aggression or rapid growth
- **Staging:** assessment of extent of tumour metastasis.
- **Survival analysis:** survival depends on many factors including primary site, grade, and stage at diagnosis.
- **Palliative surgery:** a treatment in the presence of metastatic disease to help control patients' symptoms and potentially improve prognosis and quality of life.

Learning Objectives

On completion of the chapter, the learner should be able to:

1. Describe the aetiology and epidemiology of neuroendocrine tumours (NETs).
2. Identify common presentations NETs and how they are diagnosed.
3. Understand the range of treatment options for NETs, including somatostatin analogues, liver-directed therapies, and peptide receptor radionuclide therapy (PRRT).
4. Identify management strategies for NET patients' quality of life concerns.
5. Understand the role of the specialist nurse and dietitian in supporting individuals and their families with NETs.

What does it mean to you ...

What does it mean to you…
… the Nurse Practitioner who shrugged her shoulders when I begged her for help?
… the consultant who prescribed me anti-depressants?
... the consultant who advised me to drink mint tea, eat yogurt and stay away from vegetables?
What does it mean to you, the technician who laughed as he did my scan, again, ... 'that'll do' he said. But was it clear enough?
What does it mean to you...
… the locum GP, the newly posted GP, the nearly-ready-to-retire GP, when faced with a tearful female who is complaining, yet again, of having a sore stomach?
'... she's been told it's mild gastritis and acid reflux for God's sake! What more can I do?!'

What does it mean to you, the person responsible for booking the Octreotide scan? As I sat and waited for three weeks before I asked ... 'what's going on?'
What does it mean to you, the person who told them I was away on the honeymoon I'd had to cancel, because the consultant advised strongly against the long-haul flight?
What does it mean to you, the person who failed to pass on my correct mobile number?
What does it mean to you?
It means nothing.
You sleep at night.
You aren't in pain.
You aren't worrying.
You aren't surrounded by loved ones desperate for some news on the situation.
You aren't worried about your future.
What does it mean to me?
It means 55 months have passed.
It means I face an uncertain future.
It means my cancer has probably spread.
It means my tumour (the one they've found so far) is now almost 2cm.
It means my hopes are fading fast.
It means I may never see my daughter graduate, walk down the aisle or have my first grandchild.
It means I probably won't get to do that PhD I want to.
It means I may never see Sri Lanka (my honeymoon destination) I may never make my anniversaries (I got married less than 4 weeks ago).
Will I see my 50th birthday?
Will I ever be pain free?
Or will my remaining time be filled with injections, scans, tests and appointments?
So, next time you see a patient, next time someone sits in front of you, begging for help, next time you fill in that referral form, pass on medical information, complete a scan ...
…next time, remember it may not mean much to you, but it is my life and to me, this is everything.
It is all I have!

Poem anonymised to protect patient's identity

65.1 Neuroendocrine Cells and Their Function

Neuroendocrine tumours (NETs) are a heterogenous group of cancers that arise from neuroendocrine cells. They account for around 0.5% of gastrointestinal and bronchopulmonary malignancies (Yao et al. 2008). They are most commonly found in the gastrointestinal system and lungs but can also originate in other areas, including the pancreas, ovaries, thyroid, and adrenal glands. See Box 65.1 for examples of NETS.

Box 65.1 Examples of Different Types of NETs

Gastrointestinal NETs: **gastric, duodenal, pancreatic, small intestine, appendiceal (including goblet cell), colon, rectal, ovarian**
Lung NETs
Pancreatic NETs **(non-functioning)**
Pancreatic NETs **(functioning): gastrinoma, VIPoma, insulinoma, somatostatinoma, glucagonoma**
Phaeochromocytoma and paraganglioma
Merkel cell carcinoma
Medullary thyroid cancer

Neuroendocrine cells are found in many sites throughout the body. They are specialised cells that can synthesise, store, and release hormones into the blood, integrating the nervous and endocrine systems. They are found in endocrine tissue throughout the body, e.g. endocrine glands such as the adrenal, pancreas, and thyroid glands, as well as in cells of the diffuse endocrine system, for example, within the mucosa of the lungs and the gastrointestinal tract.

When tumours arise from this tissue because of the neuroendocrine cells' ability to secrete metabolically active substances, they can cause distinct clinical syndromes. Examples of hormones the NETs release are shown in Table 65.1.

Table 65.1 Examples of hormones released by neuroendocrine tumours

Hormone	Function	Associated tumours
Serotonin	Regulating gastrointestinal activity	Range of neuroendocrine tumours
Somatostatin	Inhibits the release of growth hormone and suppresses the release of gastrointestinal hormones	Somatostatinoma
Gastrin	Regulates stomach acid production	Gastrinoma
Insulin	Regulates blood sugar levels	Insulinoma

65.2 Incidence and Risk Factors

65.2.1 Incidence and Prevalence

The overall incidence of NETs is hard to confirm, due to wide variation across different studies (Ramage et al. 2012). However, NETs are relatively uncommon cancers, with incident rates in studies varying from around 1.0/100,000 to over 5/100,000 in a recent Canadian study (Hallet et al. 2015). This represents around 1% of digestive cancer incidence; however, due to their overall good prognosis, prevalence rates are relatively high. Indeed, gastrointestinal NETs were the second most prevalent digestive tumour type in the USA after colorectal cancers (Yao et al. 2008).

Several studies show that the incidence of NETs is increasing over time. UK rates have increased fourfold from the 1970s to 2006 with similar increases in the USA (Lawrence et al. 2011) though smaller increases have been recorded in Europe (Lepage et al. 2013). This increase has also been at a greater rate than other cancers. A number of factors may account for this increase, including improved detection due to changes in imaging and endoscopic screening procedures. Similarly, over time there have been a number of changes in the recording and coding of NETs, e.g. adding in a number of poorly differentiated NETs, and also including benign and malignant tumours which could account for some of this increase (Huguet et al. 2015). However, it is unlikely that this fully explains the overall increase in incidence.

65.2.2 Risk Factors for Neuroendocrine Tumours

NETs can develop at any age, but most cases occur in people 60 years of age and older.

It is generally unclear why a particular individual may develop a NET; however, there are a number of known risk factors. A family history of cancer can increase the risk of developing NETs, and diabetes has also been implicated as a risk factor for gastric NETs (Hassan et al. 2008). Chronic atrophic gastritis is also closely linked to the development of type 1 gastric NETs (Fave et al. 2016).

65.2.2.1 NETs in Children and Young Adults

NETs are relatively rare within the paediatric and young adult population, with an incidence of 2.8 NETs per million under the age of 30 years. The incidence rate for the paediatric population alone is even lower, with a rate of less than 0.1 NETs per million under the age of 10 years, and 1 per million for ages between 10 and 14 years (Navalkele et al. 2011). The Surveillance, Epidemiology and End Results (SEER) database in the USA was analysed by Yao and colleagues showing that bronchial NETs, medullary carcinoma of the thyroid, and appendiceal NETs make up over 50% of NETs in those under 30 years of age (Yao et al. 2008). A number of those will be related to hereditary syndromes such as MEN1, MEN2, and VHL [See Sect. 65.2.3 below and Chap. 66].

65.2.3 Genetics

NETs may occur as part of familial endocrine cancer syndromes such as multiple endocrine neoplasia 1 and 2 (MEN 1, MEN2) (see Chap. 66), as well as neurofibromatosis type 1 (NF1)

and Von Hippel-Lindau disease (VHL). However, the majority of NETs occur as non-familial/sporadic isolated tumours. At diagnosis, a detailed family history and clinical examination is essential as part of the workup to check for a likely genetic diagnosis. If appropriate, genetic testing can be offered and carried out. The incidence of MEN 1 is higher in certain tumours such as gastrinoma, around 25%, and approximately 5% in insulinoma, but it is extremely rare in small intestinal NETs (Ramage et al. 2012).

65.3 Classification of NETs

NETs have previously lacked a uniform classification and grading system, but the World Health Organisation (WHO) have a new and generally agreed system. Broadly speaking they are classified according to site of origin, graded into well-differentiated and poorly differentiated tumours and staged through the anatomical spread of the disease. These will all guide the treatment decision-making process and helps to establish likely prognosis.

65.3.1 Site of Origin

NETs are now classified by their site of origin and their grade. Table 65.2 shows the classification of gastroenteropancreatic NETS (GEP-NETs) by site.

65.3.2 Grading

Grading of NETs refers to the inherent biological aggressiveness of the tumour. Differentiation and proliferation indexes are combined to provide information that should guide health care professionals as to how the disease may behave. Ki-67 is

Table 65.2 Classification of gastroenteropancreatic NETS (GEP-NETs) by site

Primary site	Description	Metastatic behaviour
Gastric Nets	Type I. Most common type of gastric NET (70–80%). Develop in association with atrophic gastritis and associated high gastrin and gastric acid levels Type II-Rare-only accounting for 5% of gastric NETs. Can occur in the context of MEN 1, and gastrinoma Type III-Around 20% of gastric NETs. Not associated with high gastrin or gastric acid output	Often small and numerous. Generally favourable prognosis. Rarely metastasise Often small and multiple. Up to 30% may metastasise Normally singular and >2 cm in size. Often invasive and metastatic
Duodenal Nets	Rare-only around 2% of NETs. Generally not associated with functional syndrome, however can be related to ZES	Around 50% have spread to local lymph nodes, though <10% have distant metastases. Overall 5-year survival >80%
Small intestinal NETs	Account for at least 25% of NETs. 20–30% have carcinoid syndrome (see Table 65.6)	Majority are well differentiated, slow growing in nature, though more than half have metastasised at diagnosis
Rectal NETs	Often present incidentally on colonoscopy or sigmoidoscopy. May have rectal bleeding, change in bowel habit	Less than 10% have metastasised at diagnosis with excellent overall survival. For those with distant metastases, prognosis is poor
Appendiceal NETs	Account for majority of appendiceal tumours. Generally found incidentally on post-operative histology	Prognosis excellent for majority, approaching 100% for localised disease
Pancreatic NETs (panNETs)	Arise from pancreatic islet cells. Can be non-functioning (majority of panNETs) or have specific function dependent on secretory hormone (See Table 65.6) Mainly sporadic but can be associated with MEN1, Von Hippel-Lindau syndrome and neurofibromatosis 1	Non-functional panNETs; Overall 5-year survival around 40%. Survival of functioning panNETs is dependent on specific tumour type

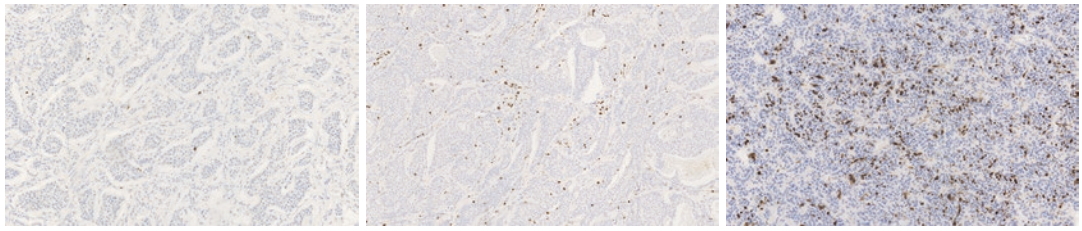


Fig. 65.1 Grading GEP NET with Ki-67 staining. Increased immunostaining highlighted as grade increases

a marker which measures the growth fraction of a given cell population and generally a higher Ki-67 suggests more cells are actively dividing and therefore the tumour may behave more aggressively (see Fig. 65.1). The World Health Organisation (WHO) proposed the following grading criteria for GI and pancreatic NETs in 2010 (Table 65.3) (Rindi et al. 2010) and bronchial (Lung) NETs in 2015 (Table 65.4) (Travis et al. 2015).

A 2017 update in pancreatic NETs has separated out high grade tumours into well-differentiated and poorly differentiated variants. This is based on evidence that some tumours with a high Ki-67 index, but with well-differentiated morphology, have a better overall prognosis and different behaviour than those which are poorly differentiated carcinomas (Basturk et al. 2015).

65.3.3 Staging

The tumour node metastases (TNM) staging system is used for the staging of NETs by both the European Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer, though no universal agreed system yet exists for NETs (Luo et al. 2016). The TNM system varies for each primary site but predominantly uses:

- The size and location of the primary (original) tumour
- Lymph node involvement (whether or not the cancer has spread to the nearby lymph nodes)
- Presence or absence of distant metastasis (whether or not the cancer has spread to distant areas of the body)

Table 65.3 ENETS/WHO classification of neuroendocrine tumours in the gastrointestinal (GI) tract

Differentiation	Grade	Mitotic count	Ki-67 index %
Well differentiated	NET Grade 1 (Low)	<2 per 10 HPF	<3%
Well differentiated	NET Grade 2 (Intermediate)	2–20 per 10 10HPF	3 to 20%
Poorly differentiated	NEC Grade 3 (High)	>20 per 10 HPF	>20%

Abbreviation: *NEC* Neuroendocrine carcinoma, *HPF* high-power fields, *ENETS* European Neuroendocrine Tumor Society, *WHO* World Health Organisation

Table 65.4 2015 WHO criteria for diagnosis of pulmonary neuroendocrine neoplasms

Grade	Criteria: morphology, mitotic count/10 HPF and necrosis
Typical carcinoid	Carcinoid morphology, <2 per 10 HPF with no necrosis
Atypical carcinoid	Carcinoid morphology with 2–10 per 10 HPF **or** necrosis
Large cell NEC	Neuroendocrine morphology, >10 per 10 HPF **with** necrosis-often extensive
Small cell NEC	Small size, >10 per 10HPF (median 80 per 10 HPF) **with** frequent necrosis

Abbreviations: *HPF* high-power fields, *NEC* Neuroendocrine carcinoma, *WHO* World Health Organisation
Adapted from Travis et al. (2015)

65.3.4 Metastatic Spread

Around half of patients present with metastatic disease though this varies dramatically in relation to the primary site. For example, over 60% of small intestinal NETs are likely to have metastasised, compared to 15% from the lung and only 5% of patients with an appendiceal primary

(Ramage et al. 2012). Also, poorly differentiated NETs are more likely to have metastasised at diagnosis compared to well-differentiated NETs. The most common sites of metastases are the liver and small intestine mesentery, with other common sites including other intraperitoneal sites, bone and the lung (Riihimäki et al. 2016). However, they may also metastasise to unusual sites such as the orbit, breast, and heart.

65.4 Survival

Data from several studies shows that the median 5-year survival of all patients with NETs may be as much as 60% though this drops to less than 50% over 10 years (Hallet et al. 2015). Survival depends on many factors including primary site, grade, and stage at diagnosis. Therefore, overall median survival rates for NETs as a broad group are not particularly helpful. For example, appendiceal NETs have survival rates in excess of 90%, whereas pancreatic NETs have a poorer prognosis with survival rates more typically 40–49% (Lepage et al. 2010).

Having metastatic disease at diagnosis is a poor prognostic factor, with a 10-year overall survival (OS) of 17.5% in a recent Canadian study (Hallet et al. 2015). Table 65.5 compares median survival for a range of primary tumour sites plus stage at diagnosis.

Poorly differentiated neuroendocrine carcinomas (NECs) are highly aggressive tumours, similar to small cell lung cancers and prognosis is comparable with 5-year survival rates generally in single figures.

Table 65.5 Median survival in months by primary tumour site

Site	Localised	Regional	Distant
Appendix	>360	>360	27
Caecum	135	107	41
Rectum	290	90	22
Duodenum	107	101	57
Gastric	154	71	13
Lung	227	154	16
Pancreas	136	77	24
Small bowel	111	105	56

Adapted from Yao et al. (2008)

65.5 Diagnosis

65.5.1 Introduction

Since NETs are a heterogenous group of tumours, they have a wide variety of clinical presentations. Symptoms will vary depending on where the NETs are located, how fast they are growing, and also if they have metastasised. Many patients with GEP-NETs present with typically vague or non-specific bowel symptoms. This, combined with their rarity, can lead to delays in diagnosis for many years. Studies have shown that it can take on average 5–7 years from initial symptoms to a diagnosis of a NET (Modlin et al. 2008). This may include multiple GP visits, inconclusive investigations, and often a diagnosis of other gastrointestinal complaints such as irritable bowel syndrome (IBS) or gastritis. The impact of this is that many NET patients begin their cancer pathway with heightened feelings of anxiety and frustration.

Even when a NET is suspected, patients often face a complex process of investigations, including a number of imaging techniques, a multitude of blood tests, and also referral to specialist centres as some tests are not available locally. This can lead to further delays and increased anxiety before treatment is commenced. Specialist nurses can play a key role within the MDT in ensuring that tests are correctly organised, carried out in a timely fashion, and that the different specialities work effectively together to reduce delays. Patients need to be kept accurately informed throughout about each investigation, why they are necessary and their likely timing. Managing anxiety, frustrations over waiting, and natural concerns about findings is a key part of good nursing support at this time.

65.5.2 Presenting Signs and Symptoms

65.5.2.1 Functioning Tumours

Many GEP-NETs have the potential to release biologically active substances into the circulation (Kaltsas et al. 2004). Those that cause clinical

Table 65.6 Functional NETs and their common symptoms

Tumour	Symptoms
Carcinoid tumour	Dry flushing, diarrhoea and abdominal cramping, asthma like wheeze, carcinoid heart disease (fibrosis of the heart valves, predominantly right sided)
Insulinoma	Confusion, sweating, dizziness, weakness, unconsciousness, symptoms relieved with eating
Gastrinoma	Zollinger-Ellison syndrome of severe peptic ulceration and diarrhoea, or diarrhoea alone
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea
VIPoma	Verner-Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia
Somatostatinoma	Cholelithiasis, weight loss, diarrhoea and steatorrhoea, diabetes mellitus

Table adapted from Ramage et al. (2012)

syndromes are termed "functioning" tumours. These include about 20% of small intestinal NETs where people experience the "carcinoid syndrome", and about 40% of pancreatic NETs which cause specific syndromes based on the peptide that they secrete (Ramage et al. 2012; Ramage and Davies 2003) [see Table 65.6 below].

65.5.2.2 Non-functioning Tumours

With non-functioning tumours, symptoms are caused by the mass effect of the primary tumour and related metastatic disease GEP-NETs often present with features such as pain, nausea and vomiting, weight loss, and fatigue. Pain and nausea may be due to local tumour invasion, bowel obstruction, or mesenteric ischaemia. (See Sect. 65.6.1.2.1 in Sect. 65.6). Weight loss may be related to diarrhoea and malabsorption of food, and general malaise in more advanced tumours. Fatigue may be due to the disease process and to exacerbating factors such as pain and anaemia.

Patients with lung NETs may present with cough, wheeze, shortness of breath, chest pain, or haemoptysis.

NETs may also be found incidentally: for example, the majority of appendiceal NETs are found either on surgery for appendicitis or colonic surgery, and around 20% of bronchial NETs are found incidentally on radiography (Ramage et al. 2012).

N.B. Patients with functioning tumours may of course also have symptoms from the mass effect of their tumour.

65.5.3 Investigations

65.5.3.1 Medical History

Presenting signs and symptoms and past medical history are important to capture accurately. This can give a clue to the possible type of NET, the length of time a person may have had symptoms, and whether or not there is a possibility of a genetic or familial element.

65.5.3.2 Laboratory Tests

A range of laboratory tests are used to help diagnose and also to assess treatment effectiveness and prognosis.

65.5.3.2.1 Routine Laboratory Tests

These will include full blood count, renal and liver function tests, and often thyroid function tests as well. Other common blood tests include serum calcium, parathyroid hormone, prolactin levels, and IGF-1 levels in pancreatic NETs to rule out MEN 1 syndrome (see Chap. 66). Some centres may test for a range of common tumour markers, e.g. CEA, CA125, CA19-9 for a differential diagnosis.

65.5.3.2.2 Specialised Laboratory Tests

As many NETs secrete a variety of bioactive products, some less common laboratory tests are an important part of the diagnostic process. These include

- Chromogranin A (and B) (CgA and CgB): This is the most sensitive biomarker in a range of NETs. It can be measured in serum or plasma. High levels are suggestive of a poor prognosis. Limitations are that it is raised by protein pump inhibitors and histamine 2

receptor antagonists, as well as in chronic gastritis and renal failure.

- Fasting gut peptides: These are used to help identify a number of NETs, including functioning pancreatic NETs. Peptides that are checked are somatostatin, gastrin, glucagon, vasoactive intestinal peptide (VIP), and pancreatic polypeptide. In gastric NETs, these laboratory tests can be difficult to interpret as gastrin and CgA are raised in many common conditions where gastric acid is reduced or absent, including atrophic gastritis.

  N.B. Chromogranin and fasting gut peptides can generally not be carried out in the community. They require to being spun and frozen shortly after they are taken and can only be processed in some specialist labs.
- 5-hydroxyindoleacetic acid (5HIAA): Raised levels are found in many small intestinal NETs as well as NETs of the stomach and respiratory system. It is the main breakdown metabolite of serotonin. It is normally measured in a 24-h urine collection though some centres now use a single urine specimen or plasma sample. 5HIAA levels can be altered by a range of drugs and serotonin-rich foods, e.g. pineapple, banana, avocado, walnuts amongst others. Many centres require patients to exclude these foods from their diet for 48 h before and during the 24 h collection to exclude false-positive results (Pape et al. 2012).
- NT-proBNP: This is a useful screen for carcinoid heart disease. Many centres would also carry out an echocardiogram. Monitoring can typically be on an annual basis, or if symptoms of carcinoid heart disease develop (Hart et al. 2017).

65.5.3.2.3 Insulinoma

For suspected insulinoma, glucose, insulin, and C-peptide levels will be measured, as well as proinsulin if available. A 48–72 h fast with serial blood glucose analysis is the gold standard diagnostic tool. However, in around 5% of patients hypoglycaemia may only be revealed postprandially (Okabayashi et al. 2013).

65.5.3.3 Imaging

Imaging of both the primary tumour and any potential metastatic disease is an essential part of the diagnostic phase. It can determine if surgical resection is possible, whether treatment for metastatic disease is appropriate, and what is likely to be the most effective treatment modality. Imaging will also be used extensively during follow-up to assess the effectiveness of any treatment as well as ongoing surveillance after potentially curative treatment.

There are a range of imaging techniques available to diagnose and stage NETs; some are available in most, if not all centres, other techniques are more specialised and only available in a few regional centres.

65.5.3.3.1 Computed Tomography (CT)/ Magnetic Resonance Imaging(MRI)

Standard CTs and MRI are well-established tools to diagnose a number of different types of NETs. They are also an excellent tool for ongoing follow-up and assessment of treatment response. However, CTs can lack sensitivity for detecting primary small intestinal NETs (Ramage et al. 2012). MRIs are sensitive in detecting bone and liver metastases and are good for surveillance due to the absence of radiation.

65.5.3.3.2 Somatostatin Scintigraphy

As NETs generally express high levels of somatostatin receptors (SSTRs), the standard nuclear medicine technique for investigating NETs has been SSTR scintigraphy with *Octreoscans* (Pape et al. 2012). Octreotide, which is a synthetic analogue of somatostatin, is radiolabelled with ^{111}indium. This attaches to tumour cells with SSTRs, and this is picked up on a gamma scanner. It is standard practice to combine this with SPECT/CT. However, in recent years ^{68}Ga Dotatate positron emission tomography (PET) imaging has become the gold standard, having greater sensitivity and specificity than *Octreoscans*. Studies confirm that this technique may have a major impact on treatment decision-making, in particular identifying additional patients who might benefit from peptide receptor radionuclide therapy (PRRT) (Deppen et al. 2016), [see Fig. 65.2 below].

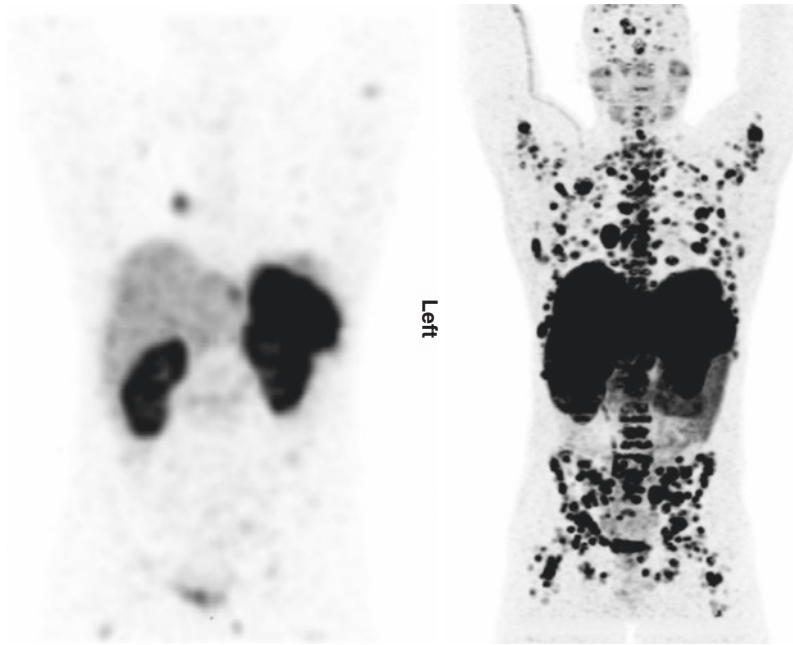


Fig. 65.2 ^{111}In-Octreotide vs ^{68}Ga Dotatate in a patient with known metastatic NET. (Written consent and permission has been obtained from the patient to use these images). Images highlight strikingly different uptake on a patient with both ^{111}In-Octreotide and 68 Ga Dotatate PET scans. The Octreoscan did not demonstrate sufficient avidity to consider use of Somatostatin analogue or Peptide Receptor Radionuclide Therapy. ^{68}Ga Dotatate PET showed high level of avidity and also greater disease burden than expected. The patient proceeded to have ^{177}Lu PRRT therapy on the basis of the ^{68}Ga Dotatate PET result

65.5.3.3.3 FDG-PET

FDG-PET lacks sensitivity with most well-differentiated NETs. However, it can be useful in staging primary bronchial and poorly differentiated aggressive NETs. Higher proliferation or Ki-67 indexing may indicate the use of PET-FDG.

65.5.3.4 Endoscopy

Gastric NETs may require endoscopy, combined with biopsy. Endoscopic ultrasound is also useful in detecting gastric, pancreatic, and duodenal NETs. Pulmonary NETs often require bronchoscopy.

65.5.3.5 Histopathology

Pathology is essential to effectively classify and diagnose NETs. NETs have a very distinctive appearance which can be identified through immunohistochemical staining. Tissue can be obtained through biopsy, via endoscopy, or during surgery. [See Sect. 65.3.2 under Sect. 65.3].

65.6 Treatment of NETs

A range of surgical and medical interventions are used in the management of NET patients. The choice of treatment depends on a number of factors including:

- The location and type of the primary tumour
- The extent of disease spread
- The patient's condition and comorbidities
- Patient preference
- Availability of treatments

The key to optimal management is early detection and diagnosis.

65.6.1 Surgery

65.6.1.1 Potentially Curative Surgery

Surgery offers the possibility of cure for patients diagnosed with small volume/resectable disease. Common examples in NETs include:

- Appendiceal NET: Appendicectomy, with right hemicolectomy for some higher risk tumours
- Bronchial NET: Wedge resection, segment, or lobe resection
- Duodenum: may vary from simple endoscopic resection for small tumours to pancreaticoduodenectomy (Whipple's procedure)
- Ileum: Small bowel resection. May include part of mesentery.
- Pancreas: distal resection of single lesion in tail of pancreas to Whipple's procedure for pancreatic head tumour

Even after successful resection many patients still need to be followed up long term as disease may reoccur many years after the initial surgery (Knigge et al. 2017).

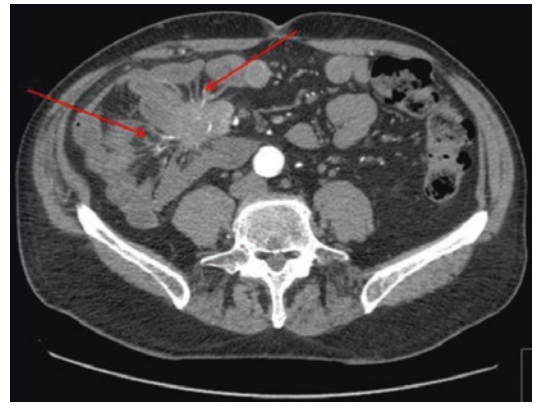


Fig. 65.3 Desmoplastic Reaction and fibrosis of Small bowel mesentery. (Written consent and permission has been obtained from the patient to use these images). Desmoplastic Reaction: CT scan showing desmoplastic reaction from mesenteric metastatic lymph node mass. This patient presented with symptoms of abdominal pain, poor appetite, weight loss and erratic bowel habit. Diagnosed with a small intestinal NET with mesenteric and liver metastases. They were commenced on a somatostatin analogue which initially improved their symptoms. However, over 18 months their symptoms and quality of life worsened, with increased pain and erratic bowel habit. They underwent a small bowel and mesenteric resection for palliation of symptoms with excellent symptomatic benefit

65.6.1.2 Palliative Surgery: Primary Tumour

Surgery is also used as a treatment in the presence of metastatic disease to help control patients' symptoms and potentially improve prognosis and quality of life. Due to the heterogeneity of NETs, the surgery type can range from small resections to extensive surgery. The rationale is that removing the primary tumour may either improve disease survival and/or the quality of life for the patients. It may also prevent the patient presenting later with small bowel resection, [see Sect. 65.6.1.2.1 below].

65.6.1.2.1 Small Intestinal Resections

The area around the primary tumour and mesenteric metastases can become fibrotic and cause a diffuse desmoplastic reaction. This may cause the small bowel to narrow and kink and can lead to bowel obstruction. The fibrosis and tumour mass can also narrow the surrounding mesenteric blood vessels and lead to bowel ischaemia (see Fig. 65.3). Patients in these situations have recurrent bowel obstruction with severe pain and may be unable to tolerate oral diet and need permanent parental nutrition [see Sect. 65.7.3]. This has a huge impact on their quality of life, and they have a poor overall prognosis (Moris et al. 2018).

Radical mesenteric and small intestinal resection may need to be considered to prevent these symptoms, stop them worsening, or to manage them if already present.

However, the mesenteric disease may be inoperable as the blood supply to the bowel would be lost during resection. Resectability of the tumour at an early stage is discussed as part of an MDT meeting, and the involvement of the surrounding blood vessels and lymph nodes will determine if surgery is possible (Capurso et al. 2012).

65.6.1.2.2 Pancreatic Surgery

Resecting a primary pancreatic mass in the presence of metastatic disease may also be consid-

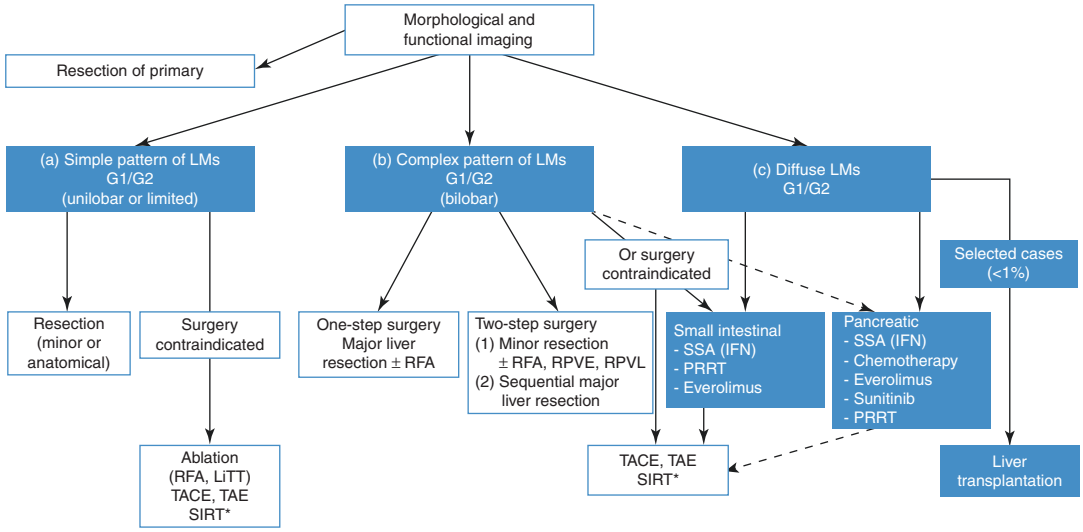


Fig. 65.4 ENETs algorithm for supporting decision making in managing metastatic liver disease. Pavel et al 2016. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site, p 173 (Open access article)

ered. It can reduce the tumour burden and improve symptoms for the patient. However, if the tumour is located in the head of pancreas a Whipple's procedure is needed. This may not be recommended in the presence of known metastatic disease due to the complication risk related to this surgery and ongoing risks related to abscess development after local liver-directed treatments (Partelli et al. 2017).

65.6.2 Liver-Directed Treatments

NETs commonly spread to the liver, often causing significant symptoms, including pain and hormonal syndromes. For those patients with functional tumours, treating the metastases can reduce the release of hormones and the associated symptoms can improve, i.e. for carcinoid syndrome patients this can mean a reduction in flushing frequency and intensity, frequency of diarrhoea, and can reduce the risk of damage to the heart valves. This approach may also improve overall survival in some cases and also benefit quality of life (Frilling et al. 2014).

There are many liver-directed therapies used for this patient group. This includes liver resections, debulking procedures, embolisation (with or without chemotherapy), radio frequency ablation (RFA), intra-arterial peptide receptor radio-targeted therapy (PRRT), and selective internal radiation therapy (SIRT) (Pavel et al. 2016).

There is no standard plan to treat liver metastases and a lack of comparative study data to support a particular approach. Therefore, each case needs to be considered individually by a specialist MDT. The size, number, and position of tumours, the overall disease burden as well as the patient's health status and preference all need considered (De Baere et al. 2015). Figure 65.4 shows an ENETS algorithm for supporting decision-making in managing metastatic liver disease (Pavel et al. 2016).

65.6.2.1 Palliative Hepatic Surgery

Hepatic surgery may be used to improve the symptoms related to uncontrolled hormone production e.g. refractory carcinoid syndrome, Verner-Morrison syndrome (VIPomas), and insu-

linomas (Pavel et al. 2016). Palliative resections for patient that are non-functional are considered if the volume of disease is causing symptoms for the patient. Surgical teams within the NET MDT are becoming more aggressive in their approach to treating these patients to try and improve patient outcomes, with two- or three-step operations occurring more often.

65.6.2.2 Radiofrequency Ablation (RFA)

RFA has been used for many years, sometimes in combination with liver resection to achieve complete responses. Ablation therapies are less invasive than surgery and patients do not need an extended hospital inpatient stay. RFA can reduce the secretion of hormones from tumours and therefore reduce symptoms, such as diarrhoea and flushing from carcinoid syndrome (Eriksson et al. 2008). Tumours need to be generally <5 cm for this treatment to be effective (Elias et al. 2005).

65.6.2.3 Hepatic Embolisation Therapies

Embolisation of the hepatic artery can result in ischaemia and necrosis of tumours within the liver. It also reduces secretions of peptides from metastatic NETs. Selective hepatic transarterial embolisation (TAE), transarterial chemoembolisation (TACE), or radioembolisation (RE) with yttrium-90 microspheres has been shown to produce objective disease responses and control symptoms in a number of patients with NET (Kennedy et al. 2015). Normal liver tissue is spared as it also receives its blood supply from the portal vein.

65.6.2.4 Liver Transplantation

Liver transplantation is generally not recommended as a treatment for advanced NETs. In highly selected patients (i.e. young patients with functional syndromes demonstrating resistance to medical therapy), this may be a treatment option if it can be confirmed that there is no extra-hepatic disease (Neychev and Kebebew 2017). Each country has individual criteria regarding transplantation.

65.6.3 Drug Therapies

There are a number of different systemic therapies available to treat NETs, including somatostatin analogues, targeted therapies such as everolimus and sunitinib, and cytotoxic chemotherapy. A number of clinical trials have shown their use in controlling disease and managing symptoms; however, there is a lack of direct comparison through clinical trials and a lack of clarity as to the order in which treatments should be used. Guidelines therefore tend to suggest a range of available options and issues to consider when choosing a particular therapy, see Fig. 65.5.

65.6.3.1 Somatostatin Analogues (SSAs)

Somatostatin is a peptide that inhibits the release of hormones/peptides including serotonin, insulin, glucagon, and VIP. Somatostatin receptors (SSTRs) are present in the majority of NETs, but far less in poorly differentiated NECs (Sharma et al. 2016). SSAs are a synthetic version of somatostatin and have been produced in short (octreotide) and long-acting formulations (Lanreotide Autogel and Sandostatin LAR).

These drugs target and block the SSTRs and have been used for many years to control the functional syndromes of both carcinoid tumours and functional pancreatic islet tumours, such as insulinomas and gastrinoma. They reduce the release of the peptides hyper secreted by NET tumours and around 75% of patients will get effective benefit from their use (Khan et al. 2011).

Studies have also confirmed the anti-tumour effect of these agents and therefore they are now also used to treat non-functional NETs, which are SSTR positive. The optimal dosages for anti-tumour effect have not been studied; however, in the two main randomised controlled trials (RCTs) Sandostatin LAR 30 mg and Lanreotide Autogel 120 mg every 28 days were studied and found to be effective in prolonging disease stability and progression-free survival (Rinke et al. 2009; Caplin et al. 2014).

Lanreotide Autogel and Sandostatin LAR are typically administered every 4 weeks. In instances where patients continue to have uncontrolled symptoms the period between

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/–	G1	midgut	+	low tumor burden
Lanreotide	+/–	G1/G2 (–10%)	midgut, pancreas	+	low and high (>25%) liver tumor burden
IFN-alpha 2b	+/–	G1/G2	midgut		if SSTR negative
STZ/5-FU	+/–	G1/G2	pancreas		progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/–	G2	pancreas		progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/–	G1/G2	lung		atypical carcinoid and/or SSTR negative
			pancreas		insulinoma or contraindication for CTX
			midgut		if SSTR negative
Sunitinib	+/–	G1/G2	pancreas		contraindication for CTX
PRRT	+/–	G1/G2	midgut	+ (required)	extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin§/ etoposide	+/–	G3	any		all poorly differentiated NEC

CAP = Capecitabine; TEM = temozolomide. *≤6–12 months. § Cisplatin can be replaced by carboplatin.

Fig. 65.5 Therapeutic options and conditons for preferential use as a first-line therapy for advancd NEN. Pavel et al 2016. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site, p174 (Open access article)

injections may be reduced or the dose increased over those mentioned above (see Sec. 65.7.2.1).

SSAs are generally well tolerated. Gut-related side-effects are quite common at the start of treatment; however, these often settle over the first few months of treatment. For management of side-effects, see Table 65.7.

65.6.3.2 Interferon

Interferon is licenced for use in Europe for patients with the "carcinoid syndrome". This treatment is often used alongside SSAs to help control refractory carcinoid syndrome and a more recent study has shown anti-proliferative effects although it is not currently licenced for this use (Yao et al. 2015; Oberg 2000). It has been found to have both symptomatic and biochemical benefit, but its mode of action remains unclear. It can be administered as a standard therapy Interferon alpha 2b or in a pegylated form Peginterferon alpha 2b.

Close monitoring is needed due to the side-effect profile including early/transient flu-like symptoms, and ongoing mood disturbances, suicidal thoughts, headache, fatigue, sleep disturbances, and haematological toxicity. It must also be stopped for a period of time before planned surgery and other treatments to allow time for the blood levels to recover.

65.6.3.3 Systemic Anti-Cancer Treatments (SACTs)

65.6.3.3.1 Targeted Agents

Targeted agents such as everolimus and sunitinib are approved for use in NETs. Everolimus is a rapamycin inhibitor which is licenced for use in progressive panNETs, G1/G2 non-functional gastrointestinal NETs, and Bronchial NETs (Yao et al. 2011, 2016). The dose and regimen for NET patients is 10 mgs once a day. Frequent side-effects are stomatitis, skin rash, diarrhoea, and myelotoxicity (Yao et al. 2011).

Table 65.7 Management of common side-effects of somatostatin analogue injections

Organ affected	Symptoms	Management
Gastrointestinal	Nausea, abdominal pain, steatorrhoea, malabsorption of fat from diet, flatulence (due to transient pancreatic exocrine insufficiency (PEI))	Anti-emetics, antispasmodics, pancreatic enzyme replacement therapy can be considered for ongoing symptoms of PEI. Measurement of fat-soluble vitamins
Altered blood sugar regulation	Potential signs of high or low blood sugars	Increased monitoring for diabetics. Otherwise occasional HbA1c is sufficient monitoring
Gallstone development	Often asymptomatic	Ultrasound of gall bladder. Prophylactic cholecystectomy if other planned surgery

Everolimus can also increase the glucose levels in patients and has a potential role in treating insulinoma (Kulke et al. 2009).

Sunitinib is a tyrosine kinase inhibitor and is licenced for use in progressive well-differentiated panNETs (Raymond et al. 2011) at a dose of 37.5 mgs once a day. Side-effects include neutropenia, hypertension, diarrhoea, and fatigue.

Both targeted agents require patients to take tablets on a daily basis. They will require regular monitoring to review and control toxicities to help with compliance and to try to ensure a good quality of life throughout treatment.

Despite the demonstration of improved progression-free survival in patients with advanced NETs, the overall tumour response rates with targeted agents have been poor, typically in single figures (Neychev and Kebebew 2017). A comprehensive review of the patient's history including the comorbidities such as diabetes or lung diseases is imperative when deciding the treatment of choice, or whether to offer the option of best supportive care, managing symptoms as they arise.

65.6.3.3.2 Cytotoxic Chemotherapy

For patients with bulky, rapidly progressive disease, or those with poorly differentiated NETs, treatment with cytotoxic chemotherapy may be considered. It is usually only considered in patients with progressive or bulky pancreatic NETs, G3 tumours, or in progressive G2 disease (Garcia-Carbonero et al. 2016).

For G1/G2 tumours streptozocin (STZ)-based chemotherapy regimens have been found to be effective for patients with progressive disease, and the additional of doxorubicin has increased the effectiveness of STZ regimens; however, due to the cumulative cardiotoxicity of doxorubicin it usage is limited (Garcia-Carbonero et al. 2016). Temozolomide-based regimens have also shown promise in the setting of pancreatic NETs (Koumarianou et al. 2015), possibly paired with capecitabine.

In high grade neuroendocrine carcinomas (NECs), platinum-based chemotherapy regimens are the mainstay for treatment in advanced and metastatic disease as long as the patient's performance status allows. Regimens with oxaliplatin and irinotecan may be used second-line although these regimens have not been fully evaluated. More research is needed regarding treatment for patients with metastatic NECs as there are limited treatment options and their overall survival is typically less than 12 months (Garcia-Carbonero et al. 2016).

65.6.4 Peptide Receptor Radionuclide Therapy (PRRT)

The expression of SSTRs in many well-differentiated NET tumours is used to identify tumours throughout the body, i.e. ^{68}Ga Dotatate PET scans and ^{111}In-octreotide scans and is also targeted by SSAs. This ability to target the receptors of the tumours is exploited further by the use of radiolabelled somatostatin analogues. With retrospective data from a number of studies suggesting response rates of over 25% (Kwekkeboom et al. 2008), this has become an established treatment for inoperable, loco-regional, and metastatic GEP-NETs in many countries. A recent randomised controlled trial comparing ^{177}Lu-octreotide to high-dose octroetide in progressive, well-differentiated, midgut NETs supports this, with an objective response of 18% for ^{177}Lu-octreotide compared to 3% in the octreotide arm (Strosberg et al. 2017). (See Fig. 65.6 for example of disease response).

The two main radionuclides used are Lutetium 177 (^{177}Lu) and Yttrium 90 (^{90}Y) with evidence suggesting lower renal toxicity with ^{177}Lu compared to ^{90}Y (Baum et al. 2015). Amino-acid infusions are

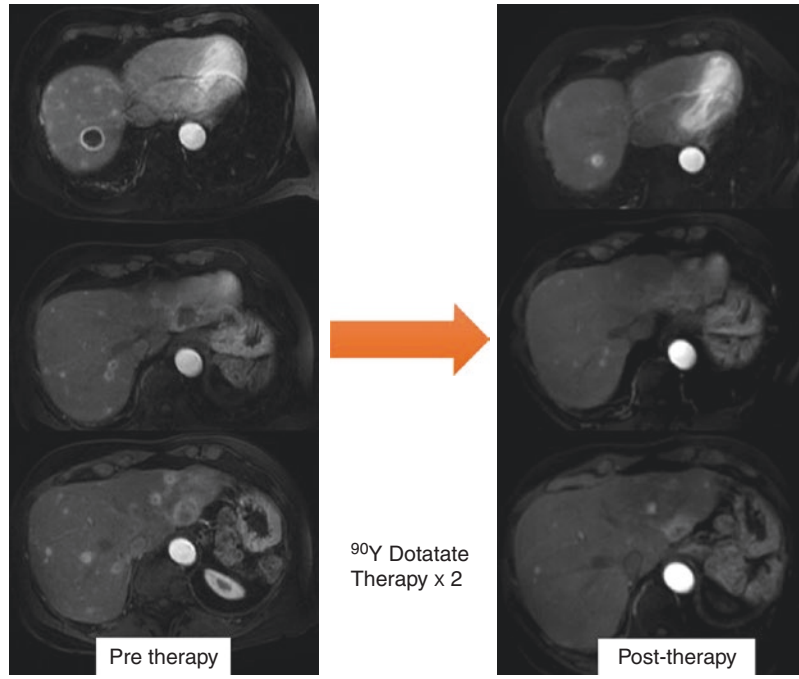


Fig. 65.6 Response to ^{90}Y Dotatate therapy. (Written consent and permission has been obtained from the patient to use these images). CT Liver, pre and post ^{90}Y-Dotatate Therapy, showing clear reduction in the size of liver metastases

given to reduce renal toxicity. Common side-effects include nausea and vomiting, alongside the amino-acid infusion, neutropenia, and thrombocytopenia. These treatments are radioactive and as such have stringent radiation protection measures that are followed. Typically patients are treated in lead-lined rooms to reduce the exposure to the hospital staff and other patients, and they need to be self-caring due to the radiation protection measures. Contraindications also include moderate-to-severe renal impairment, impaired haematological, hepatic or cardiac function, and pregnancy or breast feeding. After each cycle of treatment patients can be monitored by telephone clinics alongside fortnightly bloods to help assess their recovery.

This treatment is not currently used first-line and requires specialist knowledge so should be carried out within a NET centre to ensure selection and monitoring of patients as appropriate.

65.6.5 Treatment Decision-Making and NETs

It is clear from above that there are a wide range of active therapies available to treat patients with NET. However, there are several areas of uncertainty regarding the most effective way to utilise these. These include:

- Limited evidence on the correct sequencing of treatments, i.e. what should be first-, second-, or third-line therapy.
- Many treatments lack robust phase 3 data, and they are used based on small-scale retrospective studies and on best expert opinion. The choice of treatment may therefore vary from centre to centre as well as from region to region.
- Access to specialist therapies and imaging techniques is variable, for example, both PRRT and ^{68}Ga-Dotatate PET scans are only available in some countries and even within individual countries access may only be in a few specialist centres.

Other issues that make decision-making challenging include knowing when to change therapy and how to determine progressive disease. Should progression be defined as:

- Worsening symptoms?
- Radiological progression? or
- Biochemical progression?

NETs may be extremely slow growing and radiological imaging may not capture progression effectively. Patients may have stable disease on imaging but have worsening symptoms and changes in tumour markers. Other patients may

have slowly growing disease but remain clinically very well. Therefore, treatment decisions need to be based on an accurate assessment of all three and the clinical judgement of a specialist team.

For a number of patients with low volume/low grade disease, who are symptomatically well, an appropriate approach may be to offer active surveillance rather than a treatment which may have a number of side-effects and possibly reduce quality of life. This approach can feel intuitively wrong for someone who has just been diagnosed with cancer.

Accurately assessing the patient and family concerns, long-term goals, and hopes are essential when we lack certainty on the value of different therapeutic options. Giving people time to consider the merit of each and supporting them with the uncertainty that this brings is key to effective patient-centred decision-making.

A recent survey in the UK highlighted that NET patients are far less likely to receive written information about their type of cancer, the tests they undergo, or the treatment that they receive (Quality Health 2015). Therefore, it is essential that patients are directed to specialist NET teams and specialist information resource and are given the chance to discuss options with an expert team to help them consider all options.

65.7 Nursing Support of Patients with NETs

Caring for individual with neuroendocrine tumours is complex and challenging. There are a wide range of diagnoses which encompass neuroendocrine tumours, including different tumour types, grades, and stages. These range from small indolent tumours to widespread, aggressive cancers, with the whole range in-between. The lack of clear evidence on how to best manage many of these can make for high levels of uncertainty for patient and their families as well as health care professionals who care for them. The complex range of symptoms that many patients have requires a wide range of knowledge and skill and input from many different disciplines and specialities (see Box 65.2).

This section explores the nurse's role through focus on three common concerns that are raised by many patients living with NETs

Box 65.2 Specialist Nurses and the MDT

The care of this complex condition requires the cooperation of a multidisciplinary team covering a broad range of specialties with the patient actively involved in decision-making. Patients may live with advanced disease for many years. They face a roller-coaster ride of multiple treatments, often with different teams, ongoing symptoms, and the psychological and social burden of living with a life-limiting illness.

Specialist **nurses** are well-placed within the MDT to take on a **key worker role**, supporting patients through a **complex illness trajectory**, providing a consistent single point of contact.

The key worker role includes:

1. Liaising with the MDT to ensure the patient's treatment trajectory is effectively managed.
2. Support with treatment decision-making
3. Holistic assessment of need
4. Ongoing informational and psychological support
5. Management of symptoms

Patient Quote

"Knowing that I could always call [the nurse] at any time was a godsend. They understood my case, they were often there at my appointments or at the end of a phone and I'm not sure how I would have managed without their support. I always felt that they were fighting in my corner".

(Written consent and permission has been obtained from the patient to use this quote)

1. Health-related quality of life
2. Gastrointestinal symptoms
3. Management of nutritional issues

65.7.1 Health-Related Quality of Life and NETs

There is limited research information about the impact of neuroendocrine tumours on health-related quality of life (HRQoL). NETs are rela-

tively rare and the heterogeneity of NETs makes it difficult to draw clear conclusions about the impact on specific groups of NET patients (Yao et al. 2008). Several studies have measured HRQoL in patients with NETs and show that overall HRQoL is reduced compared to the general populations in those countries (Beaumont et al. 2012). What is also known is that hormonal related symptoms, such as diarrhoea and flushing, can greatly affect HRQoL (Vinik et al. 2016). Other tumour-related symptoms including fatigue and pain also impact on HRQoL and mental health issues such as anxiety, sadness at illness, and depression are not uncommon (Singh et al. 2016). A recent global survey of HRQoL in NET patients noted that nearly three quarters of patients stated their disease had a moderate to significant impact on their lives. Over 90% had made lifestyle changes and over half had significant stress and anxiety levels and worried about their future (Singh et al. 2016).

As many NET patients have metastatic disease, and may also have limited treatment options, HRQoL becomes the key focus of care for health care professional and patients (Pearman et al. 2016). Many NET treatments are focused primarily on reducing symptoms in an attempt to improve HRQoL, for example, somatostatin analogues or liver-directed therapies in patients with carcinoid syndrome. A few studies have examined the impact of treatment on HRQoL, suggesting that some treatments, including surgery and PRRT, can have beneficial effects on HRQoL in patients with GEP-NETs (Martini et al. 2016). However, others are less conclusive (Vinik et al. 2016), and the balance between benefits and side-effects of a range of treatments in NETs needs further exploration.

65.7.1.1 Patient Support

Specialist nurses are often well-placed to support patients by giving time for patients to talk about the impact of their illness on their quality of life, assessing their concerns and implementing strategies to respond to these. A focus on holistic health needs assessment and patient-reported concerns/outcomes (PROMs) is useful and a number of tools exist to support this (National Cancer Action Team 2011). Holistic needs assessment can uncover unexpected concerns, focus on what is most important to the patient and guide support strategies and referrals to other agencies and health care professionals.

Some concerns that patients raise may be resolved directly in consultations, through for example giving tailored information or prescribing medication. Other concerns may require input from other agencies such as psychological services, social work, or specialist palliative care teams.

Case Study 1

(Written consent and permission has been obtained from the patient to use this case study)

Psychological Assessment and Management

Joanne is a 32-year-old lady who presented with a 2-year history of intermittent chest infections. Investigations, including lung biopsy, led to the diagnosis of a *typical bronchial NET* and plans were in place for this to be excised. A preoperative FDG-PET scan showed an indeterminate liver lesion, and a further *Octreoscan* suggested possible liver metastases. Her surgery was cancelled and she was referred to the NET specialist team at her closest Centre of Excellence.

During our first meeting, she was pacing back and forward in the clinic room, tearful and clearly highly distressed. Her partner was sitting in a chair crying. Efforts were made to try to explain the diagnosis to her and the plan to biopsy her liver: meanwhile, we would commence her on a somatostatin analogue—our view was that starting a treatment might help focus her anxiety.

Further assessment by the specialist nurse that day highlighted a history of anxiety disorder since her late teens. She'd lost over 10 kg in weight since the results of her scan, 10 days earlier, she was unable to sleep, and felt sick all the time. She remained distressed throughout the visit, even after treatment was started, and she had a panic attack.

A decision was made to contact the out of hours psychological medicine team for advice. They reviewed Joanne in clinic and arranged for her GP to prescribe some mild sedatives to assist with sleep and she was commenced on anti-depressants. She was also enrolled on a depression management

programme for cancer patients available in the specialist centre.

Sadly the biopsy confirmed metastatic NET and over the next 18 months Joanne underwent a number of different treatments. Throughout this time she required intensive input from the psychological medicine team, who provided invaluable support throughout this period. Though she now has stable disease she has a daily struggle with anxiety and depression and continues to use both the specialist nurse and psychological medicine team for ongoing support.

Learning Point

This case highlights the benefit of a systematic approach to assessment and management of anxiety and depression in patients with cancer.

Questions

How could psychological assessment and support be improved within your own clinical setting?

What role could nurses play in this?

Others may be resolved by the patient taking responsibility for further action (National Cancer Action Team 2011), for example by attending a support group (see Box 65.3) or speaking to relatives about their feelings. It is well known that social support can play a key role in how patients cope with illness and this is supported in studies in NETs (Haugland et al. 2016).

Box 65.3 Patient Support Groups (NET Natter Groups UK)

In the UK, there is a large network of NET ***Natter*** groups, set up by the NET Patient Foundation charity. These groups allow patients to share experiences, deal with emotionsn and feel less isolated. They range from informal meetings of a small number of patients and family members affected by NETs to more formal meetings with specialist speakers. As they are NET specific, they can also help those with rare cancers feel less isolated and normalise their situation.

Patient/Carer Quotes

"It's been amazing meeting other patients with NETs, being able to talk about John's illness and realise we're not alone in this". "The specialist talks and information are great, but most of all it's getting together with other people with a NET, sharing tips on dealing with symptoms… having a laugh or even crying together".

For more information, see: https://www.netpatientfoundation.org/ and **Box 65.4**.

(Written consent and permission has been obtained from the patient to use these quotes)

Box 65.4 Patient Advocacy Groups: The NET Patient Foundation

The *NET Patient Foundation* was founded in 2006 by Cathy Bouvier the NET specialist nurse at the Royal Free Hospital in London. There was a small support group there called *Living with Carcinoid*, that was set up by the now Chairman, Peter Gwilliam and his wife. Cathy knew that something had to be done to address the huge unmet need she was sensing throughout the UK from the many calls she was receiving, the misinformation, and the isolation. Together with two patients, Andy and Cathy, they were able to launch a wider charity, and with Peter's permission the *NET Patient Foundation* was formed

The aim was to provide better information to all NET patients with all types of NET. The website was started, thanks to a generous donation from Paul Hunter, a well-known snooker player, who had been diagnosed with a NET and subsequently lost his battle at the age of 28. Cathy left her post at the Royal Free Hospital to carry on the work for patients in the community. It was a huge leap of faith, but one that she has never regretted 12 years on.

Cathy Bouvier highlights the five pillars of activity below:

- Support—we have two specialist nurses, a medical advisory board, two psychologists and our NET Natter programme, providing community support all over the UK, alongside supportive tools for our patients including wallet cards for easy access to the toilet and carcinoid crisis emergency prevention.
- Education—patient materials are a passion of ours. We provide "new patient pack" to 90+ hospitals in the UK. We also provide factsheets for all NET types and have "easy to read" ENETS guidelines incorporated into every factsheet.
- Advocacy—we strive to be an evidence-based advocacy group, collecting real-life data from the NET community to drive change in both commissioning for NET treatments and clinical practice. We developed our own Patient Experience Survey gathering nearly 1000 responses in England alone, we produced the first report challenging the Cancer Plan in England and the second report supporting the NET Scottish community is due out on NCD 2017. We also employ a dedicated NET Cancer Analyst who is working hard to get relevant data for us to support our NET services.
- Research—we have our clinical fund supporting pilot projects in the UK, in collaboration with UKINETs. Grants are released once a year. We also run in-house projects and projects related to diet, nutrition, quality of life, and unmet needs.
- Awareness—this incorporates and overarches all our five pillars of activity and all our work.

The future is about gathering data, pushing for qualitative research to be integrated into clinical studies, focusing on the real needs of our patient population, helping patients live better with their disease, and empowering patients and all who are involved in NET patient care to be educated and knowledgeable. We can only do this by working closely with our colleagues. Our services work alongside and complement acute services provided by health care teams. We sit on executive boards of the European NET Nurse Group, our national medical society, and the global NET group INCA. True holistic care requires all affected by neuroendocrine cancer to be supported from diagnosis through treatment and beyond, by a committed group of health care professionals and allied health care professionals, for which I believe, medical advocacy organisations, should be recognised as.

Catherine Bouvier
NET Patient Foundation
netpatientfoundation.org
hello@netpatientfoundation.org
01926 883487

65.7.1.1.1 Patient Advocacy

The NET Patient Foundation is one of a number of charities that support and advocate on behalf of NET patients. The International Neuroendocrine Cancer Alliance (INCA) has its mission to be the global advocate for NET patients, working to raise awareness of NETs, supporting research, disseminating information, and sharing best practice.

65.7.2 Gastrointestinal Symptoms in NETs

Gastrointestinal (GI) symptoms are a major cause of morbidity for many patients with NETs, impacting on their life in many ways, causing isolation and embarrassment as well as contributing to other symptoms such as fatigue and weight loss. Many patients have been treated for a range of GI symptoms prior to diagnosis, e.g. IBS, indigestion, gallstones, and gastric ulcer, with several studies confirming abdominal pain as the most common presenting symptom (Ter-Minassian et al. 2013).

Typically, patients with gastroenteropancreatic NETS will have multiple GI symptoms, for example, abdominal pain, bowel cramps, greasy/oily stools, excessive flatulence, diarrhoea, urgency, lack of appetite, early satiety, and weight

Table 65.8 Common causes of abdominal symptoms in gastroenteropancreatic NETs

Functional hormonal symptoms (Carcinoid, Verner-Morrison, Zollinger-Ellison)	Diarrhoea, abdominal cramps, weight loss
Mass effect of tumour	Abdominal pain, obstruction, poor appetite, overflow diarrhoea, weight loss, nausea
Treatments	Chemotherapy-diarrhoea, somatostatin analogues, abdominal cramping, nausea, and vomiting
Mesenteric fibrosis and mesenteric angina	Cramping abdominal pain, obstruction, erratic bowel habit-diarrhoea/constipation, early satiety, weight loss

loss. Being able to appropriately assess these symptoms, consider causes, and then treat them effectively can substantially improve quality of life. The causes of symptoms are often multifactorial (see Table 65.8 below) and to manage these effectively, systematic and detailed history taking is essential. The use of a gastroenterology team and dietetic service experienced and interested in NETs can be invaluable. Four of the most common and troublesome causes of GI symptoms and their management are described below.

Case Study 2

(Written consent and permission has been obtained from the patient to use this case study)

The Importance of Specialist NET Centre Care

Eight years ago Arnold presented with a 4-year history of lower abdominal pain, weight loss, and increasing diarrhoea. Previous endoscopic investigations had been negative and he had initially been diagnosed as having irritable bowel syndrome. However, as his weight loss increased further investigations were arranged. A CT CAP confirmed a 4 cm mesenteric mass, multiple mesenteric lymph nodes, and bilateral multiple liver metastases. A biopsy confirmed a grade 1 well-differentiated NET, with a Ki-67 of 1%. His baseline urine 5HIAA was normal and his chromogranin A was 8 × upper limit of normal. He was seen by his local surgical team, who deemed his abdominal disease inoperable and he came under the care of a local oncologist who commenced him on 4-weekly depot octreotide injections.

Arnold's disease remained stable for 4 years though he had ongoing abdominal discomfort, bloating, occasional nausea and vomiting, gradual weight loss, and fatigue. He used MST 20 mg twice a day for pain, with oramorph for breakthrough and "*thought the symptoms were a normal part of my illness*".

In 2015, he was referred to a specialist NET centre, due to progressive liver metastases. He had worsening diarrhoea and his urine 5HIAA was 5 × upper limit of normal. A ^{68}Ga-dotatate PET scan confirmed uptake, both in his abdominal and liver disease. He was therefore treated with 4 cycles of ^{177}Lu-peptide receptor radionuclide therapy. He tolerated this well, with only mild nausea and his liver metastases reduced in size slightly. His diarrhoea also improved significantly.

Over the next 6 months, regular telephone review with his specialist nurse revealed that his abdominal pain was worsening significantly, despite input from a specialist dietitian, adaptation of diet, and use of further analgesia. The hepatobiliary surgeons arranged a CT scan; confirming worsening mesenteric desmoplasia and swollen small bowel loops. The specialist MDT felt that resection of the mesenteric mass was feasible and Arnold underwent ileal and mesenteric disease resection in late 2016. His abdominal pain immediately resolved and he had improved appetite. However, he had worsening diarrhoea post-operatively, up to nine times daily, which despite codeine and loperamide did not resolve. He commenced *Creon* for possible pancreatic insufficiency due to his octreotide injections. This made a small improvement only. He

was reviewed by the gastroenterology team, a SeHCAT scan was carried out and it confirmed severe bile acid malabsorption. He commenced colesevelam with excellent results. He now opens his bowels twice daily and is currently pain free. His most recent scans show stable liver metastases.

Learning Points

Early review by specialist centres is essential to enable access to treatments possibly not considered in local hospitals. This has the ability to improve the overall outlook and quality of life for patients with metastatic NETs.

Assessment of disease progression also needs to include symptoms and quality of life not just whether disease is stable.

Table 65.9 Management of refractory carcinoid syndrome induced diarrhoea

Dose escalation of somatostatin analogue injections	Initially try injections every 3 weeks. Can consider 2 weekly Can also use short-acting octreotide as breakthroughTypically 100–200 μg three times daily (Toumpanakis and Caplin 2013) Options of IV octreotide or a syringe driver can also be considered as a palliative measure; however, these are likely only to benefit for a limited period of time
Telotristat etiprate	Tryptophan hydroxylase inhibitor, shown to reduce frequency of carcinoid induced diarrhoea in around one third of patients (Riechelmann et al. 2017)
Loco-regional therapies to reduce disease burden in liver	Radiofrequency ablation, hepatic embolisation, surgical debulking [see **Sect. 65.6.2**]
Systemic therapies	Peptide receptor radionuclide therapy, everolimus, interferon

65.7.2.1 Carcinoid Syndrome-Related Diarrhoea

This is typically found in patients with metastatic small intestinal NETs, but also some bronchial NETs. Diarrhoea is often frequent, watery, and may often not respond fully to loperamide or codeine-based treatments. It can also be accompanied with abdominal pain and cramps. Treatment is classically with long-acting somatostatin analogues, which provides excellent initial response in over 75% of patients (Toumpanakis and Caplin 2013). However, over time the effect tends to wear off and in this situation a number of options need to be considered to manage this. There is a lack of strong evidence advocating one particular approach; however, small-scale studies and years of treatment experience support a number of worthwhile strategies (Riechelmann et al. 2017) highlighted in Table 65.9 below.

65.7.2.2 Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth [SIBO] is common in patients who have undergone upper GI surgery, for example, many patients with small intestinal and pancreatic NETs. It causes malabsorption and a whole range of vague gut symptoms including bloating, flatulence, abdominal distension, abdominal pain, and diarrhoea. H_2 carbohydrate breath tests are the preferred methods for evaluating SIBO though no gold standard approach exists (Andreyev et al. 2016). Treatment involves the use of antibiotics, reviewing symptom benefit and the management of any nutritional deficiencies that may have occurred. Repeat courses of antibiotics may be required as the underlying causes cannot always be addressed (Andreyev et al. 2016).

65.7.2.3 Bile Acid Malabsorption

Patients with small intestinal NETs who've had ileal resections are at high risk of bile acid malabsorption [BAM]. Other risks include cholecystectomy and treatment with chemotherapy. Diagnosis is through a SeHCAT scan and treatment is with bile acid sequestrants such as colesevelam (Andreyev et al. 2016). Dietary fat reduction can be considered but this could exacerbate weight loss and requires expert dietetic input. Anti-diarrhoea medication can also be trialled.

65.7.2.4 Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency [EPI] is a common problem for many NET patients, due to a

combination of pancreatic disease, upper GI/hepatobiliary surgery, and the use of somatostatin analogues. Diagnosis is through a non-liquid stool sample for faecal elastase; however, many centres empirically trial pancreatic enzyme replacement therapy PERT, without confirmed faecal elastase results (See Box 65.5 Malabsorption Issues and NETs).

Box 65.5 Malabsorption Issues and NETs

Fat has been suggested as a trigger of carcinoid syndrome; however, fat triggering a loose stool bowel movement may be more related to malabsorption and exocrine pancreatic insufficiency (EPI), or bile acid malabsorption (BAM) rather than tumour function. EPI is more likely to occur if the patient is prescribed somatostatin analogues due to their effect on pancreatic function. The treatment is pancreatic enzyme replacement therapy (PERT) with: Creon®/Nutrizym®, /Pancrease HL®/Pancrex®.

Some patients benefit from taking an anti-acid drug 30 min before taking the enzymes, as a gastric pH of 4.5 or under will reduce activity of the enzymes.

- ***Suggested starting dose:***
  - One × ~25,000 units of lipase capsule with all snacks/drinks
  - Two × ~25,000 units of lipase capsule with all main meals.
- The dose can then be titrated upwards. Sometimes ~75,000 units of lipase per main meal is enough, but some people may need more than this.

BAM is more likely to occur if the gall bladder or the terminal ileum has been removed, or is diseased. The treatment for this is a low fat diet or a bile acid sequestrant.

EPI and vitamin deficiency

If EPI is not treated with sufficient PERT, fat-soluble vitamins are at highest risk of not being absorbed properly. Patients can develop night blindness from insufficient vitamin A, bone weakness from insufficient vitamin D, poor skin and immunity from insufficient vitamin E, and bruising and bleeding from insufficient vitamin K.

Where somatostatin analogues are the likely cause of EPI, low vitamin B12 levels have also been observed. A study of 54 patients mostly with serotonin-producing tumours and on somatostatin analogues found only one fifth of patients had steatorrhoea (meaning EPI was most severe in a fifth), but malabsorption was still chronic enough to result in deficiencies: 6% were deficient in vitamin A, 28% were deficient in vitamin D, 15% were deficient in vitamin E, 63% were deficient in vitamin K1, and 58% were deficient in erythrocyte vitamin E (Fiebrich et al. 2010).

It is therefore important to monitor these vitamins if EPI is diagnosed, or the patient is at risk of developing EPI through prescription of somatostatin analogues.

65.7.2.5 Nursing Care of Patients with GI Symptoms

For most patients, the GI symptoms are ongoing in nature and management strategies aim to improve quality of life where possible. Nurses have a key role in assessing patients' symptoms and guiding referral to appropriate teams such as gastroenterology and dietetics. They also need to support patients with symptom management and guiding patients in adjusting to living with complex symptoms and enabling patients to maintain privacy and dignity. This may include advice on fluid intake, dietary changes, medication, hygiene, incontinence aids, wallet cards to assist access to toilet facilities, and also psychological support.

65.7.3 Dietary Management of Neuroendocrine Tumours

Patients with neuroendocrine tumours (NETs) often have problems digesting foods, even if their

NET is not within the digestive system. For example, surgery, drug therapies, and the tumour hormone/peptide secretions can affect gut function, with weight loss, malabsorption, and nutrient deficiencies very common as a result. Even if there are no digestive issues, diet sometimes needs to be adjusted because of blood glucose levels, surgery, or obstruction. Not all patients have problems with their weight, but use of a malnutrition screening tool together with thorough anthropometrical measurements is recommended. A tool alone may not highlight any loss of muscle and muscle function and therefore early cachexia, especially in the overweight/obese.

Because NETs also behave differently and have unique treatments compared to many other cancers, NET patients do require access to specialist dietetic input, and any hospital specialising in NETs should include a NET Specialist Dietitian within their multidisciplinary team.

This section focuses on a few areas of dietary management which are unique to NET cancers.

65.7.3.1 Serotonin-Producing Tumours (Carcinoid Syndrome)

Serotonin-producing NETs were once known as "carcinoid" tumours, and although the name has been changed to specify the site of the tumour and tumour functionality, "carcinoid syndrome" still remains a physical diagnosis, and one which requires dietetic input.

65.7.3.1.1 Niacin

When the body makes large amounts of serotonin, the amino-acid tryptophan stores are used up. When tryptophan stores are too low, it cannot be converted into enough niacin. Mild niacin deficiency may lead to fatigue, sore mouth, depression, and indigestion/vomiting. If severe, this can develop into pellagra. The three main symptoms of this are:

- Dementia
- Diarrhoea
- Dermatitis

Two studies that have investigated niacin deficiency show that between 28 and 45% of patients with carcinoid tumours and carcinoid syndrome were found to be niacin insufficient or deficient (Shah et al. 2005; Bouma et al. 2016). Bouma et al. recommend that the urinary niacin metabolite N1-methylnicotinamide is checked at diagnosis and niacin is supplemented appropriately. Though the EU nutrient reference value (NRV) for niacin is 16 mg/day [a number of centres recommend patients should take a daily niacin (B3) containing tablet such as Vitamin B Strong compound], the 2016 study found that a much higher mean dose of 144 mg was required to prevent and treat niacin deficiency in the majority of serotonin-producing NET patients (Bouma et al. 2016).

65.7.3.1.2 Carcinoid Syndrome Triggers

As well as stress and anxiety, anecdotal data has shown that for some patients certain foods and drinks can "trigger" carcinoid syndrome. The types of foods/drinks that cause this reaction are individual in nature. Assessment by a specialist NET dietitian is crucial here as many patients are often told to eliminate these and other foods without knowing if they trigger symptoms or not, and as a result diets may get too restrictive, and worsen quality of life.

Possible triggers include:

- Large meals
- Spices
- Alcohol
- Meals moderate to high in amines may also trigger symptoms in some people: these include aged cheese, alcohol, smoked/salted fish and meat, yeast, fermented-tofu, miso, sauerkraut, large doses of caffeine, chocolate, peanuts, brazil nuts, coconut, avocado, banana, raspberries, most soya products, broad beans.

The foods above have been known to trigger symptoms, but it is important to let patients know that they are not harmful. The most reliable method of identifying possible "trigger foods" is with a food and symptom diary. The diary is completed by the patient over a 1–2-week period including food intake, medications, and then the symptoms experienced afterwards.

A dietitian can also play a role in investigating what type of loose stools are occurring. Hormone/peptide-related diarrhoea will continue without eating and is likely to be more watery. Malabsorption such as steatorrhoea is more likely to occur within a few hours of eating, but can occur over night if not prevented—see [**Box 65.5** Malabsorption issues in NETs].

65.7.3.2 Small Bowel Obstruction

Where small bowel primary tumour and mesenteric metastases cause a diffuse desmoplastic reaction the risk of bowel obstruction will start to increase [see Sect. 65.6.1]. Diet should be tailored to the patient and their individual obstruction risk. The diet that is recommended should depend on the risk of obstruction (has it happened before, the size of the lumen) and where obstruction is likely to occur (how digested the food should be in that part of the intestine). All patients at risk of a small bowel obstruction require detailed assessment and advice from a dietitian.

Traditionally, a "low fibre diet" was given to all patients at risk of bowel obstructions, but this approach lacks clear evidence. However, having a lot of very high fibre foods all in one go can cause an obstruction in many people, whereas too little fibre can cause constipation. Often the foods that have caused obstruction have not had any fibre in them at all and can be tough meat or fish bones. Therefore, the consistency of food may matter the most and a "staged" diet approach may be the correct approach. This would include using food consistency varying from soft solids to liquids, with small amounts of fibre (no bits) equally spaced out throughout a day. This is an area that urgently requires research.

When a patient cannot tolerate any food or liquid orally, parenteral nutrition may be the only option. These patients face very challenging symptoms, overall have a poor prognosis (Moris et al. 2018), and require intensive input from NET specialists, dietitians, and palliative care teams.

65.7.3.3 Pancreatic NETs

Pancreatic NETs (panNETs) classify a heterogenous group of tumours including both non-functioning tumours and functioning tumours such as

- Glucagonomas
- Insulinomas
- Gastrinomas

Tumours that are non-functioning can require less dietetic input than functioning tumours; however, most patients will require help if they have had surgery to the pancreas, or have EPI. Most patients with a tumour to the head of the pancreas will require PERT, whereas patients with a tumour in the body or tail of pancreas should be closely monitored for signs of EPI. Please see **Box 65.5 Malabsorption Issues in NETs** for dosing.

65.7.3.3.1 Blood Glucose

PanNETs as a group of tumours can increase or lower blood sugar levels. Functioning insulinomas and glucagonomas directly produce hormones to raise or lower glucose levels. Management of these tumours alone is challenging, but it has been known that these two tumours can co-exist too, making regular glucose monitoring even more important. All patients with a functioning insulinoma will require dietetic input at some point.

Surgery to remove part of or the entire pancreas can lead to diabetes and some treatments such as somatostatin analogues can also affect blood glucose levels. Patients with EPI will need PERT to help break down starches and prevent hypoglycaemia. See **Box 65.5 Malabsorption Issues in NETs**.

65.8 Conclusions

NETs are a diverse group of malignancies that cause characteristic hormonal syndromes, such as carcinoid syndrome. Though a number of NETs are cured by surgery, the majority present only once they have metastasised, so treatment is more often directed at control of disease, management of symptoms, and improvement in quality of life.

There are a wide range of treatments, which can improve the symptoms of carcinoid syndrome and stabilise tumour growth in many patients. However, there is lack of evidence as to the best approach to managing many patients, and overall response rates to treatment are often low.

Caring for individual with neuroendocrine tumours is therefore complex and challenging. Patients may live with advanced disease for many years and often face a roller-coaster ride of multiple treatments, ongoing symptoms, and the psychological and social burden of living with a life-limiting illness. As gastrointestinal symptoms are commonplace, the use of gastroenterologists interested in NETs and the involvement of a specialist NET dietitian are essential in managing patients' symptoms.

Specialist nurses are well-placed within the MDT to take on a key worker role, supporting patients through a complex illness trajectory, providing a consistent single point of contact.

Acknowledgement With special thanks to Catherine Bouvier from NET Patient Foundation, www.netpatient-foundation.org for her contribution to this chapter with a case study and information on the Patient Advocacy Group.

References

Andreyev HJN, Muls AC, Shaw C, Jackson RR, Gee C, Vyoral S, et al. Guide to managing persistent upper gastrointestinal symptoms during and after treatment for cancer. Frontline Gastroenterol. 2016;flgastro-2016.

Basturk O, Yang Z, Tang LH, Hruban RH, Adsay NV, McCall CM, et al. The high grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well-differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015;39(5):683.

Baum RP, Puranik AD, Kulkarni HR. Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors: current state and future perspectives. Int J Endocr Oncol. 2015;2(2):151–8.

Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41(3):461–6.

Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EGE, Kema IP, Walenkamp AME. Niacin (Vitamin B3) supplementation in patients with serotonin-producing neuroendocrine tumor. Neuroendocrinology. 2016;103(5):489–94.

Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3).

Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Fave GD, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. Br J Surg. 2012;99(11):1480–6.

De Baere T, Deschamps F, Tselikas L, Ducreux M, Planchard D, Pearson E, et al. GEP-NETS update: interventional radiology: role in the treatment of liver metastases from GEP-NETs. Eur J Endocrinol. 2015;172(4):R151–66.

Deppen SA, Blume J, Bobbey AJ, Shah C, Graham MM, Lee P, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. J Nucl Med. 2016;57(6):872–8.

Elias D, Baton O, Sideris L, Boige V, Malka D, Liberale G, et al. Hepatectomy plus intraoperative radiofrequency ablation and chemotherapy to treat technically unresectable multiple colorectal liver metastases. J Surg Oncol. 2005;90(1):36–42.

Eriksson J, Stålberg P, Nilsson A, Krause J, Lundberg C, Skogseid B, et al. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. World J Surg. 2008;32(5):930–8.

Fave GD, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):119–24.

Fiebrich H, Van den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32(11–12):1398–404.

Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15(1):e8–21.

Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology. 2016;103(2):186–94.

Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97.

Hart EA, Meijs TA, Meijer RCA, Dreijerink KM, Tesselaar ME, de Groot CA, et al. Carcinoid heart disease: a guide for screening and timing of surgical intervention. Netherlands Hear J. 2017;25(9):471–8.

Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Risk factors associated with neuroendocrine

tumors: a US-based case–control study. Int J Cancer. 2008;123(4):867–73.
Haugland T, Wahl AK, Hofoss D, DeVon HA. Association between general self-efficacy, social support, cancer-related stress and physical health-related quality of life: a path model study in patients with neuroendocrine tumors. Health Qual Life Outcomes. 2016;14(1):11.
Huguet I, Grossman AB, O'Toole D. Changes in the epidemiology of neuroendocrine tumours. Neuroendocrinology. 2015;104(2):105–11.
Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev. 2004;25(3):458–511.
Kennedy A, Bester L, Salem R, Sharma RA, Parks RW, Ruszniewski P. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference. HPB. 2015;17(1):29–37.
Khan MS, El-Khouly F, Davies P, Toumpanakis C, Caplin ME. Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). Aliment Pharmacol Ther. 2011;34(2):235–42.
Knigge U, Capdevila J, Bartsch DK, Baudin E, Falkerby J, Kianmanesh R, et al. ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms: follow-up and documentation. Neuroendocrinology. 2017;105(3):310–9. https://www.karger.com/DOI/10.1159/000458155.
Koumarianou A, Kaltsas G, Kulke MH, Oberg K, Strosberg JR, Spada F, et al. Temozolomide in advanced neuroendocrine neoplasms: pharmacological and clinical aspects. Neuroendocrinology. 2015;101(4):274–88.
Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med. 2009;360(2):195–7.
Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008;26(13):2124–30.
Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin. 2011;40(1):1–18.
Lepage C, Ciccolallo L, De Angelis R, Bouvier AM, Faivre J, Gatta G. European disparities in malignant digestive endocrine tumours survival. Int J Cancer. 2010;126(12):2928–34.
Lepage C, Bouvier AM, Faivre J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. Eur J Endocrinol. 2013;168(4):R77–83.
Luo G, Javed A, Strosberg JR, Jin K, Zhang Y, Liu C, et al. Modified staging classification for pancreatic neuroendocrine tumors on the basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society Systems. J Clin Oncol. 2016;35(3):274–80. https://doi.org/10.1200/JCO.2016.67.8193.
Martini C, Gamper E-M, Wintner L, Nilica B, Sperner-Unterweger B, Holzner B, et al. Systematic review reveals lack of quality in reporting health-related quality of life in patients with gastroenteropancreatic neuroendocrine tumours. Health Qual Life Outcomes. 2016;14(1):127. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5018190/
Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72.
Moris D, Ntanasis-Stathopoulos I, Tsilimigras DI, Vagios S, Karamitros A, Karaolanis G, et al. Update on surgical management of small bowel neuroendocrine tumors. Anticancer Res. 2018;38(3):1267–78.
National Cancer Action Team. Holistic needs assessment for people with cancer: a practical guide for healthcare professionals; 2011.
Navalkele P, O'Dorisio MS, O'Dorisio TM, Zamba GKD, Lynch CF. Incidence, survival and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975–2006. Pediatr Blood Cancer. 2011;56(1):50–7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4251713/.
Neychev V, Kebebew E. Management options for advanced low or intermediate grade gastroenteropancreatic neuroendocrine tumors: review of recent literature. Int J Surg Oncol. 2017;2017:6424812.
Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion. 2000;62:92.
Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19(6):829–37.
Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95(2):135–56.
Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. Neuroendocrinology. 2017;105(3):255–65.
Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology. 2016;103(2):172–85.
Pearman TP, Beaumont JL, Cella D, Neary MP, Yao J. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. Support Care Cancer. 2016;24(9):3695–703.
Quality Health. NET patient foundation patient experience survey [Internet]. 2015. https://www.netpatientfoundation.org/wp-content/uploads/NET-Patient-Foundation-report-FINAL-1.pdf

Ramage JK, Davies AH. Measurement of quality of life in carcinoid/neuroendocrine tumours. Endocr Relat Cancer. 2003;10(4):483–6.

Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32.

Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13. https://doi.org/10.1056/NEJMoa1003825.

Riechelmann RP, Pereira AA, Rego JFM, Costa FP. Refractory carcinoid syndrome: a review of treatment options. Ther Adv Med Oncol. 2017;9(2):127–37.

Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer. 2016;139(12):2679–86.

Rindi G, Arnold R, Bosman F, Capella C, Klimstra DS, Klöppel G, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise N, editors. WHO classification of tumours of the digestive system, vol. 4. Lyon: International Agency for Research on Cancer; 2010.

Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656–63.

Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RRP. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroenterol. 2005;100(10):2307.

Sharma P, Arora S, Karunanithi S, Khadgawat R, Durgapal P, Sharma R, et al. Somatostatin receptor based PET/CT imaging with 68Ga-DOTA-Nal3-octreotide for localization of clinically and biochemically suspected insulinoma. Q J Nucl Med Mol Imaging. 2016;60(1):69–76.

Singh S, Granberg D, Wolin E, Warner R, Sissons M, Kolarova T, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2016;3(1):43–53. https://doi.org/10.1200/JGO.2015.002980.

Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35.

Ter-Minassian M, Chan JA, Hooshmand SM, Brais LK, Daskalova A, Heafield R, et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. Endocr Relat Cancer. 2013;20(2).

Toumpanakis C, Caplin ME. Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. Semin Oncol. 2013;40(1):56–68.

Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10(9):1243–60.

Vinik A, Bottomley A, Korytowsky B, Bang Y-J, Raoul J-L, Valle JW, et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumors: results from an international phase III trial. Target Oncol. 2016;11(6):815–24.

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.

Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23. https://doi.org/10.1056/NEJMoa1009290.

Yao JC, Guthrie K, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. SWOG S0518: phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC# 704865) in advanced, poor prognosis carcinoid patients (NCT00569127). American Society of Clinical Oncology; 2015.

Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968–77.

Multiple Endocrine Neoplasia

66

Mike Tadman and Lee Martin

Contents

66.1 **Introduction** 1260

66.2 **MEN 1** 1261
66.2.1 Aetiology and Epidemiology 1261
66.2.2 Diagnosis 1261
66.2.3 Clinical Presentation 1262
66.2.4 Treatment of Specific Tumours Associated with MEN 1 1264
66.2.5 Genetic Testing 1266

66.3 **MEN 2 and 3** 1268
66.3.1 Clinical Presentation 1268
66.3.2 Diagnosis 1270
66.3.3 Genetics and Screening 1270
66.3.4 Treatment 1271

66.4 **Nursing Support and Quality of Life Issues in MEN** 1273

66.5 **Conclusions** 1276

References 1276

Abstract

Multiple endocrine neoplasia is a rare inherited condition characterised by the development of multiple tumours of the endocrine system. It is inherited in an autosomal dominant way, and there are now four distinct recognised forms. Tumours that occur in MEN patients often occur earlier in life than in sporadic cases and may also often be multiple in nature.

MEN 1 is characterised by parathyroid, pancreatic, and pituitary tumours. Parathyroid and pituitary tumours are almost universally benign, whereas pancreatic tumours can be malignant.

Management of MEN 1 therefore involves close monitoring of tumour growth, and symptoms through regular screening and then treatment of specific tumours if required. For parathyroid tumours, surgery is the definitive treatment to resolve problems of hypercalcaemia. How early this should be carried out is still debated. Pancreatic NETs are the major

M. Tadman (✉)
Oxford University Hospitals NHS Foundation Trust, Oxford, UK
e-mail: Michael.Tadman@ouh.nhs.uk

L. Martin
Barts Health NHS Trust, The Royal London Hospital, London, UK
e-mail: lee.martin@bartshealth.nhs.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_66

cause of morbidity and mortality in MEN 1 though many remain small and asymptomatic. Again there is uncertainty as to when to intervene surgically, with a need to weigh up the risk of tumour spread versus the long-term complications of major pancreatic surgery.

International guidelines have been produced to assist with management decisions and further research is required to clarify best treatment options.

MEN 2 and 3 are caused by a genetic defect in the *RET* proto-oncogene. It is characterised by medullary thyroid cancer (MTC) and phaeochromocytoma with primary parathyroid hyperplasia also common in MEN 2. Individuals with MEN 3 rarely get parathyroid hyperplasia but do get several other additional features, including mucosal neuromas, ganglioneuromatoses of the GI tract, and a Marfanoid habitus.

Early screening and total thyroidectomy early in life is the definitive approach to prevent metastatic MTC. Hyperparathyroidism is often mild in MEN 2 and treatment is similar to sporadic cases. Management of phaeochromocytomas is typically adrenal surgery. Due to the multiple nature of tumours, bilateral adrenalectomy and lifelong steroid replacement may be required. Due to the rarity and complex nature of these conditions, individuals and their families should preferably be managed within specialist multi-disciplinary teams.

Specialist nurses are well placed to support patients navigate their way through complex pathways, improve communication within the MDT, support with ongoing symptoms, aid with treatment decision-making and offer emotional and psychological support for individuals facing lifelong uncertainty.

Keywords

Multiple endocrine neoplasia · MEN 1, MEN 2 · Pancreatic neuroendocrine tumours Genetic screening medullary thyroid cancer Phaeochromocytoma · Primary hyperparathyroidism

Abbreviations

CLA	Cutaneous lichen amyloidosis
FMTC	Familial medullary thyroid cancer
GEPNETS	Gastroenteropancreatic neuroendocrine tumours
HD	Hirschsprung disease
IGF-1	Insulin growth factor-1
NET	Neuroendocrine tumours
MTC	Medullary thyroid cancer
PTH	Parathyroid hormone

Key Terms

- **Sporadic tumors:** non inherited tumours
- **Non-functioning panNETs:** non metatasising tumours
- **Proband:** person with a disease who is the point of origin for genetic testing

Learning Objectives

On completion of the chapter, the learner should be able to:

- Describe the aetiology and epidemiology of MEN disorders
- Identify common presentations of MEN disorders and how they are diagnosed
- Understand the multiple treatment options for common tumours found in MEN disorders, including parathyroid adenomas, pancreatic NETs, phaeochromocytoma, and medullary thyroid cancer
- Identify ethical issues relating to genetics and screening for the range of MEN disorders
- Understand the role of a specialist nurse in supporting individuals and their families with MEN 1 disorders

66.1 Introduction

Multiple Endocrine Neoplasia (MEN) is a rare inherited condition characterised by the development of tumours involving at least two endocrine glands in a single individual (Thakker 2014).

Table 66.1 MEN subtypes, associated tumours, and genetic mutation

MEN subtype	Associated tumours and disorders	Known genetic mutation
MEN 1: Werner's syndrome	Parathyroid, pancreatic islet, and anterior pituitary tumours; plus range of other endocrine and non-endocrine tumours	Menin mutations
MEN 2: Sipple's syndrome (previously MEN 2A) Also rare subtype known as MTC only MEN 2	Medullary thyroid carcinoma (MTC) in association with phaeochromocytoma and parathyroid tumours	Tyrosine kinase receptor mutations encoded RET proto-oncogene
MEN 3: (previously MEN 2B)	MTC and phaeochromocytoma, Marfanoid habitus, mucosal neuroma, medullated corneal fibres, and intestinal autonomic ganglion dysfunction—leading to megacolon	*RET* mutations
MEN 4	Parathyroid and anterior pituitary tutors in possible association with tumours of the adrenals, kidneys, and reproductive organs	Cyclin-dependent kinase inhibitor (*CDNK18*) mutations

Four major forms are now recognised, each with tumour development in specific endocrine glands, and each with its own different genetic abnormality (Table 66.1). All forms of MEN may be inherited as an autosomal dominant syndrome, though around 10% occur sporadically, de novo.

This chapter will focus initially on MEN 1 and then on MEN 2A and 2B (now known as MEN 2 and 3) in the final section.

66.2 MEN 1

66.2.1 Aetiology and Epidemiology

MEN 1 is a rare disorder, affecting around 1/30,000 with an equal distribution across the sexes (Marini et al. 2009). The pathology was first described in the early 1900s, but it was not till 1954 that the familial nature of the syndrome was described by Dr. Wermer in 1954. The MEN 1 gene was discovered in 1997.

It affects all age groups, with a reported range from 5 to over 80 years of age, with a 98% biochemical penetrance and 80% clinical penetrance by the fifth decade. Diagnosis before the age of 10 is rare (Marini et al. 2009). Inheritance is autosomal dominant, with a 50% chance for a parent to transmit the disease to their children. The MEN 1 gene is located on Chromosome 11q13 and codes for a protein called menin. This has a role in genome stability, and regulating transcription, cell division, and proliferation (Thakker et al. 2012).

Table 66.2 Prevalence of endocrine tumours in MEN 1 patients

Tumour localisation	Prevalence
Parathyroid adenoma	95%
Gastroenteropancreatic (GEP) tumours. Vast majority are gastrinoma, insulinoma, and non-functioning pancreatic tumours. More rarely, ViPoma, glucagonoma, and somatostatinoma	~40%
Anterior pituitary tumours (majority are prolactinoma, but also somatotropinomas, corticotropinomas, and non-functioning adenomas)	~30%
Adrenal gland tumours	~20% (but many small adenomas as well)
Other neuroendocrine tumours, e.g. bronchial, thymic, gastric NETs	~10%

Adapted from: Marini, F. *et al.* (2009)

MEN 1 mutations can be identified in between 70 and 95% of MEN 1 patients (Marini et al. 2009).

66.2.2 Diagnosis

Diagnosis of MEN 1 can be defined by 1 of 3 criteria:

1. Clinical: a patient with 2 or more MEN 1-associated tumours
2. Familial: a patient with 1 MEN 1-associated tumour and a first-degree relative with an established diagnosis of MEN 1

3. Genetic: an individual who has an identified germline MEN 1 mutation but who is currently asymptomatic and does not have any biochemical or radiological evidence of tumour development (Thakker et al. 2012; Thakker 2010)

66.2.3 Clinical Presentation

MEN 1 is associated with a wide range of endocrine tumours (Table 66.2), but patients typically present with:

- tumours of the parathyroid gland presenting as hyperparathyroidism (95% of cases)
- pancreatic neuroendocrine tumours (~40%)
- anterior pituitary tumours (~30%)

Other endocrine and non-endocrine tumours also occur, such as carcinoids, lipomas, meningiomas, and facial angiofibromas (Table 66.2) (Marini et al. 2009).

66.2.3.1 Primary Hyperparathyroidism

By far the most common presentation, around 90% of patients, is with primary hyperparathyroidism (Thakker 2010). The hypercalcaemia caused by primary hyperparathyroidism may present as kidney stones, vague hypercalcaemic symptoms, e.g. polyuria, polydipsia, constipation, malaise, or may be asymptomatic and picked up on screening (Table 66.3). Severe hypercalcaemia is rare. It differs from the more common sporadic form of the disease in a number of ways, e.g. presenting earlier in life and more commonly with multiple gland disease (Eller-Vainicher et al. 2009) (see Table 66.4 for more detail).

Table 66.3 Common clinical signs and symptoms of hypercalcaemia

Gastrointestinal tract	Constipation, anorexia, nausea and vomiting, constipation
CNS	Lethargy, depression, decreased alertness
Kidneys	Excessive urination, dehydration, hypercalciuria, increased risk for kidney stones
Skeletal changes	Increased bone resorption, fractures
Cardiovascular system	Hypertension, shortened QT interval

Table 66.4 Comparison of clinical features of sporadic and MEN-associated tumours

Sporadic Tumours	MEN 1-associated tumours
Sporadic parathyroid adenomas Onset usually sixth decade Generally single tumour Female/male prevalence 2:1 Usually cured by surgery No hypocalcaemia or hypoparathyroidism after surgery	MEN 1 parathyroid adenomas Onset usually third decade Often multiple tumours and all parathyroid glands affected No sex prevalence Common recurrences after subtotal parathyroidectomy Permanent hypoparathyroidism after total parathyroidectomy
Sporadic insulinomas Usually during or after fourth decade. Usually single lesion	MEN 1 insulinomas Typically third decade, can be single or multiple
Sporadic gastrinomas Onset during or after fifth decade. More commonly in pancreas	MEN 1 gastrinomas Multiple, small. Onset usually before fifth decade 90% in duodenum
Sporadic pituitary adenomas Rarely macroadenomas. Good response to medical therapy	MEN 1 pituitary adenomas Frequently macroadenomas, often secrete multiple hormones
Sporadic carcinoids Often midgut or hindgut. Often associated with carcinoid syndrome, secrete serotonin	MEN 1 carcinoids Higher prevalence in bronchi, thymus, and pancreas. Normally non-secreting

Adapted from: Marini, F. *et al.* (2009)

66.2.3.2 Pituitary Adenomas

Series reports vary but between 15 and 40% of patients with MEN 1 will have pituitary adenomas, most commonly prolactinomas, but somatotroph, corticotroph, gonadotroph, and non-functioning tumours can also occur (Brandi et al. 2001). Compared to pituitary tumours in non-MEN 1 patients they may present more typically as larger and more aggressive tumours with hypersecretion more difficult to normalise. However, treatment remains similar to those with sporadic adenomas (Arnold 2017).

66.2.3.3 Gastroenteropancreatic Neuroendocrine Tumours [GEPNETS]

Parathyroid tumours and pituitary adenomas are typically benign causing their effect either through the overproduction of hormones or the local mass effect (Marini et al. 2009). However, other tumours, such as GEP NETs, thymic and bronchial carcinoids, are associated with a risk of malignancy (Thakker et al. 2012) and have become the main tumour-related cause of death in patients with MEN 1. Up to 70% of patients who are symptomatically affected by MEN1 may die early from MEN 1-related cancer, with a French case series showing around half of patients dying by around 50 years of age (Goudet et al. 2010). The vast majority of GEP NETs are gastrinomas, insulinomas, and non-functioning NETs.

66.2.3.3.1 Gastrinomas

Between 30 and 70% of patients with MEN 1will have GEP NETs, with the most common clinical presentation being Zollinger-Ellison syndrome (ZES), caused by gastrinomas, which can lead to severe peptic ulcer disease. Typical symptoms include dyspepsia, epigastric pain, vomiting, chronic diarrhoea, and weight loss (Marini et al. 2009). In contrast to sporadically occurring gastrinomas, those in patients with MEN 1 are often multifocal, small, and occur overwhelmingly in the duodenum (Table 66.4), making cure by surgery difficult (see Sect. 66.2.4).

66.2.3.3.2 Insulinomas

Insulinomas are often small, may be multiple, and typically present before the age of 40. Around 20% of MEN 1 patients will have insulinoma and 50% of patients with multiple insulinomas will have MEN 1. Though predominantly benign in behaviour, their multiple nature can lead to the need for more extensive pancreatic surgery, with corresponding morbidity.

66.2.3.3.3 Non-functioning Pancreatic Nets (panNETs)

Non-functioning panNETs are amongst the most common GEPNET tumours in patients with MEN 1, occurring in up to 50% of MEN 1 patients. They are not associated with a clinical syndrome, which can make them more difficult to diagnose early. Due to their malignant potential and the ability to metastasise to the liver, they are a major cause of morbidity and mortality in MEN 1 patients (Thomas-Marques et al. 2006). Most clinicians would therefore suggest early radiological screening for these tumours (Thakker et al. 2012) though the clinical significance of small non-functioning tumours (<2 cm) has yet to be established.

66.2.3.3.4 Other Neuroendocrine Tumours

These occur in more than 3% of patients with MEN 1 and may occur in the lung, GI tract, or thymus (Thakker et al. 2012). Though thymic carcinoids are not common in patients with MEN 1, for example, occurring in only 2.6% in a French retrospective series (Goudet et al. 2009), they are typically aggressive with a poor overall prognosis. Heavy smoking may be a risk factor and they appear mainly in men. Screening with chest radiography may be prudent and prophylactic thymectomy is recommended by several groups in patients undergoing parathyroidectomy (Thakker et al. 2012).

Bronchial carcinoids, on the other hand, tend to be less aggressive and may not impact significantly on overall survival of MEN 1 patents (Thakker et al. 2012).

Gastric NETs are typically small and multiple and may be detected incidentally during gastric endoscopy. They may be found in over 70% of patients with MEN1 and typically behave in a benign manner.

66.2.3.3.5 Other Tumours

There are a range of other tumours which also occur with increased frequency in MEN 1, including adrenal tumours, meningiomas, and cutaneous tumours. Cutaneous tumours include lipomas, facial angiofibromas, and collagenomas. Their frequency varies in different case series but lipomas may occur in over one third of MEN 1 cases and facial angiofibromas and collagenomas may be even more common.

Management of lipomas is conservative but they can be removed for cosmetic reasons. Facial angiofibromas and collagenomas may aid in early diagnosis of MEN 1 during screening. They do not normally require treatment.

66.2.4 Treatment of Specific Tumours Associated with MEN 1

Treatment modalities for MEN 1-related tumours are similar to those used for similar tumours in non-MEN 1 patients. However, the treatment can be more challenging and outcomes are often poorer, partly due to the early occurrence of tumours in MEN 1 as well as the presence of multiple tumours, making full surgical resection harder. Full details of treatment will not be explored in this chapter as they are covered throughout the rest of the book.

66.2.4.1 Parathyroid Tumours

Surgical excision is the definitive treatment in hyperparathyroidism, but there is no consensus on how early this should be performed in the course of the disease (Thakker et al. 2012). Surgical intervention is indicated in symptomatic hypercalcaemia, nephrolithiasis (renal calculi), and evidence of reduced bone density (Arnold 2017). Since hypercalcaemia may also exacerbate hypergastrinaemia, parathyroidectomy may reduce gastrin levels in MEN1 patients with ZES. In asymptomatic patients, most centres follow a regime of continuing active surveillance (Arnold 2017).

Once surgery is indicated, open bilateral neck exploration is recommended since all four glands are usually affected with hyperplasia or adenomas (Thakker et al. 2012). Subtotal parathyroidectomy (3½ gland removal) is recommended to reduce the risk of persistent disease and to leave some functioning parathyroid tissue. Prophylactic thymectomy may also be performed as there is often parathyroid tissue found within the thymus. It can also reduce, but not completely remove the future risk of thymic carcinoid (Goudet et al. 2009).

Recurrent hypercalcaemia can occur after subtotal surgery in around half of MEN 1 patients (Schreinemakers et al. 2011). If all four glands are clearly affected, then total parathyroidectomy may be carried out, sometimes with a small parathyroid autograft, often in the forearm muscles. This is less likely to lead to persistent hyperparathyroidism but more likely to cause hypoparathyroidism (Arnold 2017). The autograft can avoid the need for vitamin D replacement, and if recurrent hyperparathyroidism is observed then it can be removed under local anaesthetic, though this can be difficult if the tissue becomes embedded in the skin. An alternative approach is to treat the often mild hypercalcaemia with cinacalcet.

Persistent hypocalcaemia is treated with oral calcitriol or one alfa-calcidiol (1,25-dihydroxyvitamin D) although management of hypoparathyroidism can be challenging even with vitamin D and calcium replacement. Many patients experience ongoing chronic symptoms such as muscle aches, fatigue, and low mood. Many clinicians would therefore suggest that total parathyroidectomy should be reserved for symptomatic hypercalcaemic patients, with close surveillance for all others. It is possible that recombinant PTH will provide a more effective, albeit expensive, form of replacement.

66.2.4.2 Pancreatic NETs

66.2.4.2.1 Gastrinomas

Gastrinomas cause a high rate of morbidity and mortality in MEN 1 patients, due to the marked gastric acid production and recurrent peptic ulceration. Management with proton pump inhibitors, often in high dose, is a standard first approach to inhibit gastric secretion and relieve peptic ulcer symptoms. Some patients may also require additional treatment with H2 antagonists such as ranitidine which reduce production of gastric acid (Thakker et al. 2012).

The role of surgery is controversial. Due to multiple tumours within the duodenum and the high prevalence of lymph node spread, gastrinoma surgery is rarely curative with only a small percentage of individuals disease free long-term after surgery (Thakker et al. 2012). However, larger gastrinomas are at higher risk of metastasising, which is difficult to treat successfully, though overall survival at 15 years has been reported at around 50% (McKenna and Edil 2014). Some authors therefore recommend surgery for tumours over a certain size, e.g. 2 cm (Thakker et al. 2012) though again there is a lack of consensus as to the long-term benefit of such an approach. Major surgery such as Whipple pancreaticoduodectomy may achieve an effective cure rate (Imamura et al. 2011) though the long-term quality of life implications are extensive, including diabetes mellitus, weight loss, and malabsorption syndromes.

Considering the lack of definitive evidence an individualised approach is required when deciding

on how best to manage this situation, considering patients' wishes, comorbidities, age, and life-expectancy. A detailed and open discussion with patients is essential to highlight the risks and potential benefits of surgery, exploring any possible reduction in risk of metastatic disease versus the morbidity and mortality associated with surgery.

For low grade metastatic disease somatostatin analogues can be used and in higher grade disease chemotherapy is also an option. Liver metastases can also be treated with specific directed therapies such as ablation, debulking, and embolisation. Peptide Receptor Radionuclide Therapy (PRRT) can also be considered in patients with ^{111}In-octreotide or ^{68}Ga-dotatate PET scan positivity (Falconi et al. 2016).

66.2.4.2.2 Insulinomas

Medical treatment of insulinoma in MEN 1 patients consists of diazoxide, corticosteroids, and somatostatin analogues (see Chap. 65). It is not often successful long term and surgery is generally the most successful primary treatment. If possible, pancreatic surgery should be minimised, e.g. enucleation of a single lesion or partial pancreatectomy. However, in MEN 1 simple enucleation may well not be curative and in patients with multiple tumours total pancreatectomy may be necessary (Okabayashi et al. 2013). In metastatic disease, PRRT can have excellent results for octreotide avid disease, with remissions of several years reported in case series (van Schaik et al. 2011). Other options include hepatic embolisation and chemotherapy (Okabayashi et al. 2013).

Case Study 1

(Written consent and permission has been obtained from the patient to use this case study)

Management of Functional NETs in MEN 1

Jane is a 23-year-old student with MEN 1. She was screened from an early age, her father had sadly died from MEN 1, and was used to regular blood and imaging tests. She has a known pituitary micro adenoma and an MRI aged 11 showed several pancreatic lesions in the tail of her pancreas. As these started to enlarge, she had a distal pancreatectomy aged 13 and was clinically well for 3 years.

Aged 16 she developed multiple duodenal gastrinomas, with Zollinger-Ellison syndrome. Despite PPIs, her gastric symptoms worsened and she had a pancreas sparing duodenectomy which confirmed Grade 2 well-differentiated NET, which was strongly gastrin positive.

Jane made a good recovery from surgery and her gastrin level normalised. However, 8 months later she was waking at night hungry and sweating and this was relieved by eating. A 72 h fast confirmed an insulinoma and she was commenced on diazoxide to control blood sugars. This was poorly tolerated, with nausea, headaches, and hirsutism particularly distressing for this young woman. An MRI scan confirmed several cystic lesions in the pancreas and a specialist nuclear medicine scan confirmed that a central lesion was the likely insulin-secreting lesion. After extensive information and counselling support from the surgeons and specialist nurse she agreed to have a completion pancreatectomy aged 19. The pathology confirmed 7 NETs, the largest of which stained for insulin.

Jane has recovered well from the surgery; however, at a regular follow-up visit she was in tears and described how traumatic she'd found the whole experience. She was having recurrent nightmares, every night, about the experience which was impacting heavily on her life.

After further assessment of her concerns, her specialist nurse felt that Jane needed high level psychological input. Despite not having a cancer diagnosis, she was able to arrange for Jane to meet with the specialist teenage young adult cancer psychologist. Through a period of focused counselling this has helped reduce her anxiety significantly and her nightmares have now stopped. She will continue on lifelong surveillance and is aware that she has a risk of metastatic NET in the future.

Learning Points

The impact of lifelong surveillance and treatment should not be underestimated in teenage/young adult population.

Skilled psychological assessment and support can be key to successful management of patients with MEN 1.

Questions to Consider

Would Holistic Needs Assessment assist in picking up complex psychosocial needs and concerns?

How could you integrate these into your everyday role?

66.2.4.2.3 Non-functioning Neuroendocrine Tumours

Management of asymptomatic non-functioning panNETs is controversial. Surgery can be successful in excising the majority of tumours. However, surgical complications including diabetes, steatorrhoea, and other chronic gut symptoms may be experienced by patients. The natural history of these small tumours is not known, and early surgery has the potential to reduce an individual's quality of life when they may have remained well and at low risk of metastatic spread for many years (Falconi et al. 2016). This has to be balanced against the risk of metastatic disease being difficult to treat.

There is no consensus on the size of tumours at which to suggest surgery, with recommendations ranging from as low as 1 cm, to over 2 cm whilst approaches to surveillance also vary (Thakker et al. 2012).

Metastatic pancreatic NETs have been shown to respond to both tyrosine kinase inhibitors (Raymond et al. 2011) and the mTOR inhibitor everolimus (Yao et al. 2011). Chemotherapy, and other liver directed therapies may also be considered. Median survival for metastatic disease is around 24 months (Yao et al. 2008).

66.2.4.3 Pituitary Tumours

Clinical features and treatments are the same as in non-MEN 1 patients, (see Part III). However, medical treatment may be overall less successful than in non-MEN 1 patients, leading to more frequent use of surgery (Thakker et al. 2012).

66.2.5 Genetic Testing

Since discovery of the MEN 1 gene, it has been possible to test the DNA of individuals for detection of pathogenic gene variants even before clinical signs occur. However, there are limited data to show whether this early detection leads to interventions which in turn reduces morbidity or mortality (Arnold 2017).

There are a number of potential benefits of DNA testing including:

- Confirming the clinical diagnosis of MEN 1 syndrome in a proband
- Determining if specific testing can be offered to relatives of a proband
- Determining whether or not asymptomatic relatives of a proband carry the mutant gene (Thakker et al. 2012)

Individuals who have a negative genetic test can be spared invasive and time-consuming screening and will have the reassurance that they cannot transmit the disease to their offspring. For those who test positive a screening programme can be discussed with them. Their individual concerns and risk need openly talked through with an expert team and a screening regime can be tailored around the available evidence, their wishes, and the views of the clinical team.

Based upon the possible benefits of screening an international group of MEN 1 experts suggested offering DNA analysis to

- Any index patient with clinical MEN 1 (two or more tumours of MEN1 type)
- All first-degree relatives of known MEN 1 mutation carriers
- Individuals with suspicious or atypical MEN 1 (e.g. multiple parathyroid tumours, multiple panNETs) (Thakker et al. 2012)

Parents may give consent for genetic testing in children but the child's best interests should be the

main influence on determining when genetic testing should be carried out (The British Society for Human Genetics 2010). Genetic testing is regarded as appropriate, where it will determine the potential need for screening or treatment. However, if there is no immediate benefit for the child then the recommendation would be to delay until a child is old enough to choose for themselves. Advice is that parents should be supported to make decisions in open discussion with the clinical genetics team (The British Society for Human Genetics 2010).

66.2.5.1 Approaches to Screening

Asymptomatic individuals with MEN 1, known MEN 1 pathogenic mutation carriers and those in whom risk has not been eliminated through negative DNA analysis, should be followed up with an ongoing programme of screening surveillance. The inclusion of annual clinical and biochemical screening is well established, with the aim to get earlier diagnosis and treatment to reduce morbidity and mortality.

This would involve looking for:

1. Signs and symptoms of MEN-1-associated tumours
2. Biochemical measurement of serum calcium, PTH, prolactin, and IGF-1 to screen for hyperparathyroidism and pituitary adenomas.

The addition of further radiological and biochemical screening tests may vary across centres and the evidence to support the value of one particular approach is limited. However, published guidelines do exist which support a more aggressive and early approach to screening in those individuals deemed at risk, with extensive biochemical and radiological screening (see Table 66.5). This approach is based on the possible early manifestation of MEN 1 tumours, including non-functioning panNETs which are known to play a major part in early MEN 1 morbidity and mortality (Newey et al. 2009).

66.2.5.2 Childhood Genetic Screening

In adults viewed as being capable and provided with potential risks and benefits then they are making an informed decision. For children and young people, there are three main concerns: that genetic knowledge may introduce possible psychological or social harms, that minors are

Table 66.5 Suggested screening regime for individuals at high risk of developing MEN 1

Tumour	Age to start	Annual biochemical test	Imaging regime (time interval)	Nursing issues
Parathyroid	8	Calcium, PTH	None	Close support required if children needle phobic
Pancreatic NET				
Gastrinoma	20	Gastrin	None	Some young patients may find MRI/CT distressing Discuss risk/benefits closely with family. May need to reduce frequency of imaging dependent on blood results and family preference
Insulinoma	5	Fasting glucose, insulin	None	
Other pNET	<10	Chromogranin-A, Fasting gut peptides	MRI, CT, or endoscopic ultrasound annually	
Anterior pituitary	5	Prolactin, IGF-1	MRI every 3 years	Can be combined as part of annual imaging above
Adrenal	<10	None, unless signs and symptoms of functioning tumour or identified tumour on imaging	MRI or CT (annually with pancreatic imaging)	Can be combined as part of pancreatic imaging above
Thymic and Bronchial carcinoid	15	None	CT or MRI (every 1–2 years)	None

Adapted from Thaker et al. (2012)

not autonomous individuals, and that they may not be capable of fully assessing the potential risks and benefits of this knowledge (McConkie-Rosell and Spiridigliozzi 2004). Some children may struggle both with imaging approaches such as MRI, which can be stressful and traumatic, as well as blood sampling. Parents may also experience anxiety and guilt at the possibility of having passed on the condition to their child, whilst others may be reluctant to subject their asymptomatic child to investigation. Some families may decide not to have their children undergo clinical biochemical and radiological surveillance until seen to be autonomous enough to make an informed decision.

When children are not competent to give informed consent, the main consideration should be the welfare of the child. Building close links with patients and families is essential. To support families in deciding whether to take-up clinical surveillance, it is important to present them with the risks and benefits of evidence-based pre-symptomatic surveillance. It is not uncommon for paediatric endocrine centres to have an evidenced-based screening table to promote equity and uniformity in the surveillance of families (see Table 66.5). The use of specialist paediatric teams and experienced counselling support can help build trust and manage the uncertainty of decision-making (see Box 66.1).

Box 66.1 Information Sharing and Support with Children and Young People

Information sharing with a child or young person about genetic testing is important, and they should not be excluded from the discussion under the false belief that this will protect them. The developmental level of the child needs to be taken into account when deciding when and how to share this information. This is where support from other affected families can be of great help through the sharing of experiences.

Supportive interventions such as web-based discussion forums and patient-run support groups can play a hugely important role for families of affected children. They are particularly good at serving as an ongoing means of addressing information and supportive needs; from families who are going through similar experiences.

66.3 MEN 2 and 3

Multiple Endocrine Neoplasia type 2 (MEN 2) is a rare autosomal dominant disorder. Its prevalence is estimated at around 1/30,000 (Lips and Ball 2017a) with two main subtypes: MEN 2A, accounting for 75% of cases and MEN 2B 25%. These have recently been renamed as MEN 2 and MEN 3 respectively.

66.3.1 Clinical Presentation

MEN 2 is characterised by medullary thyroid cancer (MTC), phaechromocytoma, and primary parathyroid hyperplasia. There are four variants which are highlighted in Table 66.6. In MEN 3, parathyroid hyperplasia is extremely rare, but there are several other additional features—mucosal neuromas, ganglioneuromatoses of the GI tract, and a Marfanoid habitus (El-Kholy 2005) (see Table 66.6).

Classical MEN 2 is the most common subtype, virtually all patients develop MTC and smaller numbers develop phaeochromocytomas or hyperparathyroidism depending on the specific *RET* mutations (Frank-Raue et al. 2010).

66.3.1.1 Medullary Thyroid Cancer

75% of medullary thyroid cancers are sporadic, with 25% relating to MEN 2 and 3 and Familial Medullary Thyroid Cancer (FMTC) (Perros et al. 2014). It only accounts for around 5% of thyroid cancers but treatment of this condition is challenging, with early diagnosis being of vital importance. In MEN 2 and 3, nearly all patients develop MTC (Wells Jr et al. 2015). In MEN 2-associated MTC the peak incidence of index

Table 66.6 Clinical manifestation of MEN 2 and 3

MEN type 2	MEN type 3
Classical MEN 2; Medullary thyroid cancer (100%), phaechromocytoma (50%), hyperparathyroid hyperplasia (20–30%)	Medullary thyroid cancer
MEN 2 with cutaneous lichen amyloidosis (CLA)	Phaeochromocytoma
MEN 2 with Hirschsprung disease (HD)	Other: Mucosal neuroma Intestinal ganglioneuromas Marfanoid habitus[a]
Familial Medullary Thyroid cancer (FMTC)—MTC but no other manifestations of MEN 2A or 2B	

[a]Marfanoid habitus: a group of symptoms including long limbs, a crowded oral maxilla, sometimes with a high arched palate, **arachnodactyly**, and hyperlaxity

(new) cases is between 20 and 30 years of age. It is usually multifocal and presents as a thyroid nodule, cervical lymphadenopathy, or symptoms of an increase in serum calcitonin, e.g. diarrhoea and flushing (Wells Jr et al. 2015). Spread to adjacent cervical lymph nodes is common and can make cure difficult. Most tumours fortunately do not display aggressive behaviour and can run an indolent course for many decades: 10-year survival in observational studies has been shown to be up to 75% (Modigliani et al. 1998).

MTC tends to be more aggressive in MEN 3, often with an early age of presentation, i.e. before the age of 5 and a poorer prognosis (Lee and Norton 2000). De novo mutations account for around half of cases. Poor prognostic factors include nodal disease, large primary tumour, and metastatic disease (Lips and Ball 2017a). More aggressive tumours can spread to bone, lung, and/or liver.

In asymptomatic patients, found through screening in a known MEN 2 family, MTC is often diagnosed in its pre-cancerous state, known as C-cell hyperplasia (CCH). Serum calcitonin levels will usually correlate with tumour size and are nearly always high in patients who have palpable tumours. There is also a higher likelihood of residual disease if it is discovered clinically rather than through screening (Lips and Ball 2017b).

66.3.1.2 Phaeochromocytoma

Phaeochromocytomas occur in about 50% of MEN 2 patients, with frequency depending on the specific *RET* mutation. They occur earlier than in sporadic forms, with an average age of presentation in the third to fourth decades and are frequently bilateral, which is extremely rare in the sporadic form (Webb et al. 1980). It is unusual for them to precede MTC as the initial presentation of MEN 2, and they are normally identified through ongoing surveillance screening. Diagnosis is the same as sporadic cases with biochemical testing and imaging studies. They are almost invariably benign in behaviour.

66.3.1.3 Primary Hyperparathyroidism

Hyperparathyroidism is not associated with MEN 3 or FMTC. In MEN 2, it is almost always multiglandular and occurs in up to 20–30% of MEN 2A patients (El-Kholy 2005). It is normally mild and asymptomatic and has a low recurrence rate post-surgery after subtotal parathyroidectomy (O'Riordain et al. 1993).

66.3.1.4 MEN 2 with Cutaneous Lichen Amyloidosis (CLA)

CLA is a rare disorder that can occur sporadically, but also in a hereditary pattern associated with MEN 2. The CLA associated with MEN 2 occurs almost exclusively with *RET* codon 634 mutations. It can occur at a young age and is characterised by skin lesions, particularly in the scapular region, with symptoms of intense itching that worsen due to stress but can respond to sun exposure. Typical treatments include moisturising creams, local steroid cream, antihistamines, and phototherapy though benefits are normally partial (Wells Jr et al. 2015).

66.3.1.5 MEN 2 with Hirschsprung Disease (HD)

Hirschsprung disease occurs in less than 10% of MEN 2 cases (Wells Jr et al. 2015) and is normally present at birth. It is the result of failure of nerve cell development in the large bowel and affects the colon causing problems with passing stool.

Symptoms include constipation, swollen belly, vomiting, and diarrhoea. Treatment is by surgery to bypass the affected part of the bowel (Amiel and Lyonnet 2001).

66.3.1.6 MEN 3

In MEN 3, the MTC often presents in infancy and is highly aggressive, metastasising to regional lymph or distant sites (Wells Jr et al. 2015). Around 50% also develop phaeochromocytomas.

MEN 3 patients have unique physical appearance: Marfanoid habitus, ophthalmologic abnormalities (thickened and inverted eyelids, inability to make tears, ptosis), and intestinal ganglioneuroma. Most have abdominal symptoms, with bloating, constipation, and diarrhoea and can develop intestinal obstruction requiring surgery (Cohen et al. 2002).

Most MEN 3 cases present as new (de novo) *RET* mutations, with only around 25% occurring in known families with MEN 3 (Kloos et al. 2009).

66.3.2 Diagnosis

Diagnosis of MEN 2 and 3 is through the presence of the clinical features of the disease, a relevant family history and genetic testing. If no *RET* germline mutation or inheritance pattern can be identified, then at least two of MTC, phaeochromocytoma and primary parathyroidism are needed to clinically diagnose MEN 2 and a majority of features of MEN 3 are needed to make a clinical diagnosis of that disorder (Kloos et al. 2009).

Familial MTC is a subset of MEN 2, in which individuals only develop MTC, without any other manifestations of MEN 2 or 3. In small families, there is a risk of misclassifying FMTC and failing to appreciate the risk of phaeochromocytoma. Proposed criteria for confirmed FMTC therefore are:

- Kindred more than 10 carriers or with multiple carriers or affected members older than 50
- Adequate medical review to exclude phaeochromocytoma and hyperparathyroidism, particularly in older subjects (Wells Jr et al. 2015)

66.3.3 Genetics and Screening

The genetic defect in MEN 2 involves the *RET* proto-oncogene, discovered in 1985 by Takahashi (Wells Jr et al. 2015). The *RET* gene is on chromosome 10 (10q:11-2) and mutations result in a gain in function. Since its discovery over 100 different types of mutation have been discovered in patients with MEN 2, but the vast majority are associated with codon 634. Mutations involving different codons on the gene lead to different manifestations of MEN 2 (Lee and Norton 2000). Most cases of MEN 3 are attributable to a mutation at codon 918.

Genetic testing should be carried out in all patients with clinical MEN 2 and 3 in order to identify the specific RET mutation and establish appropriate family screening. In known MEN 2 families, it is usual to sequence the known area of mutation only. In new families, as the cost of sequencing continues to decrease, the entire gene is normally sequenced. All individuals should be offered genetic counselling as part of this process (Wells Jr et al. 2015).

If no germline mutation is found, then only a small risk of hereditary MTC remains as virtually all MEN 2 and 3 patients will have a *RET* mutation (Wells Jr et al. 2015). Once a *RET* mutation is discovered in an index case, genetic testing should also be performed in first- and second-degree family members.

66.3.3.1 Sporadic MTC DNA Analysis

RET mutation screening should also be offered to patients with apparently sporadic MEN 2-related tumours if age younger than 35, multicentric tumours or two different organs affected. Some clinicians would support all patients with sporadic MTC having RET mutation screening (Kloos et al. 2009). Unsuspected familial cases are identified in up to 7% of cases despite apparent negative family history (Wells Jr et al. 2015).

66.3.3.2 Ethical Issues Around Genetic Screening

In clinical genetics, there is a potential tension between confidentiality and disclosure because

of the shared nature of genetics information (Lucassen and Hall 2012). In most situations, individual with a diagnosis of MEN 2 or 3 will be willing to share that information with appropriate members of their family who may ultimately be at risk and no dilemma therefore exists. Doctors and nurses can support patients to identify and tell at-risk family members, but this is best carried out with trained genetic counsellors, who will be able to talk through fully the risk that the family members may have. The seriousness of the disease and management strategies, including prevention, screening, and treatments should all be included in these discussions. Consent can be given orally or in writing and should be clearly recorded in the individual's health records by the health professional (Lucassen and Hall 2012).

However, Rosenthal and Diekema (2011) highlight that uptake of screening is significantly less than 100% (Rosenthal and Diekema 2011). Barriers to screening may include education level, literacy, culture, and social/family relationships as well as access to genetics counselling services. Ethical dilemmas arise when individuals refuse to inform family members and in particular refusal to disclose to children the risks that they face. In this situation, the affected individual's right to autonomy and confidentiality conflicts with the risk of harm to others. In such situations, health professionals need to balance their duty of care to their patient with the duty to help or protect someone from serious harm. In such a situation, professionals should seek advice from legal and ethical experts within their organisation to support their decision-making.

66.3.3.3 Screening Programmes

Screening for MEN 2 and 3 associated tumours is essential in all individuals with germline *RET* mutations and should begin immediately on diagnosis and continue annually with appropriate biochemical and clinical testing as highlighted in Tables 66.7 and 66.8 below. The age to commence screening varies depending upon the specific *RET* mutation. In MEN 3 (Codon 918), thyroidectomy should be carried out within the first year of life. In other high-risk categories screening for MTC with neck examination, U/S and serum calcitonin should begin aged 3 and thyroidectomy is recommended by age 5, depending on the specific mutation (Wells Jr et al. 2015). In lower risk patients, annual screening is ongoing and thyroidectomy will be recommended if serum calcitonin starts to rise.

Annual screening for phaeochromocytoma and hyperparathyroidism should begin by age 11 in the high-risk categories and otherwise by age 16. Note that those with MEN 3 do not need screening for hyperparathyroidism (Lips and Ball 2017b).

66.3.4 Treatment

66.3.4.1 MTC: Preventative Surgery

The key to successful management of MTC in MEN 2 and 3 is through early and preventative

Table 66.7 Screening for phaeochromocytoma and hyperparathyroidism in MEN 2 and 3 patients

		Phaeochromocytoma: Annual screening	Hyperparathyroidism: Annual screening
Risk	*RET* codon mutation	TEST: Plasma and/or urinary metanephrines If positive then adrenal imaging	TEST: Serum calcium If elevated, then PTH
Highest (MEN 3)	918	11 years	Not applicable
High	634,883	11 years	11 years
Moderate	533, 609, 611, 618, 620, 630, 666, 768, 790, 804, 891, 912	16 years	16 years

Adapted from Lips and Ball (2017b), data originally published by Wells Jr et al. (2015)

Table 66.8 Screening and timing of thyroidectomy for MTC

Risk	*RET* codon mutation	Recommended age to begin annual screening for MTC—annual physical examination, neck U/S, and serum calcitonin	Recommended timing of thyroidectomy
Highest	918 (MEN 3)	Not applicable	In the first months to year of life
High	634,883	3 years	At or before the age of 5 years
Moderate	533, 609, 611, 618, 620, 630, 666, 768, 790, 804, 891, 912	5 years	Childhood or young adulthood

Adapted from Lips and Ball (2017b), data originally published by Wells Jr et al. (2015)

surgical intervention with total thyroidectomy (Kloos et al. 2009). It is possible to remove the thyroid before signs of cancer or at least whilst still confined to the thyroid gland. Though the term prophylactic thyroidectomy suggests there being no cancer present, in most cases C-cell hyperplasia (CCH) or MTC is already present when the surgical specimen is sent to pathology. Around 90% of young patients with *RET* mutations have no evidence of recurrence 7 years post-surgery (Perros et al. 2014).

The optimal timing of surgery is based on the specific *RET* DNA mutation as the behaviour of the disease correlates with particular genotypes (different codon mutations). However, there is clear variation in behaviour amongst different families with the same genetic mutation and also within individual families. Surgery should preferably be before the age of 6 months in MEN 3 but within the first year and before the age of 5 for the most common 634 mutated MEN 2 (Perros et al. 2014).

It is essential to assess for the presence of phaeochromocytoma before proceeding with surgery by measuring plasma metanephrines, urinary metanephrines, or both. If a phaeochromocytoma is found, it should be removed first to reduce the risk of surgical morbidity and mortality.

Baseline calcitonin also provides useful information in determining the risk of and extent of lymph node metastases.

Surgery should be total thyroidectomy with dissection of adjacent nodal tissue and modified neck and/or mediastinal dissections if positive nodes are found. In very young children, it can be hard to identify the parathyroid glands, which increases the risk of hypoparathyroidism post-surgery and if no positive nodes are noted during the operation then central neck dissection can be reasonably avoided (Wells Jr et al. 2015). Such surgery should obviously only be carried out by a specialist endocrine or paediatric surgeon (Perros et al. 2014).

Post-surgery patients should be screened regularly with calcitonin levels to assess for possible relapse (Perros et al. 2014). Long-term management is essentially the same as for sporadic MTC and can be found in Chap. 29.

66.3.4.2 Treatment of Phaeochromocytoma

For patients with bilateral phaeochromocytoma, bilateral adrenalectomy is the required treatment, with subsequent glucocorticoid and mineralocorticoid replacement. It can also be considered in patients with unilateral phaeochromocytoma but with a family history of aggressive bilateral adrenal disease. Otherwise, unilateral adrenalectomy is the treatment of choice in patients with unilateral disease. Though there is a high risk of requiring further surgery in the future, many patients will not require this, and relapse may not occur for many years (Lips and Ball 2017a). Subtotal (cortical sparing) adrenalectomy prevents the need for corticosteroid supplementation. However, this does increase the risk of relapse over the patient's lifetime.

66.3.4.3 Treatment of Primary Hyperparathyroidism

Once biochemically confirmed the approach is the same as for sporadic primary hyperparathyroidism. However, it should be noted that it is often mild or asymptomatic in patients with MEN 2. In asymptomatic patients, surgery can be deferred with ongoing surveillance of calcium, creatinine, and bone density. If any of these deteriorates, then surgery should be considered (Bilezikian et al. 2014). In a recent review and retrospective study (Scholten et al. 2010), subtotal parathyroidectomy or minimally invasive parathyroidectomy have been shown to be effective, thus reducing the requirement for total parathyroidectomy and the risk of hypoparathyroidism. If required, forearm grafting of parathyroid tissue can reduce the risk of long-term hypoparathyroidism.

Hypoparathyroidism is often diagnosed at time of thyroidectomy for MTC and enlarged glands are removed at that time. For patients who've had previous thyroidectomy, localisation studies with sestamibi scanning, ultrasound, or CT should be carried out pre-surgery. Enlarged parathyroid glands should be removed. PTH monitoring may be carried out intraoperatively and further exploration until PTH normalises.

66.4 Nursing Support and Quality of Life Issues in MEN

Being diagnosed with a genetic disorder affects not only the physical health of an individual, but also has psychological and social impacts on the individual and their families. As nurses working with these individuals/families, we need to be prepared and understand the implications of the diagnosis and learn to anticipate a wide range of reactions to such a diagnosis (New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services 2009).

A diagnosis has the potential to help or harm a patient; therefore, responses may include guilt, fear, and anger but also relief due to getting an explanation for ongoing health issues. Diagnosis can also provide access to support services and ongoing treatment and surveillance options.

Individuals face a potential lifetime of investigation and treatments, but without the possibility of a cure. They may have concerns over difficult treatment decisions with high levels of uncertainty both as to the best approach to managing the disease and the likely outcomes of treatment. There is also the challenge of living with the risk of a shortened life-expectancy.

MEN Case Study 2: Management of Metastatic Disease in MEN 1

(Written consent and permission has been obtained from the patient to use this case study)

Ian is a 42-year-old male with MEN 1, his mother also having had MEN 1. He started annual screening aged 21. By age 30 he'd had a distal pancreatectomy for a non-functioning pancreatic NET and a subtotal parathyroidectomy for hyperparathyroidism. He was clinically well.

At 33 years of age, two liver metastases were found on MRI. These were completely resected and confirmed metastatic non-functioning pancreatic NET. Two years later, an MRI showed progressive liver metastases, throughout both lobes of his liver. As surgery was now not an option, he commenced streptozocin and capecitabine chemotherapy. At this point, he met the NET specialist nurse who then supported him throughout his future treatments. After 6 cycles of chemotherapy, a scan confirmed stable disease.

Eighteen months after stopping chemotherapy, Ian had further progression of liver metastases. A trial of everolimus was not well tolerated, with diarrhoea, mucositis, and poorly controlled blood sugars, and it was stopped after only 3 cycles. A post-treatment scan sadly confirmed further progression. He was then treated with Selective Internal Radiation Therapy (SIRT) and had extensive reduction of the known liver metastases.

Over a 3-year period, the metastases slowly enlarged again. A ^{68}Ga Dotatate scan showed good uptake in his liver metastases. He was therefore treated with 4 cycles of

^{177}Lutetium PRRT over an 8-month period. He found being isolated for treatment extremely stressful and needed intensive support from his specialist team to enable him to safely complete all of the therapy. A post-treatment CT and MRI showed excellent disease response, with a greater than 50% reduction in the liver metastases. 18 months on his disease remains stable.

Ian is currently well but clearly faces an uncertain future. His main physical symptoms relate to his pancreatic surgery. He is an insulin controlled diabetic and has a number of gut-related issues including frequency and steatorrhoea. Through regular nursing support and focused holistic assessments Ian has also opened up about his anxiety and low mood, his inability to plan for the future. He also has feelings of guilt related to his eldest child who is MEN 1 positive. He has been referred to a specialist MEN counsellor to help manage these issues. He has not yet had genetic screening of his second and third children, aged 11 and 9.

Questions to Consider

Ian is currently well but clearly has non-curative disease. At what point would you consider introducing specialist palliative care services for this man?

How would you support him to make appropriate decisions about whether or not to screen his younger children?

For children with an inherited endocrine tumour condition, the severity of reaction to this diagnosis is often dependent on the individual's perception of how it impacts their life. Important variables to consider in relation to the psychological impact on a child include: pain, cognitive difficulties, visibility and appearance factors, and the interference or impact any of these might have on daily life (Edwards and Titman 2010). Children and young people affected by an inherited endocrine tumour condition will undergo regular clinical surveillance and hospital visits that are a reminder of their illness state; and since these conditions are inherited the child will often have experience of a parent's tumour diagnosis and treatment.

For adults, regular hospital visits for surveillance or treatment may impact on their employment and career. Health or life insurance may be impacted upon, all potentially impacting on their financial security. In a recent survey in the UK (Winter and Grey 2016), over half of respondents with an MEN inherited condition felt that it had a negative impact on their long-term mental/emotional well-being, their employment/career and family life. A recent survey of over 200 MEN 1 patients in the USA also found that MEN 1 patients reported worse health-related quality of life scores compared with the general population. Persistent hypercalcaemia after surgery was associated with higher levels of anxiety, depression, fatigue, and decreased social functioning; travelling greater than 50 miles to appointments and having more than 20 appointments per year were associated with lower health-related QoL (Goswami et al. 2017).

Diagnosis can affect relationships and family dynamics, having implications for a decision to have children, or causing parental guilt when finding out that their offspring have inherited the disorder. Individuals with MEN planning to have children should be offered access to specialist genetic counsellors. Options include natural conception, with or without prenatal testing, *in vitro* fertilisation (IVF), either using donor sperm/eggs or with preimplantation genetic diagnosis (PGD), and adoption (Winter et al. 2016). Prenatal testing is via chorionic villus sampling or amniocentesis. Preimplantation genetic diagnosis involves testing newly fertilised embryos in a laboratory for the MEN 2 or 3 gene mutation that the parent is known to carry. Embryos which do not have the affected gene can be transplanted back into the womb. This process has been approved for MEN 1 and MEN 2 or 3 within the UK by the Human fertilisation and Embryology Authority (HFEA 2017).

Family members without the condition can experience guilt that they are not affected and parents may focus more time and attention on siblings who are affected (New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services 2009).

Nurses are often well placed to provide in-depth information and support for patients and their families in these situations. They are often the first point of contact, helping with coordination of scanning or biochemical investigations for adults or their children, discussing the meaning of results and the nature of treatments. Enabling individuals to access specialist supports is essential, for example, genetic counsellors, psychologists, and social workers as well as support groups, either local or national. All individuals should be offered genetic counselling and detailed information about the condition. Several countries also have charities that offer information and support for individuals and families with MEN, e.g. AMEND in the UK.

Box 66.2 Association for Multiple Endocrine Neoplasia Disorders (AMEND)

AMEND was established by patients, for patients, in 2002 when there were no patient information resources or support services for families with multiple endocrine neoplasia disorders. Living with a rare disease can feel isolating for the patient, and therefore meeting others with the condition can be an enormously positive experience. In addition, the provision of patient-appropriate information on the disorders empowers patients to seek the best medical care and treatments.

AMEND offers free membership, a free counselling service, free patient events, and free information resources for families affected by MEN disorders, sporadic medullary thyroid cancer (MTC), SDH syndromes, and Adrenocortical Cancer (ACC). We develop information resources for children through to adults with the help of our expert Medical Advisory Team, and a specialist Consultant Psychotherapist provides our counselling service. In order to connect patients for mutual support and reduce isolation, we run and moderate several private social media groups, and have a nationwide network of trained regional volunteers who organise local, informal events.

AMEND works closely with researchers and leaders in the field, including as a European Patient Advocacy Group (EPAG) in the European Reference Networks for Rare Adult Cancers (EURACAN) and Rare Endocrine Disorders (ENDO-ERN), and on the NHS England Specialist Endocrinology Clinical Reference Group. We offer research grants when funds allow, and offers to connect patients with researchers and research projects where appropriate.

Patients often find it difficult to talk or to contact the specialists caring for them or their family, especially if they feel that their query may be seen as trivial. AMEND is an easily accessible network of expert patients backed up with an expert Medical Advisory Team. As shown in the case study below, empowering patients with the correct information in an easily digestible format can result in not just the relief of patients' anxieties, but also in improvements in MDT communication and care.

Case Study

A mother with MEN1 who has a 24-year-old son, also with MEN1, contacted AMEND in 2018. She was seeking clarification as to why a surgeon might suggest surgery, including a possible Whipple's procedure, for her son's 1.2 cm pancreatic islet cell tumour. We spoke with and listened to the mother at length to fully understand her situation, then shared her question anonymously with AMEND's expert Medical Advisory Team. Their advice—that surgery for a 1.2 cm pancreatic tumour would be unusual and not in line with current guidelines—was shared with the mother. This gave both her and her son the confidence to return to their medical team and successfully challenge the suggestion. The process highlighted a breakdown in communication within the medical team that was then successfully resolved.

> *"Thank you very much….I talked with James last night….and he's less anxious. ….we will go to the next consultation better informed and more confident about what to ask".*

AMEND can be reached by the following methods:

Website—www.amend.org.uk (HONCode Accredited)

Email—info@amend.org.uk

Telephone—01892 516076

AMEND CEO—Mrs. Jo Grey

AMEND Administrator—Ms. Helen Blakebrough

All our information resources can be downloaded for free via our website, and event presentations can be accessed via our YouTube channel (AMEND3).

This level of support is best provided in a specialist centre and multi-disciplinary team (MDT) used to seeing a wide range of patients and their families. With MEN patients it is essential to have an endocrinologist with expertise in MEN to coordinate this care but the MDT should be able to access endocrine, hepato-biliary, pituitary, and cardiothoracic surgeons; oncologists; radiologists including those with expertise in nuclear medicine, histopathologists, geneticists, and specialist nurses.

66.5 Conclusions

Multiple endocrine neoplasia is a rare inherited conditions characterised by the development of multiple tumours of the endocrine system. Tumours often occur earlier in life than in sporadic cases and may also often be multiple in nature.

MEN 1 is characterised by parathyroid, pancreatic, and pituitary tumours. Parathyroid and pituitary tumours are almost universally benign, whereas pancreatic tumours can be malignant. Management involves close monitoring of tumour growth, and symptoms through regular screening and then treatment of specific tumours if required. Pancreatic NETs are the major cause of morbidity and mortality in MEN 1 though many remain small and asymptomatic. There is uncertainty as to when to intervene surgically, with a need to weigh up the risk of tumour spread versus the long-term complications of major pancreatic surgery. International guidelines have been produced to assist with management decisions and further research is required to clarify best treatment options.

MEN 2 and 3 are caused by a genetic defect in the *RET* proto-oncogene, characterised by medullary thyroid cancer (MTC) and phaeochromocytoma with primary parathyroid hyperplasia also common in MEN 2. Early screening and total thyroidectomy early in life is the definitive approach to prevent metastatic MTC.

Due to the rarity and complex nature of these conditions, individuals and their families should preferably be managed within specialist multidisciplinary teams. Specialist nurses are well placed to support patients navigate their way through complex pathways, improve communication within the MDT, support with ongoing symptoms, aid with treatment decision-making, and offer emotional and psychological support for individuals facing lifelong uncertainty.

Acknowledgments With special thanks to Jo Grey, CEO of Multiple Endocrine Neoplasia Disorders (AMEND)—www.amend.org.uk for her contribution to this chapter with a case study and information on the Patient Advocacy Group.

References

Amiel J, Lyonnet S. Hirschsprung disease, associated syndromes, and genetics: a review. J Med Genet. 2001;38(11):729 LP–739. http://jmg.bmj.com/content/38/11/729.abstract

Arnold A. Multiple endocrine neoplasia type 1: clinical manifestations and diagnosis. In: Drezner M, editor. . Waltham, MA: UpToDate; 2017. https://www.uptodate.com.

Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol

Metab. 2014;99(10):3561–9. https://doi.org/10.1210/jc.2014-1413.

Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. CONSENSUS: guidelines for diagnosis and therapy of MEN Type 1 and Type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71. https://doi.org/10.1210/jcem.86.12.8070.

Cohen MS, Phay JE, Albinson C, DeBenedetti MK, Skinner MA, Lairmore TC, et al. Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Ann Surg. 2002;235(5):648.

Edwards M, Titman P. Promoting psychological well-being in children with acute and chronic illness. Jessica Kingsley Publishers; 2011 Feb 15.

El-Kholy L. Multiple endocrine neoplasia syndromes. In: Henderson K, Baranski T, Bickel P, editors. Endocrinology subspeciality consult: Lippincott Williams and Wilkins; 2005. p. 213–22.

Eller-Vainicher C, Chiodini I, Battista C, Viti R, Mascia ML, Massironi S, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. J Bone Miner Res. 2009;24(8):1404–10. https://doi.org/10.1359/jbmr.090304.

Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103:153–71.

Frank-Raue K, Rondot S, Raue F. Molecular genetics and phenomics of RET mutations: impact on prognosis of MTC. Mol Cell Endocrinol. 2010;322(1):2–7.

Goswami S, Peipert BJ, Helenowski I, Yount SE, Sturgeon C. Disease and treatment factors associated with lower quality of life scores in adults with multiple endocrine neoplasia type I. Surgery. 2017;162(6):1270–7.

Goudet P, Murat A, Cardot-Bauters C, Emy P, Baudin E, du Boullay CH, et al. Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). World J Surg. 2009;33(6):1197–207. https://doi.org/10.1007/s00268-009-9980-y.

Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, et al. Risk factors and causes of death in MEN1 Disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34(2):249–55. https://doi.org/10.1007/s00268-009-0290-1.

HFEA. Human Fertilisation & Embryology Authority-PGD Conditions. 2017 [cited 2017 Dec 21]. https://www.hfea.gov.uk/pgd-conditions/

Imamura M, Komoto I, Ota S, Hiratsuka T, Kosugi S, Doi R, et al. Biochemically curative surgery for gastrinoma in multiple endocrine neoplasia type 1 patients. World J Gastroenterol. 2011;17(10):1343–53. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068271/

Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19(6):565–612.

Lee NC, Norton JA. Multiple endocrine neoplasia type 2B—genetic basis and clinical expression. Surg Oncol. 2000;9(3):111–8.

Lips CJM, Ball DW. Approach to therapy in multiple endocrine neoplasia type 2. UpToDate. 2017a. http://www.uptodate.com/contents/approach-to-therapy-in-multiple-endocrine-neoplasia-type-2

Lips CJM, Ball DW. Clinical manifestation and diagnosis of MEN type 2. In: UpToDate. 2017b. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-multiple-endocrine-neoplasia-type-2

Lucassen A, Hall A. Consent and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information. Clin Med (Northfield Il). 2012;12(1):5–6.

Marini F, Falchetti A, Luzi E, Tonelli F, Brandi ML. Multiple Endocrine Neoplasia Type 1 (MEN 1). In: Riegert-Johnson D, Boardman L, Hefferon T, Roberts M, editors. Cancer syndromes: National Center for Biotechnology Information (US); 2009. https://www.ncbi.nlm.nih.gov/books/NBK1825/pdf/Bookshelf_NBK1825.pdf.

McConkie-Rosell A, Spiridigliozzi GA. "Family matters": a conceptual framework for genetic testing in children. J Genet Couns. 2004;13(1):9–29.

McKenna LR, Edil BH. Update on pancreatic neuroendocrine tumors. Gland Surg. 2014;3(4):258–75. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4244504/

Modigliani E, Cohen R, Campos J-M, Conte-Devolx B, Maes B, Boneu A, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. Clin Endocrinol (Oxf). 1998;48(3):265–273. doi:https://doi.org/10.1046/j.1365-2265.1998.00392.x.

New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services. Understanding genetics: a New York, mid-Atlantic guide for patients and health professionals. Washington, DC: Genetic Alliance; 2009.

Newey PJ, Jeyabalan J, Walls GV, Christie PT, Gleeson FV, Gould S, et al. Asymptomatic children with multiple endocrine neoplasia type 1 mutations may harbor nonfunctioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab. 2009;94(10):3640–6.

O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. Surgery. 1993;114(6):1031–9.

Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19(6):829–37.

Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard BA, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol. 2014;81(s1):1–122.

Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13. https://doi.org/10.1056/NEJMoa1003825.

Rosenthal MS, Diekema DS. Pediatric ethics guidelines for hereditary medullary thyroid cancer. Int J Pediatr Endocrinol. 2011;2011(1):847603.

Scholten A, Schreinemakers J, Pieterman C, Valk G, Vriens M, Rinkes I. Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. Endocr Pract. 2010;17(1):7–15.

Schreinemakers JMJ, Pieterman CRC, Scholten A, Vriens MR, Valk GD, Borel Rinkes IHM. The optimal surgical treatment for primary hyperparathyroidism in MEN1 patients: a systematic review. World J Surg. 2011;35(9):1993–2005. https://doi.org/10.1007/s00268-011-1068-9.

Thakker RV. Multiple endocrine neoplasia type 1. In: De Groot L, Jameson JL, editors. Endocrinology. 6th ed. Philadelphia: Elsevier; 2010. p. 2719–41.

Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). Mol Cell Endocrinol. 2014;386(1–2):2–15. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4082531/

Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011. https://doi.org/10.1210/jc.2012-1230.

The British Society for Human Genetics. Report on the Genetic Testing of Children 2010. 2010. http://www.bsgm.org.uk/media/678741/gtoc_booklet_final_new.pdf

Thomas-Marques L, Murat A, Delemer B, Penfornis A, Cardot-Bauters C, Baudin E, et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. Am J Gastroenterol. 2006;101(2):266–73. https://doi.org/10.1111/j.1572-0241.2006.00367.x.

van Schaik E, van Vliet EI, Feelders RA, Krenning EP, Khan S, Kamp K, et al. Improved control of severe hypoglycemia in patients with malignant insulinomas by peptide receptor radionuclide therapy. J Clin Endocrinol Metab. 2011;96(11):3381–9. https://doi.org/10.1210/jc.2011-1563.

Webb TA, Sheps SG, Carney JA. Differences between sporadic pheochromocytoma and pheochromocytoma in multiple endocrine neoplasia, type 2. Am J Surg Pathol. 1980;4(2):121–6.

Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. American Thyroid Association guidelines task force on medullary thyroid carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610.

Winter K, Grey J. Psychosocial impact of multiple endocrine neoplasia disorders. Presented at Society for Endocrinology BES 2016. In: Endocrine Abstracts. 2016. p. P121.

Winter K, Grey J, Lalloo F. AMEND: Starting a Family; Your choices. AMEND; 2016.

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.

Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23. https://doi.org/10.1056/NEJMoa1009290.

Part XIII

Advanced Practice Nursing in Endocrinology

Sofia Llahana

67 Conceptualization, Definition, and Competencies of Advanced Practice Nursing with a Focus on Endocrinology

Sofia Llahana, Andrew A. Dwyer, and Christine Yedinak

Contents

67.1 **Introduction** 1283

67.2 **Global Definition of Advanced Practice Nursing** 1283

67.3 **Conceptualization of Advanced Practice Nursing** 1284

67.4 **Global History of the Development of Advanced Practice Roles** 1286

67.5 **Competencies for Advanced Practice Nursing** 1288
67.5.1 Definition of APN 1288
67.5.2 Direct Clinical Practice 1288
67.5.3 Education and Coaching 1290
67.5.4 Consultation 1290
67.5.5 Research and Evidence-Based Practice 1291
67.5.6 Leadership and Management 1292
67.5.7 Collaboration and Innovation 1292
67.5.8 Independent Nurse Prescribing 1293

S. Llahana (✉)
School of Health Sciences, City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

A. A. Dwyer
William F. Connell School of Nursing, Chesnut Hill, MA, USA

Boston College, Chesnut Hill, MA, USA
e-mail: andrew.dwyer@bc.edu

C. Yedinak
Northwest Pituitary Center, Oregon Health and Sciences University, Portland, OR, USA
e-mail: yedinakc@ohsu.edu

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_67

67.6 **Operational Definitions of Advanced Practice Nursing** 1294
67.6.1 The Clinical Nurse Specialist (CNS) 1294
67.6.2 The Nurse Practitioner 1294
67.6.3 The Nurse Consultant 1294
67.7 **An APN Competency Framework for Endocrine Nurses** 1295
67.8 **Implementation of an APN Role** 1297
67.9 **Nurse-Led Clinics** 1297
67.10 **Conclusions** 1298
References 1299

Abstract

Advanced practice roles emerged from a combination of economic factors, staffing needs, political action, and supportive legislation. Fuelled by similar issues, there is a global movement for the development and implementation of advanced practice roles in primary care (general practice) and specialty roles, including endocrinology. Predicted shortages of physicians, particularly for practice in rural and underserved populations, along with spiralling health care costs have made more attractive the philosophy of integrating independent advanced practitioners into an organization and health care system.

To this end, a global definition is needed that clarifies the concept of 'advanced' practice and forms a basis for operationalization of these roles. Scope of practice regulations, and credentialing requirements for practice, are dependent on this conceptualization. Specialty practice can be further delineation with a description of competencies.

The increasing complexity of illness and knowledge explosion have resulted in more specialization and driven the need for higher education in nursing. This is also a global trend.

Utilization of nurses as physician substitutes and different country and organizational specific practice models have resulted in role confusion and poor standardization. Using a unifying concept can help to alleviate this confusion for patients and other health care practitioners. More standardization allows for comparative research to further support the efficacy and quantify improvement in patient outcomes achievable by advanced practice nurses.

In this chapter, these issues are explored with recommendations for the application in endocrine nursing.

Keywords

Advanced practice nursing · Advanced nursing practice · Nurse practitioner · Nurse consultant · Clinical nurse specialist · Global Definition · Endocrinology · Endocrine nurse Competence framework

Abbreviations

APN	Advanced practice nurse
CNS	Clinical nurse specialist
NC	Nurse Consultant
NHS	National Health System (Trust)
NP	Nurse practitioner
RN	Registered nurse
WHO	World Health Organization

Key Terms

- **Sustainable development goals:** Health and wellness related goals for the world set by the UN General Assembly
- **Advanced practice nurses:** A title to articulate professional role identity, clinical competencies and expertise
- **Role conceptualization:** Theories and models that provide a framework for role development

Key Points

- Advanced practice nurses are in demand globally, driven by factors such as cost containment, physician shortages, and underserved populations.
- Role titles and role descriptions within and between countries differ, creating confusion for patients, physicians, other health care providers and regulatory bodies.
- There is significant overlap in clinical competencies for all advanced practice roles, but practice specialties, environment, and culture differ.
- The International Council of Nurses identifies Nurse Practitioner/Advanced Nursing Practices, defining these roles as meeting specific criteria.
- A US Consensus Model recognized APNs to include certified: Clinical Nurse Specialists, Nurse Practitioners, Nurse Midwifes, and Nurse Anaesthetists.
- The APN should include the following agreed competencies, independent of area of practice: Direct clinical practice; Education and coaching; Consultation; Research and evidence-based practice; Leadership and management; and Collaboration and innovation.
- An endocrine specialist APN is defined by general criteria and achievement of specific clinical competencies, but the role should encompass all APN agreed competencies.

67.1 Introduction

The demand for skilled advanced practice nurses is no evident in half the world's nations. Political and economic goals as well as United Nations (UN) sustainable development goals have all contributed to growth or APNs internationally (UN General Assembly, 2015). In rural, isolated and underserved regions, nurses have practised independently or with remote support for many centuries. Midwives represent the oldest independent nursing role. In times of health threats or physician shortages, nurses have often filled the gaps. Although many countries have enacted legislation allowing autonomous APN practice, full and unrestricted practice remains elusive in some countries and in over half of US states.

Lack of clarity in a global concept of APN and its definition continues to inhibit role development, international mobility, and credentialing. This leads to role confusion for nurses, patients, physicians, administrators, and other health care professionals. Without clarity in the definition and conceptualization of advanced practice, targeted political action, role development; role-related research and the determination of scope of practice are challenged.

Patient acuity is rising, new diseases have emerged and many populations are ageing. This demands more nursing skill and knowledge. Although a Master's degree and/or a postgraduate certification may be required for practice, this is not a global standard.

Understanding the historical background and current direction of advanced practice globally is vital to sustaining and developing AP roles. Advanced practice nurses have been shown to provide high-quality patient care, improve outcomes and patient satisfaction. Despite health care leadership and governmental commissioned reports supporting the need for APNs to practice to the full extent of their education and training, this is not a reality in many regions, countries, or clinical settings.

This chapter explores components and competencies indicative of advanced practice and specific roles recognized as AP roles in numerous countries. These aspects of APN are discussed with reference to AP roles in endocrinology.

67.2 Global Definition of Advanced Practice Nursing

Advanced practice nursing (APN) is rapidly expanding globally. Over 70 countries currently have or are paving the way to implement APN care models (ICN 2015). It is estimated that 70% of the hospitals in the world have embraced some form of nursing advanced practice (Parker and Hill 2017).

A conceptual model for APN should answer some of the following questions (Arslanian-Engoren, 2018):

- What is the scope and purpose of APN and how does it differ from those of other providers offering similar services?
- Can an overarching conceptualisation of advanced nursing be articulated?
- How can one distinguish among basic, expert and advanced levels of nursing practice?
- What are the characteristics of APN and in what setting does this practice occur?
- What knowledge and skills are required and what support do APNs need to develop?
- Which patients benefit from APN care and what type of pressing health problems are APNs a solution in terms of improving outcomes, quality of care, and cost effectiveness?

Fig. 67.1 Key questions relating to a conceptual APN model

In 2015, the UN General Assembly announced 17 sustainable development goals (SDG), pledging world commitment to achieving these by 2030. The third SDG is pertinent to nurses 'ensure healthy lives and promote well-being for all at all ages' (United Nations General Assembly 2015). Subsequent briefs from the International Council of Nurses (ICN) to, and supported by, the World Health Organization (WHO), emphasized nurses as linchpins, essential to achieving these goals (White 2016; Squires et al. 2018). Research demonstrates that quality of care and patient outcomes are improved when nurses are provided with adequate educational preparation, resources, policy, and organizational support in care delivery (Squires et al. 2016). The Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing at the Institute of Medicine in the USA and the Triple Impact report by the All-Party Parliamentary Group on Global Health in the UK, both endorsed nurses practicing to the full extent of their training as a means to achieve better regional and global health care outcomes (IOM 2010; APGGH 2016). Advanced practice nursing is seen as a driving force for innovation and for developing new models of care delivery, and as integral to achieving health care reform (Bryant-Lukosius 2014).

Despite conceptual support and rapid expansion of advanced practice roles, global consensus of the definition of advanced practice is lacking. However, some common features emerge on analyses. Most countries require a higher academic level, such as a Master's degree or graduate level of education. Although clinical competencies are outlined, this may include the management of chronic conditions, generalist or specialist roles. Not all countries include a function in illness diagnosis and treatment in their definitions of APN and only one reviewed was found to mention autonomous practice (Fig. 67.1). Some outline roles that are considered APN and others do not (Table 67.1).

Terminology used to describe APN roles also varies and adds to the confusion regarding role definitions (Bryant-Lukosius and Dicenso 2004). All practice roles and titles are significantly influenced by political, regulatory, organizational, and site/country-specific factors. The ICN International NP/APN network was established as a global professional voice to promote standardization in the definition of APN practice, but fails to outline roles considered as advanced practice (Sheer and Wong 2008).

67.3 Conceptualization of Advanced Practice Nursing

Conceptual models are generally used to guide research and theory development. When thinking of advanced practice nurses (APN), conceptual models may help APNs to articulate professional role identity and competencies, providing a basis for further development of knowledge and clinical expertise (Arslanian-Engoren 2018).

Table 67.1 Definitions of advanced practice

Organization/country	Definition of APN
International Council of Nurses (2008)	A registered nurse who has acquired the expert knowledge base, complex decision-making skills, and clinical competencies for expanded practice, the characteristics of which are shaped by the context and/or country in which he or she is credentialed to practice
Canadian Nurses Association (2008)	Advanced level of clinical nursing practice that maximizes the use of graduate educational preparation and expertise in meeting the health needs of individuals
American Nurses Association https://www.nursingworld.org/practice-policy/scope-of-practice/	• Registered Nurses (RN) • Treat and diagnose illnesses • Advise the public on health issues • Manage chronic disease, and engage in continuous education to remain ahead of any technological, methodological, or other developments in the field • Hold at least a Master's degree
Royal College of Nursing (UK) (2010)	• Autonomous practice • Critical thinking and assessment • High levels of accurate decision-making and problem solving • Values-based care • Improves practice • High degree of knowledge, skill, and experience applied in the nurse–patient/client relationships • Achieves optimal outcomes through critical thinking • Prepared at Master's level • May work in a specialist or generalist capacity

A conceptual model is designed to answer such questions as:

- What activities are performed by APNs that are considered 'advanced'? How do these differ from a traditional practice nurse?
- What education is required for nursing practice to be considered 'advanced'?
- To what extent do APNs become a physician replacement? To be considered 'advanced practice', is it necessary to incorporate activities traditionally done by physicians and does this make them 'mini doctors' or 'maxi nurses'?
- What does the term 'clinical expertise' mean? Does this refer to a narrower or a broader scope of practice? i.e. Would APNs with subspecialty clinical expertise such as pituitary conditions, but no clinical experience in general endocrinology, still be considered APNs in endocrinology?
- Is autonomy of practice an essential component of APN practice?

Conceptual clarity of APN (what it is and what it is not) is important not only for patient safety, and role regulation but also for effective intra- and inter-professional collaboration. Historical documents have recorded some nurses practising at what would now be considered advanced practice levels at a minimum in the nineteenth century but without clear formalized structure, education, and regulation. Advanced practice nursing was theoretically conceptualized in the 1980s (Hamric and Spross 1983), and many nurse authors have developed models that aimed to support and provide clarity to the advanced practice.

Despite progress made to date, challenges remain. One of the main challenges is the lack of a well-defined and consistent vocabulary to conceptualize APN. For example, in the USA and Australia the term *advanced practice nursing* is used. In Canada (CAN 2008), the UK and Europe, the preferred term is *advanced nursing practice*. This lack of consensus is apparent even within the auspices of the International Council of Nurses, which has adopted the term *advanced practice nursing* (ICN 2008), yet the title of the ICN-endorsed textbook is 'Advanced Nursing Practice' (Schober 2016). Similarly, the ICN refers only to Nurse Practitioners (NP) and Clinical Nurse Specialists (CNS) (Bryant-Lukosius and Martin-Misener 2016), and does not mention other role titles. This lack of a consistent and coherent terminology creates confusion. A global concept of advanced practice is

further hampered by diverse cultures and practice environments. This lack of clarity in definition ultimately impacts scope of practice, practice regulation, and role implementation (Hamric and Tracy 2018).

67.4 Global History of the Development of Advanced Practice Roles

Over time advanced practice nursing and the scope of practice in advanced roles have been influenced and shaped by social, political, economic, legislative, environmental, and technological issues. Demand for nurses to take on more medical roles is apparent in times of physician shortage (Lusk et al. 2018). This has driven 'expanded' practice roles, particularly during military activity. Nurses are recorded as administering anaesthesia during the American civil war (1861–1865) with a nursing manual of the time giving specific instructions regarding the use of chloroform and hypodermic syringes (Lusk et al. 2018). Beginning in 1889, nurse anaesthetists were formally trained at Mayo clinic in the USA. Although isolated institutions and physicians supported the development of nurse administered anaesthesia, there was a concomitant push back and legal action from several medical associations claiming nurses were 'practicing medicine without a licence'. Although challenges were rebuked by appellate courts, a decision in Kentucky US legalized nurse anaesthesia but as 'subordinate' to a physician (Lusk et al. 2018). This has had long standing ramifications for advanced practice across the USA with respect to independent practice in state practice act legislation.

From the growing complexity of nursing, specialty roles have emerged and along with these, the need for more specialized knowledge. The role of clinical nurse specialist (CNS) emerged in psychiatry during Quaker reform movement in mid-nineteenth century in England (Lusk et al. 2018). Other specialties adopted a CNS role which remained the dominant APN role. In the USA in 1980s, the role slowly transitioned from direct clinical care to administrative roles. The introduction of cost-cutting measures, coded billing, and capitated payments resulted in many CNS roles being cut from hospital budgets. The CNS role was not reinstated until federal legislation allowed payment for their services in the late 1990s (Lusk et al. 2018). However in the UK, with the support of the National Health System (NHS) and the recognition of potential cost savings, 87% of hospitals reported employing CNSs, and 37% APNs (Sibbald et al. 2006). Midwifery, though a long standing, traditionally autonomous role, was challenged by medicalization during the late nineteenth century, and evolved with formal training in the UK after 1872 and in the USA at the beginning of the twentieth century.

The role of nurse practitioner (NP) emerged in 1965 with a certificate programme developed by Loretta Ford and Henry Silver MD in Colorado USA, for the purpose of providing improved access to paediatric well child care (Lusk et al. 2018; Keeling 2015). This heralded the beginning of NP training. Eventually, education at Master's and Doctoral levels along with specialty credentialing was recommended or required for NP credentialing. Almost simultaneously, the NHS (UK) instituted payment to physicians for meeting chronic care and illness prevention targets. Primary care or general practice facilities employing APNs were more able to meet these targets (Sibbald et al. 2006). The trend to employ ANPs was further enhanced in 2004 with payment to practices that attain quality care goals.

In the UK, Australia, New Zealand, Canada, and the USA, nurses have been not only been seen as an economic advantage, but also willing to provide cost-effective care for economically disadvantaged populations and in remote rural areas (CIE 2013; Halcomb et al. 2014; Duffield et al. 2009; Lusk et al. 2018). These practice environments often required more medical and nursing knowledge and skills and autonomous practice. Nursing practice autonomy, such as previously exercised prescribing authority, appears to have been limited in the early nineteenth century by medical practice acts and legislative changes. Despite limitations on independent pre-

scribing and drug dispensation, rural nurses in the USA continued operating autonomously in rural remote and underserved areas using 'standing or verbal orders' authorized remotely by a physician (Keeling 2015). In 1955, the American Nurses Association issued a narrow definition of extended nursing practice. This was intended to clarify practice yet actually curtailed the use of advanced skills and limited nursing autonomy for treatment decisions (Keeling 2015).

The advent of the first NP certificate programme by Loretta Ford and Dr. Henry Silver essentially paved the way to restore autonomy and ANP via advanced practice certification (Keeling 2015). NPs were sanctioned to practice in primary care in New South Wales, Australia in 2000 in response to efforts to contain health care costs and provide broader access to care (MacLellan et al. 2015). As in the USA, each state regulated nursing practice. However, federal regulation in Australia in 2010 with the passage of the *Health Legislation Amendment* (Midwives and Nurse Practitioner) Act 2010 (Health Legislation Amendment 2010; MacLellan et al. 2015), created a single, national, practice act for NPs. This act also allowed direct reimbursement for services for qualified, endorsed ANPs and, thereby, independent practice. In the UK, advanced practice roles emerged from general (primary care) practices with the introduction in 1997 of the role of the nurse consultant supported by several governmental practice development projects (Duffield et al. 2009). Role confusion continues to limit practice in the UK. Likewise, nurse practice regulation continues to be restricted in autonomy and require the oversite of a physician in some states in the USA (Maier 2015; Lusk et al. 2018).

The demand for skilled personnel in the context of physician shortages, changing patterns, and higher acuity of illness and ageing populations have continued to fuel demand for nurses with more knowledge and skills. Nursing specialization is an evolution based on the growing complexity of care. Insightful leadership, political action, and legislative support have resulted in higher educational requirements and credentialing standards for advanced practitioners and has given rise to rapidly expanding roles (Hamric and Tracy 2018). In endocrinology, knowledge and skill development has been supported by the development of a competency framework developed in the UK to guide nurses through a career progression from novice to expert (Kieffer et al. 2015; Casey et al. 2013). However, these have not been supported by empirical work or an evidence-based approach.

APN development in endocrinology is anticipated to follow the same pattern of expansion, driven by similar demands as previously described. On the contrary, a large body of empirical evidence at national and European level is found from clinical nurse specialists working in diabetes supporting their role has followed a distinct APN development (Llahana et al. 2001; Llahana et al. 2004; Llahana 2005; Davis et al. 2008; Vrijhoef et al. 2009). Diabetes was reported to affect 8.7% of the global population in 2014 and is projected to be the seventh leading cause of death by 2030 (Global Report on Diabetes 2016). Low- and middle-income countries are disproportionately affected. A global epidemic of hypo- and hyperthyroidism is reported (Taylor et al. 2018). A US-based analysis in 2014 reported a shortfall of approximately 1500 adult and 100 paediatric full time equivalent endocrinologists, with a projected need for a 5.5% increase in trainee intake per year to meet estimated future demands (Vigersky et al. 2014). Regardless, endocrine diseases, such as diabetes and thyroid disease, threaten to overwhelm resources. APNs such as nurse practitioners, nurse diabetes specialists with a high level of education and specialized expertise, are well positioned to provide collaborative care to these populations and those with other endocrine diseases. Advanced education or Master's degree is required for credentialing as an ANP or NP in a number of countries (Duffield et al. 2009). Tertiary education programmes in endocrine nursing at a Master's degree level are currently being offered in the UK and the USA (Evans Kreider and Iris Padilla 2018).

67.5 Competencies for Advanced Practice Nursing

67.5.1 Definition of APN

The most extensive work on developing and clarifying the APN role has been undertaken by Hamric and Hanson over the 6 editions of their 'Advanced Practice Nursing' textbook. Their conceptual definition of APN is adopted in this textbook:

'Advanced practice nursing is the patient-focused application of an expanded range of competencies to improve health outcomes for patients and populations in a specialized clinical area of the larger discipline of nursing' (p. 65) (Hamric and Tracy 2018). Barron et al. (2005) identified three primary criteria which must be met before a nurse can be considered an advanced practice nurse. These include: Graduate education at Master's or Doctoral level, professional certification for practice at an advanced level within a nursing speciality, and practice focused on patients and their families with direct clinical practice as a central focus.

One of the earliest conceptual models to apply across all APN roles was introduced by McCaffrey-Boyle et al. (1996) and refined further in the later editions of the textbook (Spross 2014). Key components of the model (Fig. 67.2) include the primary criteria required by a nurse to perform an APN role, the central competency which is direct clinical practice and seven additional core competencies which are dependent on clinical practice. The model also takes into account the environmental and contextual factors which must support and be managed for APN roles to flourish and be supported (Spross 2014).

67.5.2 Direct Clinical Practice

The role of the APN was established to provide expert clinical care and improve the quality of patient care and nursing practice.

APNs function in many specialties, settings, patient or client populations. Despite variability in role description and implementation, Tracy (2018) suggests that the following six characteristics should be common across all APN roles:

1. Use of holistic perspective
2. Formation of therapeutic partnerships with patients/clients
3. Expert clinical performance in their area of practice
4. Use of reflective practice
5. Use of evidence as a guide to practice
6. Use of diverse approaches to health and illness management.

As an expert practitioner, the APN provides nursing care at an advanced level in his or her area of practice and demonstrates excellent clinical judgement (Tracy 2018). Moreover, the APN is able to develop clinical protocols for the care of patients and have the ability to manage those patients throughout the course of their condition/illness.

The several stages of role development (refer to Chap. 67), the acquisition of more advanced skills than those of general nurses, and the length of clinical experience enables the APN to move away from rules towards a more intuitive approach in interventions by integrating theory into practice (Benner 1984).

APNs, as expert practitioners, assess the patients' condition with a high level of discriminative judgement. They determine priorities of care and design a plan of care with advanced knowledge and skills. Furthermore, they implement comprehensive and individualized care and evaluate the quality of the care provided. This continuity of care assists patients/caregivers and complements their capacity to achieve or maintain optimum health and functioning. In the context of endocrine practice, this equates to maximizing the individuals capacity for self-management of endocrine disorders and assist the patient to maximize quality of life.

The clinical expertise of the APN should not only improve the level of care received by those patients with whom they interact, but also overall quality of nursing care. The APN functions as a role model for other nursing staff and provides guidance in professional career by modelling expert care for patients using a theoretical basis

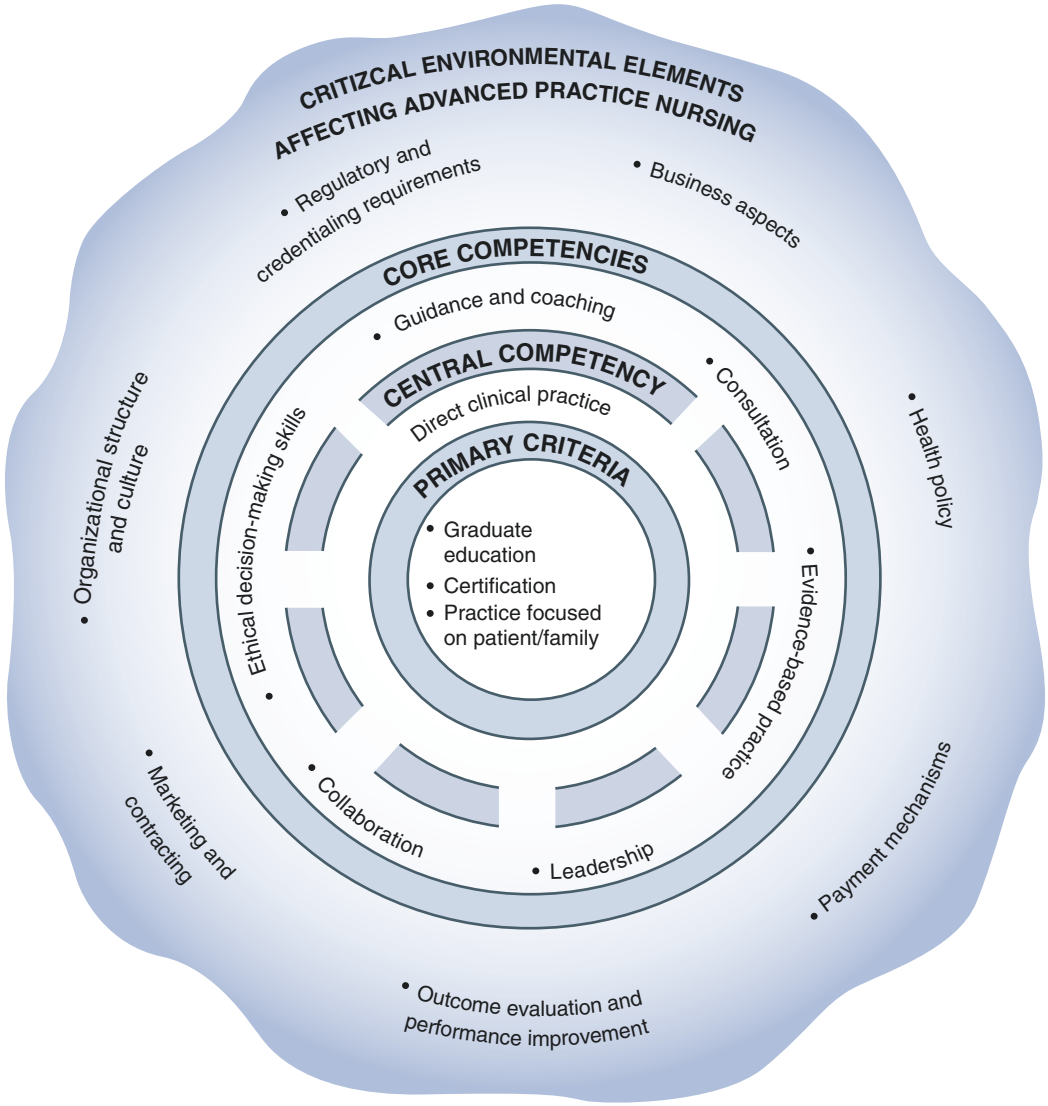


Fig. 67.2 Hamric's model of advanced practice nursing. Used with permission from Spross JA (2014) Conceptualisations of Advanced Practice Nursing. In: Hamric, A. B., Hanson, C. M., Tracy, M. F. & O'Grady, E.T. (Eds). *Advanced practice nursing: An integrative approach*, 5th Edition. Elsevier Health Sciences, pages: 27–65. [Fig. 2-4, page 44]

for care. However, in order to act as a role model, the APN needs to be accepted by other members of the health care team as an advanced practitioner. Therefore, effective and sustained impact on clinical practice requires APNs to prove their competence and skills as expert practitioners.

If APNs lack such skills or are unable to efficiently translate knowledge into the clinical practice setting, nursing staff may not value the APN's suggestions and may consider the APN as an intruder/threat (Llahana 2005). Moreover, 'hands-on' practice of patient care increases the visibility of APNs and direct contact with patients/clients and other health professionals enables the APN to advocate for both patients and staff.

In direct care delivery, APNs participate in quality assurance activities and establishing standards of care. They use evidence-based prac-

tice, generate research questions applicable to clinical practice, and identify translational opportunities to implement research findings (Llahana 2005; Tracy 2018).

67.5.3 Education and Coaching

Educational responsibilities are a key part of the APN role. The practice of remaining up-to-date on relevant, new, and emerging information and sharing information in a clear and timely manner is characteristic of effective APN teaching interventions (McCaffrey-Boyle 1996).

'Patient-focused instruction' is the mainstay of the APN education role and is the characteristic which most differentiates the APN role from staff development educators and academics. The APN has expert knowledge and skills and holds a strategic position for critical patient and family education. Open discussion of patient problems, individualized assessment, and shared decision-making are the hallmarks of conjoint patient-specific care planning (and staff learning). Teaching may be structured or impromptu one-to-one or in a group setting either face-to-face or via mobile health communication (telenursing, web-enabled, SMS, etc.) (Spross et al. 2000).

Development of new educational tools and programmes is another example of the APN educational involvement. The APN's clinical experience yields data on patient and family health and informational needs. The APN is in an ideal position to identify needs, select and implement the most appropriate teaching method for each patient or situation (McCaffrey-Boyle 1996). Proficiency in the utilization of learning theory in APN multifaceted education roles is paramount for both professional and non-professional learners (Llahana 2005).

Part of the APN's role as an educator is to teach and inform not only patients and their families/carers, but also their colleagues, staff, and/or students. Integrating counselling and effective communication into routine one-to-one exchanges is an efficient way to integrate professional development into practice—in particular when discussing challenges and problems.

APNs act as role models for other health professionals by demonstrating the practical integration of theory and evidence-based practice, maintaining a focus on continuous process improvement of clinical care, and integrating new knowledge into practice. The APN has a professional responsibility to be an educator and mentor for graduate nursing students, sharing their knowledge, and modelling advanced practice nursing for the next generation of APNs (Llahana 2005; Spross and Babine 2013).

67.5.4 Consultation

Consultation refers to providing assistance and fostering the consultee's ability to master a given situation. It requires several essential elements: Availability, willingness, insight, clinical expertise, communication skills, and a non-judgemental attitude (McCaffrey-Boyle 1996; Llahana 2005; Vosit-Steller and Morse 2014). It is important to note that these are functions of all advanced practice and is independent of the role of the APN role of nurse consultant.

The degree of importance placed on the consultative component of the APN practice is largely determined by the needs of the staff and patients with whom the APN is working, the expertise of the staff, plus the philosophy, goals, and priorities of nursing administration (Barron and White 2005). Effective consultation on a complex patient problem requires sensitivity. Emphasis is given to the patient's feelings and on how he or she may be assisted to accept the respective health condition and adapt to a new way of living (McCaffrey-Boyle 1996).

The APN is expected to be a content expert assisting in a wide range of approaches and solutions to clinical/health system problems, either internal or external to the practice setting. Moreover, the APN is a resource who provides pertinent information and alternatives, enabling nurses and other health professionals to make decisions that are responsive to dynamic clinical situations (Vosit-Steller and Morse 2014).

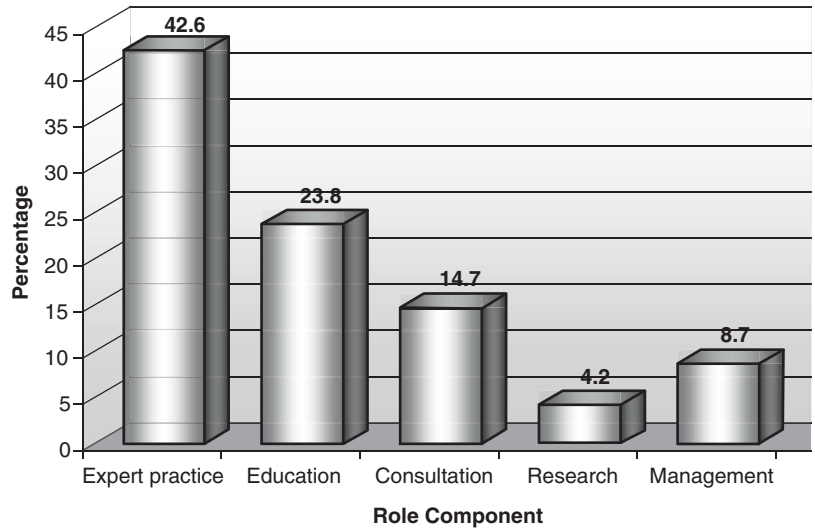


Fig. 67.3 Percentage of total working time allotted to each role component in a national study of clinical nurse specialists in diabetes in the UK (Llahana 2005)

The emphasis placed on the fluctuation of the consultative role over time, but nursing consultation remains an essential and valued activity for most APNs. It is worthwhile to distinguish between formal and informal consultation (Barron and White 2005). The latter often occurs spontaneously and may involve brief questions regarding patient care, a setting or an organizational issue. Informal consultation often occurs when the APN is available and present in a patient care unit. Such rapid consultations are just as likely to be initiated in a corridor or stairwell. Informal consultations occur regularly but as Pearson (2018) emphasizes, APNs need to be cautious and capable of determining when a problem is complex and a quick answer is not appropriate. In these types of scenarios, APNs should direct the consultation towards a more formal and planned approach. Documentation of consultations and decision-making process is also crucial.

67.5.5 Research and Evidence-Based Practice

Although research is an equally important APN competency, there is evidence suggesting that the least amount of APN time is dedicated to research, audit, and evidence-based practice (Scott 1999; Melnyk et al. 2014). A nationwide study involving 334 clinical nurse specialists (CNSs) in diabetes, revealed that only 4.2% of time was spent on research-related activities (Llahana 2005) (Fig. 67.3). The research competency facilitates the APN improving quality of nursing care via scholarly inquiry and translational application of research findings to clinical practice. Research is essential for building and extending the knowledge base for nursing practice. It guides and facilitates clinical decision-making and provides greater understanding of the impact of nursing interventions on patient outcomes (Llahana 2005; Gray 2018).

Frequently, research involvement is collaborative and interdisciplinary in the form of an audit or service evaluation. As a member of a research team, an APN is in a unique position to contribute to the generation of clinically based knowledge, to create a link between practical application and theoretical design, and to support continuous quality improvement. An APN is the clinical expert who understands clinical issues and has access to patients. In contrast, a nurse researcher is the research expert, well understands research methodology, and has access to the tools and resources that are essential for conducting research (Sparacino 2000).

A perceived barrier that may preclude APNs from active participation in research activities is the assumption that research is only worthwhile if one is a principal investigator. This is an overly narrow

view and neglects the fact that research encompasses a continuum of activities that includes scholarly inquiry, conducting prospective or retrospective research as well as utilizing research findings. This may involve (1) interpretation and use of research, (2) evaluation of practice, and (3) participation in collaborative research (Sparacino 2005; Llahana 2005) (see Research Chap. 69).

67.5.6 Leadership and Management

Leadership includes the APN's responsibility for clinical innovation and change, as well as formal and informal impact/influence on patient care and health system (Sparacino 2005). Clinical leadership, management knowledge, skills, and processes enhance APNs' effectiveness as leaders, regardless of position within the organizational hierarchy. The APN has significant formal and informal influence and must strike a balance between visionary and practical. Moreover, the APN may serve as a link between a variety of resources and nursing staff and asserts clinical and professional leadership in the practice setting, health care system, in health care policy and delivery decisions, or in the administration of direct care programmes (Sparacino 2000).

Clinical and leadership competencies articulate with the other APN competencies to support the overall purpose and goals of an organization relating to the provision of patient care. To external observers, many health care organizations/systems may resemble a maze with lack of coordination and bureaucratic hurdles. For this reason, the APN plays an important role by working with staff, patients, and families to help them comprehend the complexities and navigate the health care system. The APN can also serve as an advocate during times of organizational change (Llahana 2005; Carter and Reed 2018).

67.5.7 Collaboration and Innovation

In their practice, APNs collaborate with nurses, physicians, other health care providers, as well as patients and their families. Therefore, they must have skills and abilities that foster effective interdisciplinary collaboration and teamwork. Collaboration is a key component for team building, developing synergism, and finding/implementing integrative solutions. It contributes to overall high-quality and cost-efficient patient care. According to Sparacino (2000), collaboration is an essential competency of an APN, and it is the product of clinical competence, effective communication, mutual trust, valuing complementary knowledge/skills, collegiality, and a favourable organizational structure. It is a transversal competency, meaning that the APN collaborates and coordinates activities when performing other role components.

One outcome of APN-coordinated collaboration is empowering nurses and recognizing nurses as critical members of the health care team. APNs build collaborative relationships with patients and families. This provides an interface between patients, families, physicians, and other health care professionals to promote effective and efficient health care (Carter et al. 2018).

Innovation is perhaps the most challenging role to describe, perform, and/or understand, and it is not a distinct competency. Rather, innovation results from the performance of the other role competencies. It has been posited that the ultimate goal of the APN is to be a successful change agent. Lancaster (1982) defined change agent as one who:

'…generates ideas, introduces the innovation, develops a climate for planned change by overcoming resistance and marshalling forces for acceptance, and implements and evaluates the change' (p. 20).

The role of the APN as a change agent aims to improve patient care and nursing practice and promote effective communication and collaboration with other health care personnel. Change is a never ending process, which, as Hanson and Malone (2000) state, '…must be woven into the fabric of everyday life and work' (pp. 284–285). Change can be both challenging and invigorating, but at the same time, can be difficult and painful. Understanding and using theories of change and implementation frameworks can help

the APN develop strategies and skills to introduce innovation in their work environment and be successful agents of change.

67.5.8 Independent Nurse Prescribing

Prescriptive authority was the focus of APN political action in the USA in the late 1980s. Oregon and Washington State were the first to attain prescriptive autonomy (Lusk et al. 2018). Many states were subsequently granted prescriptive authority to nurses under the supervision of a licenced physician. In 2017, all 50 states and the District of Columbia had legalized prescriptive authority for APNs but the scope of independent prescribing is limited in some states and dependent on a physician licence in others. Currently, 18 US states allow ANPs independent prescriptive privileges. All states require formal graduate level coursework and registration as an APN before granting initial privileges and most require continuing education credits for recertification (AANP 2018; APRN Consensus Statement 2008). The American Association of Nurse Practitioners (AANP 2015) position statement declared unrestricted nurse prescribing, as essential to ANP role performance.

However, prescription of controlled substances in the USA was under the auspices of the Comprehensive Drug Abuse Prevention and Control Act of 1970 and regulated by the Drug Enforcement Agency (DEA). Prescription of controlled 'scheduled' substances required the issuance of a registration number. This was only issued to licenced physicians and dentists until the 1990s. Nurses were first issued registration under the licence of a physician with whom they had a working relationship. Independent DEA registration numbers were granted to NPs according to state-specific prescriptive scope of practice in 1993 (Department of Justice 1993).

In the UK, non-medical prescribing was first recommended by the Cumberlege Report in 1986 to facilitate care provided by community nurses. The subsequent Crown Report supported independent, formulary based, nurse prescribing but legislative support and implementation did not occur until 1992 (Cope et al. 2016). Nurses were mandated to prescribe within a supervised framework termed 'dependent' and later 'supplementary' prescribing. The formulary was extended in 2005 to any licenced medicine, which included specified controlled substances and was expanded to allow independent prescribing limited to the practitioners area of clinical expertise.

'Non-medical' prescribers must be a registrant in their profession and meet a set of criteria prior to being granted privileges. Prerequisite requirement is a minimum three years post-registration clinical experience with 1 year in the clinical area or specialty in which they wish to prescribe. Completion of a programme of at least 26 weeks of didactic training plus 12 days of supervised clinical experience is required to achieve qualification (Cope et al. 2016). Courses are offered at a number of tertiary education facilities at bachelor's and Master's degree levels or as independent courses. The content may include:

- Assessment, consultation skills, and history taking
- Legal and professional issues relating to non-medical prescribing
- Decision-making and evidence-based prescribing
- Psychological and ethical issues applied to prescribing
- Pharmacology and drug actions
- Leadership, accountability, and clinical governance
- Development of clinical management plans as a supplementary prescriber (from Middlesex University London).

Nurse prescribing has been demonstrated to be safe, to improve patient outcomes, and is appreciated by patients. The practice has also been introduced in Australia, New Zealand, Canada, Sweden, Finland, Ireland, Netherlands, and Spain according to country-specific limitations (Cope et al. 2016).

67.6 Operational Definitions of Advanced Practice Nursing

There are four APN roles: Clinical nurse specialist (CNS), nurse practitioner (NP), nurse midwife, and certified registered nurse anaesthetist. However, depending on health system and culture, titles may vary (i.e. nurse consultant (NC), clinical nurse consultant). For the field of endocrinology, roles are primarily CNS, NP, and NC.

67.6.1 The Clinical Nurse Specialist (CNS)

In the 1950s, the CNS role developed in the USA to provide an expert practitioner service at the bedside of the patient. Today, the role of the CNS has expanded beyond the hospital setting, with a client-based focus. The National Association of Clinical Nurse Specialists (USA) defines the CNS role as practicing in three spheres of influence: the patient/client sphere (e.g. advocacy), the nurse/nursing practice sphere (e.g. teams), and the organization/system sphere (e.g. implementing evidence-based practice) (NACNS 2004). Specialization in nursing implies a deeper level of knowledge, skills, and qualifications within a particular field of nursing care than one typically acquires during general training (Llahana 2005). Since the early 1980s, the American Nurses Association (1984) defined specialization as a narrow focus on a part of the whole field of nursing, which requires the application of a broad range of theories to selected nursing phenomena. This secures depth of understanding as a basis for advances in nursing. The reduction in the range of knowledge expected of CNSs results in the development of the depth of knowledge and skills that can be applied directly in the clinical setting to enhance patient care (Llahana 2005). Therefore, as Wade and Moyer (1989) categorically stated, CNSs know more and more about less and less.

From its inception, the CNS role has been firmly grounded in clinical practice but includes other components such as expert coaching and guidance, consultation, research, clinical and professional leadership, collaboration, and ethical decision-making (Hamric and Spross 1989; Sparacino 2005; Llahana 2005; Tracy and Sendelbach 2018). The CNS role is multifaceted and complex. CNS practice is often flexible and responsive to the needs of patients and/or institutions.

67.6.2 The Nurse Practitioner

The nurse practitioner (NP) is a role that was developed in 1960s in the USA. NPs have grown in number nationally and have spread internationally. While rooted in the discipline of nursing, the NP principally functions in a physician replacement model. In contrast to the CNS role that focuses on three distinct spheres, the NP is rigorously trained in the '3-Ps' pathophysiology, pharmacology, and physical examination. This training enables nurse practitioners to assess, diagnose, and treat patients (National Council of State Boards of Nursing. https://www.ncsbn.org/index.htm—accessed 07.07.2018). Notably, autonomy and prescriptive authority vary across nations, states/territories, and localities. In some situations, NPs may practice independently while in other areas, additional restrictions may exist related to the level of autonomy for assessing, diagnosing, and treating based on regulatory scope of practice.

A Master's degree is frequently required for entry to practice as an NP and in some countries a clinical doctorate is either required or strongly recommended. Post master's graduate certificate with a focus on paediatric, family, geriatric, psychiatric care, or women's health is required for certification to practice in many states in the USA.

67.6.3 The Nurse Consultant

The Nurse Consultant (NC) role exists primarily in the UK and Australia. Initial NC posts were introduced in the UK in 1999 to advance nursing practice, research, and education, as well as to provide

professional leadership and quality care to improve patient outcomes (Department of Health 1999). The NC role is based on four components: (1) clinical practice, (2) education and training, (3) leadership, and (4) research and service development (Mitchell et al. 2010; Llahana 2010). Currently, there are more than 500 NCs across the UK working in different specialities. NCs are typically the most senior APNs in the UK and at the top rank of the profession both in status and in salary. At least half of the NC's work is dedicated to direct clinical care, while education, leadership, research, and strategic involvement in service and policy development comprises the remaining time. NCs have a national and international profile and influence in their area of specialty. A Master's level of education is required but more organizations expect NCs to have or undertake a Doctoral degree.

A study by Mitchell et al. (2010) found that NCs contribute service-wide to the implementation of public health policy, service delivery, and policy development, achieving expected competencies and improving health outcomes. They identified four consistent themes in relation to the NC role: (1) entrepreneurial activity and innovation; (2) clinical autonomy and role dynamism; (3) influential national and international research conduct; (4) consultancy and education across discipline boundaries. These included descriptions of higher order skills that surpass usual requirements for the APN practice and the role differs from that of the Nurse Practitioner (NP) or CNS in several aspects (Table 67.2) (Mitchell et al. 2010, Maylor 2005). Figure 67.4 provides an example from the CN role of one of the authors of this chapter. The framework of the NC in endocrinology role with core components and sources of expectations for the role is delineated in Fig. 67.5.

In Australia, the role of Clinical Nurse Consultants (CNC) was introduced in 1986. This APN role closely resembles that of the Clinical Nurse Specialists in the UK and the USA and differs from the Nurse Practitioner role (Fernandez et al. 2017; Baldwin et al. 2013). The multiple titles can lead to role confusion—especially at an international level. For clarity, it seems most appropriate to refer to these roles under the broader APN umbrella.

Table 67.2 Perceived differences between the CN and CNS roles [adapted from Mitchell et al. (2010) and Maylor (2005)]

Consultant nurse (CN)	Clinical nurse specialist (CNS)
Role dynamism	Role description
Makes decisions where there is no precedent	Makes decisions based on protocols and policies
Clinical practice at 50% of working time; broader patient group focus	Majority of working time spent in clinical practice; manages individual patient caseload
Works alongside senior medical	Often answers to senior medical staff
Advanced research adviser	Resource for current research-based practice
Conducts and coordinates research to generate knowledge	Uses research to inform practice
Authority and strategic influence	Might have vision but not authority to influence strategy and bring about change
Clinical and strategic planning	Acts as a specialist consultant and advisor—often not hands on
Has power vested in role	Seeks vicarious power through others to support own perspective

67.7 An APN Competency Framework for Endocrine Nurses

The goal of a competency framework is to provide standardization, consistent high level of care. Competencies that distinguish the APN are shared by all APN roles whereas clinical competencies are specific to the specialty and some to the organization or practice setting. (Kieffer et al. 2015) (Table 67.3).

Detailed competency frameworks provide a guide for new nurses entering the field regarding role expectations and a path for career development to achieve expert practice. The framework provides a structure on which to build an objective career ladder at an organizational level. Such a framework can serve to demonstrate competency to patients and collaborators or other stakeholders.

The reader is referred to recommended readings, Kieffer et al. (2015) for a detailed descrip-

Following appointment as a CNS in Endocrinology in 2004 and in collaboration with the Clinical Lead, the management team, the Chief Nurse and relevant stakeholders, we identified that the contextual background of the endocrine services at UCLH fully supported the necessity of the CN role to develop and provide the following:

- A more patient centred approach to enhance the quality and level of care.
- Expert, innovative and evidence-based endocrine nursing care.
- An educational strategy and a new pathway for clinical nursing within endocrinology
- A national and international profile of endocrine nursing as pivotal and equal member within the multidisciplinary team.

Being involved in writing the job description for this post and discussing it with key stakeholders enabled me to determine how the components of the CN role fitted in endocrinology care at local but also national/international level.

As seen in Fig. 67.5. The CN has five essential domains (core components) to their role; only 50% of working time is clinical practice based which allows for protected time for research and service development away from the pressures of the clinical practice. Changing roles in the same organisations came with the challenge of ensuring the CN role was "visible". During the first 3 months in the CN post I met with a large number of colleagues and key stakeholders from different areas and disciplines within the Trust. I talked about my role and asked for their input on how I could make this role successful. I have incorporated their views and suggestions into my role structure and objectives.

If I can share a few words of advice from my personal experience for endocrine nurses pursuing an APN career progression, these would be:

- Ensure you are up to the challenge of the role and the increased responsibilities. Also, that you are prepared, and you have the relevant competence and qualifications required by the role; in many counties a Master's degree is an entry criterion and Independent Nurse Prescribing is also required for example in the UK and Netherlands.
- Ensure you write a strong proposal to justify the need for an APN CN in your Organisation. What more can an APN offer compared to your current role? Unless you can prove that this role will show a significant and cost-effective improvement in patient care, it may not be approved.
- It will be impossible to achieve this on your own, independently of how competent you are. I was very fortunate to work with a supportive team and in an organisation, who valued the input of nursing in patient care and supported career progression. If you believe this is not the case for you, perhaps it is time to move to a different organisation.
- Talk to other APNs and find out what their role entails and how they made it a success? I spent about 12 months gathering information and talking to people before finalising the job description and proposal for the CN role.
- Finally, remember that in many organisations the APN posts, once advertised, will be open to anyone to apply. Be prepared for a rigorous interviewing process involved in selecting the right candidate. Have you thought about what you will do if, after all your hard work, you do not get the job?
- Persevere and do not give up! You will face a lot of hurdles, especially in today's financial climate, but if you really believe you have what it takes, the APN role whether this is NP, CNS or CN, role will be a reality.

Fig. 67.4 A case study of a Nurse Consultant in Endocrinology role development in the UK

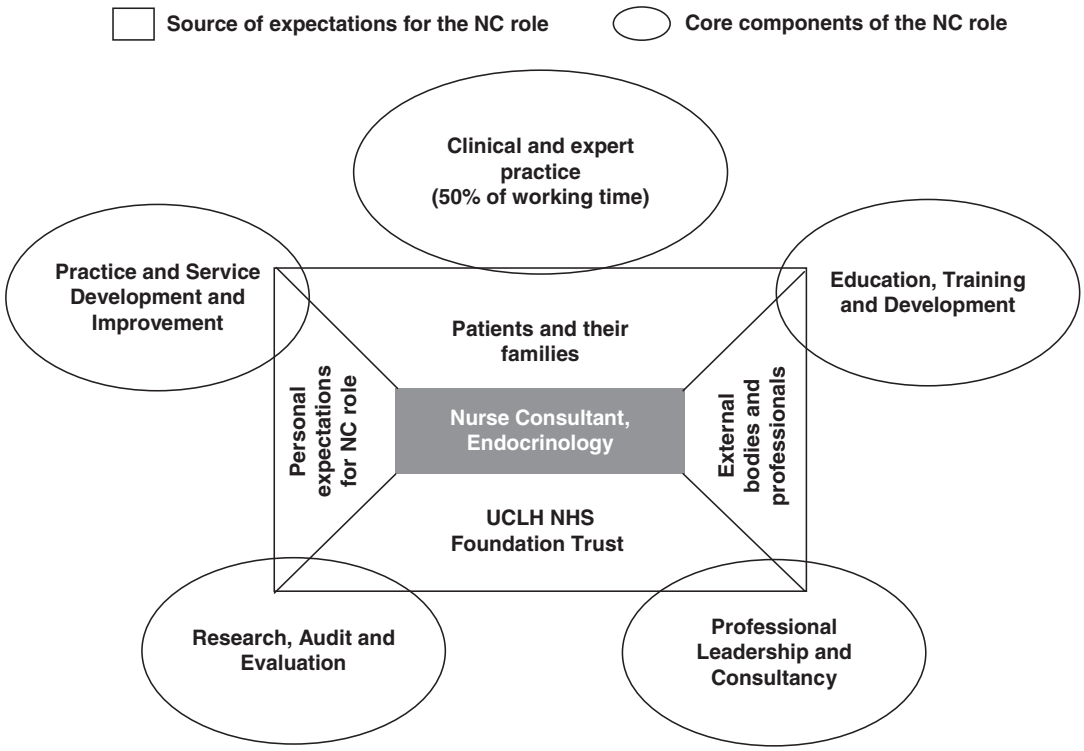


Fig. 67.5 Nurse Consultant Framework: core components and sources of expectations for the role (developed by S. Llahana)

tion of a number of specific endocrine clinical competencies. An APN in endocrinology is expected to be an autonomous expert.

67.8 Implementation of an APN Role

The implementation of APN roles into health care organizations and systems has been challenging and has generally followed an ad hoc, unregulated course in most countries. One approach that has been demonstrated to be effective for introducing APN roles in diverse health systems from Europe to Latin America is the participatory, evidence-based, patient-focused process for guiding the development, implementation, and evaluation of advanced practice nursing (P.E.P.P.A.) framework. Formal policies and guidelines are important for supporting effective APN role implementation (Bryant-Lukosius and Dicenso 2004; Boyko et al. 2016; Oldenburger et al. 2017). Indeed, legislation for title protection, education at accredited educational institutions, clear professional competencies and licensure regulations are crucial to the success of the APN role. Thus, reaching consensus on role definition and a guiding conceptual framework is highly relevant.

67.9 Nurse-Led Clinics

In some settings, nurse-led clinics have been established to fill a service gap, but may also be a novel care model to provide service for management of chronic conditions. Nurses are required to have advanced specialty knowledge and usually work autonomously (Khair and Chaplin 2017). Nurse-led clinics improve access to care, foster inter-professional collaborative relationships, foster nurse leadership development, and improve patient outcomes.

Table 67.3 General and specialty APN competency framework

Competency dimensions	
Research	Care management
Clinical and professional	Evidence-based practice
Leadership	Professional autonomy
Mentoring and coaching	Health promotion
Collaboration and inter-professional relationships	Communication
Ethical and legal practice	Cultural competencies
Education and teaching	Advocacy
Quality management and safety	Change management
Consulting	Expert clinical judgement
	Consulting
Specialist competencies	
Competency 1: Acromegaly	Competency 7: Hypogonadism
Competency 2: Benign adrenal tumours	Competency 8: Hypopituitarism
Competency 3: Cushing's syndrome	Competency 9: Osteoporosis
Competency 4: Endocrine dynamic function testing	Competency 10: Polycystic ovary syndrome
Competency 5: Growth hormone deficiency	Competency 11: Steroid replacement therapy disorders of the pituitary and adrenal glands
Competency 6: Hypo- and hyperparathyroidism	Competency 12: Thyroid disease

In this environment, nurses make detailed physiological and psychologic assessments with subsequent care planning. They perform diagnostic tests, deliver treatments, monitoring of the patient's condition, prescribe and manage medications. Teaching is a large component of all ANP roles in this, as in all types of practice. Patients are usually directly referred to the nurse-led clinic for care (Khair and Chaplin 2017).

Conditions such as diabetes, atrial fibrillation, and bronchiectasis have been successfully managed using this practice model (Jacob 2017; Lawton et al. 2018). A recent study of patients with diabetes and heart disease found significant improvement in HA1c and cardiovascular endpoints that were sustained at a 2-year follow-up in patients managed at a nurse-led diabetes clinic (Wallymahmed et al. 2011). In a systematic review of 15 nurse-led clinics involving a total of >3000 patients, positive outcomes were demonstrated, patient satisfaction was increased but cost-effectiveness was equivocal (Randall et al. 2017).

Nurse-led clinics are found in the UK, Australia, and the USA. In the USA, NPs are licenced independent practitioners in 21 states plus the District of Columbia. Thereby, an NP with an entrepreneurial spirit can establish a sole practice, usually in general practice or primary care. Care delivered by NPs in this setting has been shown to achieve comparable outcomes to similar physician practices (Swan et al. 2015).

67.10 Conclusions

Economic and physician workforce shortages have historically driven a need for APNs. Restructuring of reimbursement models based on quality and illness prevention benchmarks continue to drive the demand for APN models of care. Endocrinology is not immune to these changes, and demand for APNs is likely to increase. However, standardizing the concept of advanced practice is needed, particularly in the context of endocrinology. Raising the profile of endocrine nurses through political activities, advocacy, research, and publications will be needed to improve role awareness. To develop the potential of APNs in endocrinology, achievement of expert levels of care, regardless of the setting, is essential.

Demonstration of the efficacy of care provided by APNs with comparative and outcome focused research is paramount. Working within organizations, through political action via participation in regional, national, and international networks, strengthens collaboration and provides a unified voice. It is vital that AP nurses, particularly in endocrinology, demonstrate and achieve the full potential of their practice capacity.

Acknowledgement The author acknowledges Phillip Yeoh RGN BSc MSc NIP who is the Consultant Nurse in Endocrinology, The London Clinic, 5 Devonshire Place London W1G 6HL UK.

References

All-Party Parliamentary Group on Global Health (APGGH). Triple Impact—how developing nursing will improve health, promote gender equality and support economic growth. London; 2016. http://www.appg.globalhealth.org.uk/.

American Association of Nurse Practitioners. Position statement: Nurse practitioners prescription privileges last reviewed and revised 2015. 2015. https://www.aanp.org/images/documents/publications/prescriptiveprivilege.pdf. Accessed 13 July 2018.

American Association of Nurse Practitioners. State Practice Environment. 2018. https://www.aanp.org/legislation-regulation/state-legislation/state-practice-environment. Accessed 13 July 2018.

American Nurses Association. 1984. Issues in professional nursing 2: Specialisation in nursing practice. Kansas City: American Nurses Association.

APRN Consensus Work Group & National Council of State Boards of Nursing APRN Advisory Committee. The consensus model for APRN regulation: licensure, accreditation, certification, education. 2008. https://www.ncsbn.org/Consensus_Model_for_APRN_Regulation_July_2008.pdf. Accessed 11 July 2018.

Arslanian-Engoren C. Conceptualisation of advanced practice nursing. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 26–61.

Baldwin R, Duffield CM, Fry M, Roche M, Stasa H, Solman A. The role and functions of Clinical Nurse Consultants, an Australian advanced practice role: a descriptive exploratory cohort study. Int J Nurs Stud. 2013;50:326–34.

Barron A-M, White PA. Consultation. In: Hamric AB, Spross JA, Hanson M, editors. Advanced practice nursing: an integrative approach. 3rd ed. Philadelphia: Elsevier Health Sciences; 2005. p. 187–224.

Benner P. From novice to expert: excellence and power in clinical nursing practice. Menlo Park: Addison-Wesley; 1984.

Boyko JA, Carter N, Bryant-Lukosius D. Assessing the spread and uptake of a framework for introducing and evaluating advanced practice nursing roles. Worldviews Evid-Based Nurs. 2016;13(4):277–84. https://doi.org/10.1111/wvn.12160. Epub 2016 Apr 13.

Bryant-Lukosius D. Back to the future: advancing the global evolution of advanced practice nursing. Keynote address. International Council of Nurses, Nurse Practitioner/Advanced Practice Nurse Network Conference. Helsinki; 2014.

Bryant-Lukosius D, Dicenso A. A framework for the introduction and evaluation of advanced practice nursing roles. J Adv Nurs. 2004;48(5):530–40.

Bryant-Lukosius D, Martin-Misener R. Advanced practice nursing: an essential component of Country Level Human Resources for Health. ICN Policy Brief. 2016. http://www.who.int/workforcealliance/knowledge/resources/ICN_PolicyBrief6AdvancedPracticeNursing.pdf . Accessed 8 July 2018.

Canadian Nurses Association (CAN). advanced nursing practice: a national framework. Ottawa: CAN; 2008.

Carter M, Reed L. Leadership. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 256–85.

Carter M, Dabney C, Hanson CM. Collaboration. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 286–309.

Casey A, Davies K, Langham S, et al. Competences: an integrated career and competency framework for children's nurse endocrine specialists. London: Royal College of Nursing; 2013. https://www.rcn.org.uk/professional-development/publications/pub-003264.

Cope LC, Abuzour AS, Tully MP. Nonmedical prescribing: where are we now? Ther Adv Drug Saf. 2016;7(4):165–72. https://doi.org/10.1177/2042098616646726.

Davis R, Turner E, Hicks D, Tipson M. Developing an integrated career and competency framework for diabetes nursing. J Clin Nurs. 2008;17:168–74.

Department of Health. Making a difference: strengthening the nursing, midwifery and health visiting contribution to health and healthcare. London: The Stationery Office; 1999.

Department of Justice. Drug Enforcement Administration 21 CFR Parts 1301 and 1304 Definition and Registration of Mid-Level Practitioners. Final rule. Federal Register/Vol. 58, No. 103/Tuesday, June 1, 1993/Rules and Regulation. 1993. p. 31172. https://www.deadiversion.usdoj.gov/fed_regs/rules/prior_1998/fr0601_1993.htm. Accessed 13 July 2018.

Duffield C, Gardner G, Chang AM, Catling-Paull C. Advanced nursing practice: a global perspective. Collegian. 2009;16(2):55–62. Review. PMID: 19583174.

Kreider KE, Padilla BI. Development of an Innovative Endocrinology Training Program for Nurse Practitioners. J Nurs Educ. 2018;57(8):506–9. https://doi.org/10.3928/01484834-20180720-11. Posted August 3, 2018

Fernandez RS, Sheppard-Law S, Manning V. Determining the key drivers and mitigating factors that influence the role of the Nurse and/or Midwife Consultant: a cross-sectional survey. Contemp Nurse. 2017;53:302–12.

Global Report on Diabetes. Geneva: World Health Organization; 2016. http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=CE0193C9B3363B3B17F164C4D14C6231?sequence=1. Accessed 11 July 2018.

Gray M. Evidence-based practice. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 225–55.

Halcomb EJ, Salamonson Y, Davidson PM, Kaur R, Young SA. The evolution of nursing in Australian general practice: a comparative analysis of workforce

surveys ten years on. BMC Fam Pract. 2014;15:52. https://doi.org/10.1186/1471-2296-15-52.
Hamric AB, Spross JA. The clinical nurse specialist in theory and practice. Philadelphia: WB Saunders; 1983.
Hamric AB, Spross JA. The clinical nurse specialist in theory and practice. Philadelphia: WB Saunders; 1989.
Hamric AB, Tracy MF. A definition of advanced practice nursing. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 61–79.
Hamric AB, Hanson CM, Tracy MF, O'Grady ET. Advanced practice nursing: an integrative approach. St. Louis, MO: Elsevier Health Sciences; 2016.
Health Legislation Amendment (Midwives and Nurse Practitioners) Act 2010. https://www.legislation.gov.au/Details/C2010A00029.
Institute of Medicine (IOM). The future of nursing: leading change. Advancing Health the Robert Wood Johnson Foundation (RWJF); 2010.
ICN (International Council of Nurses). The scope of practice, standards and competencies of the advanced practice nurse. Geneva: ICN Regulation Series, ICN; 2008.
ICN (International Council of Nurses). The most frequently asked questions of the ICN International Nurse Practitioner/Advanced Practice Nursing Network. Geneva: ICN; 2015. http://international.aanp.org/Home/FAQ.
Jacob L. Nurse-led clinics for atrial fibrillation: managing risk factors. Br J Nurs. 2017;26(22):1245–8. https://doi.org/10.12968/bjon.2017.26.22.1245.
Keeling A. Historical perspectives on an expanded role for nursing. Online J Issues Nurs. 2015;20(2):2. https://doi.org/10.3912/OJIN.Vol20No02Man02.
Khair K, Chaplin S. What is a nurse-led service? J Haem Pract. 2017;4(1) https://doi.org/10.17225/jhp00100.
Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, Shepherd L, Yeoh P. Society for endocrinology competency framework for adult endocrine nursing: 2nd edition. Endocr Connect. 2015;4:W1–W17.
Lancaster J. Change theory: an essential aspect of nursing practice. In: Lancaster J, Lancaster W, editors. The nurse as a change agent. St Louis: CV Mosby; 1982. p. 3–28.
Lawton K, Royals K, Carson-Chahhoud KV, Campbell F, Smith BJ. Nurse-led versus doctor-led care for bronchiectasis. Cochrane Database Syst Rev. 2018;6:CD004359. https://doi.org/10.1002/14651858.CD004359.pub2. [Epub ahead of print] Review.
Llahana S. A theoretical Framework for Clinical Specialist Nursing: an example from diabetes. Fivepin Publishing, Salisbury. 2005. www.books.google.co.uk/books?isbn=1903877369.
Llahana SV. Consultant Nurse in Endocrinology: a role that has become a reality. Endocrinologist. 2010;97:14–5. http://www.endocrinology.org/endocrinologist/097/097.pdf.
Llahana SV, Coates VE, Poulton BC. Survey: role components, functions and activities of the DSN. J Diabetes Nurs. 2001;5(6):181–7.
Llahana SV, Coates VE, Poulton BC. Exploring the relevance of the DSN role to the Greek healthcare setting. J Diabetes Nurs. 2004;8(4):145–51.
Lusk B, Cockerham AZ, Keeling AW. Historical and developmental aspects of advanced practice nursing. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 1–24.
MacLellan L, Higgins I, Levett-Jones T. A game of snakes and ladders: negotiating the 'ups and downs' of endorsement as a nurse practitioner in Australia. Contemp Nurse. 2015;50(2–3):139–48. https://doi.org/10.1080/10376178.2015.1101351.
Maier CB. The role of governance in implementing task-shifting from physicians to nurses in advanced roles in Europe, U.S., Canada, New Zealand and Australia. Health Policy. 2015;119(12):1627–35. https://doi.org/10.1016/j.healthpol.2015.09.002. Epub 2015 Sep 25. Review. PMID: 26474745.
Maylor M. Differentiating between a consultant nurse and a clinical nurse specialist. Br J Nurs. 2005;14(8):463–8.
McCaffrey-Boyle D. The clinical nurse specialist. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced nursing practice: an integrative approach. Philadelphia: W. B. Saunders; 1996. p. 299–336.
Melnyk BM, Gallagher-Ford L, Long LE, Fineout-Overholt E. The establishment of evidence-based practice competencies for practicing registered nurses and advanced practice nurses in real-world clinical settings: proficiencies to improve healthcare quality, reliability, patient outcomes, and costs. Worldviews Evid-Based Nurs. 2014;11(1):5–15.
Mitchell T, Butler-Williams C, Easton K, et al. The consultant nurse—expert practitioner and much more. Br J Nurs. 2010;19(8):481–8.
National Association of Clinical Nurse Specialists (NACNS). Statement on clinical nurse specialist practice and education. Harrisburg, PA; 2004.
Oldenburger D, De Bortoli Cassiani SH, Bryant-Lukosius D, Valaitis RK, Baumann A, Pulcini J, Martin-Misener R. Implementation strategy for advanced practice nursing in primary health care in Latin America and the Caribbean. Rev Panam Salud Publica. 2017;41:e40.
Parker JM, Hill MN. A review of advanced practice nursing in the United States, Canada, Australia and Hong Kong Special Administrative Region (SAR), China Parkera JM, Hill MN. International Journal of Nursing Sciences. 2017;4:196e204.
Pearson GS. Consultation. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 203–24.
Randall S, Crawford T, Currie J, River J, Betihavas V. Impact of community based nurse-led clinics on patient outcomes, patient satisfaction, patient access and cost effectiveness: a systematic review. Int J

Nurs Stud. 2017;73:24–33. https://doi.org/10.1016/j.ijnurstu.2017.05.008.

RCN. Advanced nurse practitioners, an RCN guide to advanced nursing practice, advanced nurse practitioners and programme accreditation. 2010. www.rcn.org.uk.

Schober M. Introduction to advanced nursing practice: an international focus: Springer Nature; 2016.

Scott RA. A description of the roles, activities, and skills of clinical specialists in the United States. Clin Nurse Spec. 1999;13(4):183–90.

Sheer S, Wong FKY. The development of advanced nursing practice globally. J Nurs Scholarsh. 2008;40(3):204–11.

Sibbald B, Laurant MG, Reeves D. Advanced nurse roles in UK primary care. Med J Aust. 2006;185(1):10–2.

Sparacino PSA. The clinical nurse specialist. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced nursing practice: an integrative approach. 2nd ed. Philadelphia: W. B. Saunders; 2000. p. 381–405.

Sparacino PSA. The clinical nurse specialist. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced practice nursing: an integrative approach. 3rd ed. St Louis: Elsevier Saunders; 2005. p. 415–46.

Spross JA. Conceptualisations of advanced practice nursing. In: HAMRIC AB, Hanson CM, Tracy MF, O'Grady ET, editors. Advanced practice nursing: an integrative approach. 5th ed: Elsevier Health Sciences; 2014. p. 27–65.

Spross JA, Babine RL. Competence of advanced practice nursing: guidance and coaching. In: Hamric AB, Hanson CM, Tracy MF, O'Grady ET, editors. Advanced practice nursing: an integrative approach. 5th ed. St Louis: Elsevier Saunders; 2013.

Spross JA, Clarke EB, Beauregard J. Expert coaching and guidance. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced nursing practice: an integrative approach. 2nd ed. Philadelphia: W. B. Saunders; 2000. p. 299–336.

Squires SI, Boal AJ, Naismith GD. The financial impact of a nurse-led telemedicine service for inflammatory bowel disease in a large district general hospital. Frontline Gastroenterol. 2016;7(3):216–21. https://doi.org/10.1136/flgastro-2015-100630. Epub 2015 Oct 9. PMID: 28839858.

Squires A, White J, Sermeus W. Quantity, quality and relevance of the nursing workforce to patient outcomes ICN policy. 2018 accessed via: http://www.who.int/workforcealliance/knowledge/resources/ICN_PolBrief3QuantityQualityworkforcePatientOutcomes.pdf. Accessed 8 July 2018.

Swan M, Ferguson S, Chang A, Larson E, Smaldone A. Quality of primary care by advanced practice nurses: a systematic review. Int J Qual Health Care. 2015;27(5):396–404. https://doi.org/10.1093/intqhc/mzv054. Advance Access Publication Date: 3 August 2015.

Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14(5):301–16. https://doi.org/10.1038/nrendo.2018.18. Epub 2018 Mar 23. Review. PMID: 29569622.

The Center for International Economis (CIE). [www.theCIE.com.au] Final report. Responsive patient centred care: the economic value and potential of Nurse Practitioners in Australia. Canberra. 2013. http://www.acnp.membes3.com.au/public/25/files/CIE-2013-final_report_value_of_community_nps_0.pdf. Accessed 10 July 2018.

Tracy MF. Direct clinical practice. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 143–79.

Tracy MF, Sendelbach S. The clinical nurse specialist. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 343–73.

UN Sustainable Development Goals. 17 goals to transform our world. 2018. https://www.un.org/sustainabledevelopment/. Accessed 8 July 2018.

United Nations General Assembly. Transforming our world: the 2030 agenda for sustainable development. 2015. www.un.org/ga/search/view_doc.asp?symbol=A/70/L.1&Lang=E

Vigersky RA, Fish L, Hogan P, Stewart A, Kutler S, Ladenson PW, McDermott M, Hupart KH. The clinical endocrinology workforce: current status and future projections of supply and demand. J Clin Endocrinol Metabol. 2014;99(9):3112–21. https://doi.org/10.1210/jc.2014-2257.

Vosit-Steller J, Morse AB. Consultation. In: Hamric AB, Hanson CM, Tracy MF, O'Grady ET, editors. Advanced practice nursing: an integrative approach. 5th ed: Elsevier Health Sciences; 2014. p. 213–36.

Vrijhoef HMJ, et al. Study of European Nurses in Diabetes. EDN. 2009;6(1):34–8.

Wade B, Moyer A. An evaluation of clinical nurse specialists: implications for education and the organisation of care. Sr Nurse. 1989;9(9):11–6.

Wallymahmed ME, Morgan C, Gill GV, Macfarlane IA. Nurse-led cardiovascular risk factor intervention leads to improvements in cardiovascular risk targets and glycaemic control in people with Type 1 diabetes when compared with routine diabetes clinic attendance. Diabet Med. 2011;28(3):373–9. https://doi.org/10.1111/j.1464-5491.2010.03224.x.

White J. World Health Organization Global Strategy on Human Resources for Health in the era of the post 2015 Sustainable Development Goals: Nursing's Essential Contribution. ICN Policy Brief Publication date: 2016. http://www.who.int/workforcealliance/knowledge/resources/ICN_PolicyBriefforNNAsNursingHRandSDGs.pdf. Accessed 8 July 2018.

Key Reading

1. Hamric AB, Spross JA. The clinical nurse specialist in theory and practice. 2nd ed. Philadelphia: WB Saunders; 1989.
2. Iglehart JK. Expanding the role of advanced nurse practitioners—risks and rewards. N Engl J Med. 2013;368:1935–41. https://doi.org/10.1056/NEJMhpr1301084.
3. Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, Shepherd L, Yeoh P. Society for Endocrinology competency framework for adult endocrine nursing: second edition. Endocr Connect. 2015;4:W1–W17.
4. Llahana S. A theoretical Framework for Clinical Specialist Nursing: an example from diabetes. Salisbury: Fivepin Publishing; 2005. www.books.google.co.uk/books?isbn=1903877369.
5. Tracy MF, O'Grady E. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018.

68 Role Development and Performance Facilitators in Advanced Practice Nursing

Sofia Llahana

Contents

68.1 **Introduction** 1305

68.2 **The Theoretical Framework for the APN Role Development and Performance** 1305

68.3 **Personal Characteristics** 1307
68.3.1 Educational Qualifications and Experience 1307
68.3.2 Personal Attributes 1307
68.3.3 Skills and Competencies 1308

68.4 **Context for Role Performance** 1309
68.4.1 Role Description 1309
68.4.2 Relationships with Generalist Nurses and Other Health Professionals 1309
68.4.3 Support from the Medical Profession 1310
68.4.4 Administrative Support 1310
68.4.5 Peer Support and Presence of Role Models 1310
68.4.6 Available Time and Material Resources 1310
68.4.7 Professional Autonomy and Accountability 1311

68.5 **Role Expectations** 1311
68.5.1 Role Stress and Role Strain 1311

68.6 **Role Development** 1313
68.6.1 Facilitators and Barriers to Role Development 1313
68.6.2 APN Role Development Process 1313

68.7 **Role Performance** 1316

68.8 **Conclusions** 1317

References 1317

Abstract

The advanced practice nurse (APN) has a multifaceted role which includes many competencies and core components. As we saw in the previous chapter, APNs work independently and are highly skilled senior nurses.

S. Llahana (✉)
School of Health Sciences, City, University of London, London, UK
e-mail: Sofia.Llahana@city.ac.uk

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_68

Their role however does not exist in isolation and it is important to understand factors that influence the role performance and development of the APN. This chapter will provide a general overview of the factors that influence role performance and development and will discuss the contextual and organisational factors salient to the APN role. The process of role development and strategies to facilitate this process will also be discussed based on a theoretical framework of developmental phases experienced by APNs throughout their career. The literature regarding the APN role is very broad and covers a wide area of various concepts, not all related to role performance. For these reasons, a theoretical framework derived from role theory and from the author's previous empirical work has been adopted to guide the discussion in this chapter. There is very limited literature on the role of endocrine nurses practising at an advanced level and this is either observational work or expert opinion statements such as the competence frameworks. Therefore, this chapter provides a comprehensive overview of the APN concepts in relation to role performance and development aiming to stimulate critical thinking and to generate research questions for empirical work related to advanced practice in endocrinology nursing.

Keywords

Advanced practice nursing · Role performance · Role development · Positive and negative developmental phases · Personal characteristics · Contextual factors · Clinical nurse specialist · Nurse practitioner

Abbreviations

APN	Advanced practice nursing
CNS	Clinical nurse specialist
NP	Nurse practitioner
CN	Consultant nurse
UK	United Kingdom
DSN	Diabetes specialist nurse

Key Terms

- **Advanced Practice Nurse:** a title to articulate professional role identity, clinical competencies and expertise.
- **Role Theory:** represents a collection of concepts and a variety of hypothetical formulations that predict how individuals perform in a given role, or under what circumstances certain types of behaviour can be expected.
- **Role development:** how role expectations are conveyed, and roles are learned in order to perform competently certain tasks or activities.
- **Role performance:** represents the result of the development process of an individual into a role. Role performance also indicates the behaviour of a person given a set of role expectations.
- **Role description:** a set of clear tasks and expectation performed by an individual in a specific role or job (otherwise known as job description).
- **Role stress:** is experienced by an individual when the social structure creates very difficult, conflicting, or impossible demands for them to meet within their set role description.

Key Points

- The APN role is influenced by expectations that APNs themselves and significant others hold for this role.
- Incompatible role expectations lead to role stress and role strain.
- Role theory provides a useful theoretical framework to explain and guide the multifaceted APN role development and performance.
- APNs experience positive and negative developmental phases during their career and this can be influenced by personal and/or contextual factors.
- Prolonged exposure to negative phases and role stress should be avoided, although short exposure to role stress can act as a motivating factor for role development and change.

68.1 Introduction

Role performance and development of the advanced practice nurse (APN) does not exist in isolation, but it is influenced either positively or negatively by many factors and expectations. The utilisation of a theoretical (conceptual) framework in understanding the role of the APN is of vast importance. According to Brink and Wood (1994), a theoretical framework is simply an explanation, based on the available literature, of how and why different concepts are expected to relate to each other.

Llahana (2005) devised a theoretical framework underpinning the role performance and development of the APN based on concepts from the field of role theory and following empirical testing in a national study involving 653 APNs working in diabetes in the UK. According to Conway (1988a):

> '…role theory represents a collection of concepts and a variety of hypothetical formulations that predict how actors will perform in a given role, or under what circumstances certain types of behaviour can be expected' (p. 63).

The exploration of the term *role* in relation to nurses' activities has constituted a significant part of the nursing literature since 1970s, although the empirical exploration of this role has focused only on partial aspects of it (Georgopoulos and Christman 1970; Robichaud and Hamric 1986; Tarsitano et al. 1986; Hamric and Spross 1989; Aikin et al. 1993; Nuccio et al. 1993; McGee and Castledine 1999; Sparacino 2005).

Role theory concepts can be related to health professions and in particular to nursing (Hardy and Conway 1988). Hence, it can be a useful theoretical framework in understanding the factors and aspects that influence the APN role development and performance. Biddle was one of the earliest role theorists who conceptualised *role* and determined that '…the role concept centres upon behaviours that are characteristic of persons in a context' (p. 56) (Biddle 1979).

This chapter explores the role behaviour of APNs in their occupational context. Role theory, as defined by Biddle (1979), is concerned with the study of human behaviours and the factors that influence those behaviours.

The APN role is influenced by expectations that APNs themselves and significant others hold for this role.[1] Incompatible role expectations lead to role stress and role strain. Moreover, this role is determined by the APN socialisation into role; that is, the process in which APNs acquire the knowledge and skills to perform their role.

68.2 The Theoretical Framework for the APN Role Development and Performance

Based on the above assertions derived from the role theory field, Llahana (2005) developed a theoretical framework to understand and guide the role performance and development of APNs. It is suggested that the following concepts are significant in understanding the APN role:

Personal Factors (personal characteristics, attributes, and skills of the APN in relation to their role performance), Context (the organisational context in which the APN role performance takes place), Role Performance, Role Socialisation (development of role), Role Expectations, Role Stress, and Role Strain resulting from incompatibility of role expectations. Figure 68.1 depicts the construction of these concepts into a theoretical framework based on available literature and empirical evidence (Llahana 2005).

The concepts within this theoretical framework that derive from role theory disciplines and are applicable to the APN role as follows:

- Behaviours are patterned and characteristic of persons within contexts (Biddle 1979). Individuals and their behaviours are dominated and shaped by their social environment, but,

[1]The term APN in the chapter includes Clinical Nurse Specialist (CNS), Nurse Practitioner (NP) and Nurse Consultant (NC).

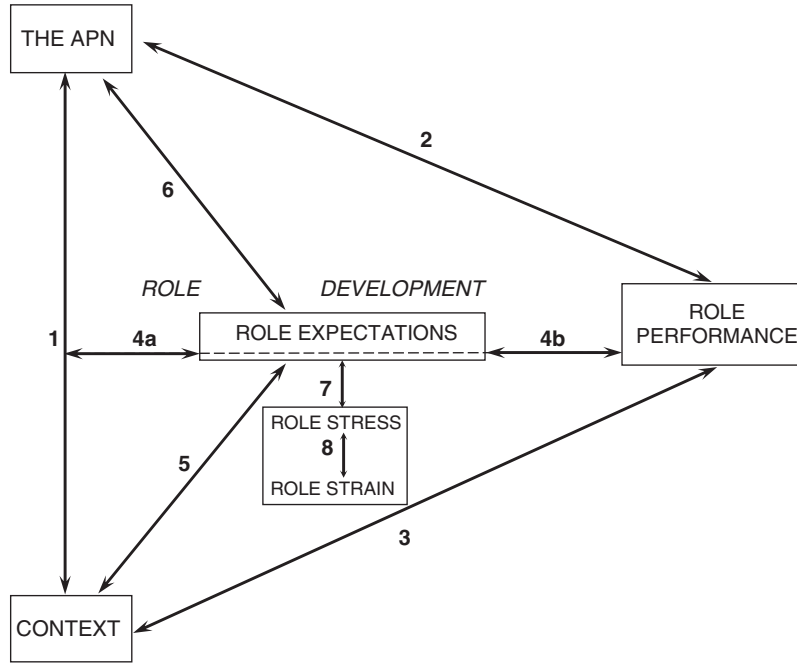


Fig. 68.1 Theoretical framework underpinning the role performance and development of the advanced practice nurse (from Llahana (2005); copyrights remain with the author)

under favourable conditions, they can change and mould social environment. [*Arrow 1*]

- Characteristics possessed by individuals such as attitude, appropriate experience, and specific training, result in effective and convincing role enactment (Sarbin and Allen 1968). The individuals' values, attitudes, motives, and beliefs influence their role performance within the social and organisational environment. Similarly, effective performance increases satisfaction and motivation to enact a particular role (Katz and Kahn 1978). [*Arrow 2*]
- The occupant's role performance is influenced by the context and the individuals who perform in this context. On the other hand, adequate role performance can shape the context in which role takes place in response to expectations for this role (Katz and Kahn 1978; Biddle 1979). [*Arrow 3*]
- The concept of socialisation relates to role development and explains how role expectations are conveyed and roles are learned (Biddle 1979). It is a continuous non-ending process by which individuals acquire the knowledge and skills to perform their roles adequately within society. The occupants' socialisation is influenced by a third-party standpoint (context) which indicates what role behaviour is expected from the occupant (Bandura 1977). [*Arrow, 1; Arrow, 4a-b*]
- Role expectations affect role performance, operate as imperatives pertaining to individuals' conduct and cognition while they enact their roles, and integrate individuals with the social structure. Occupants of interdependent positions hold role expectations for each other, and their expectations are determined to a considerable extent by the broader organisational context (Katz and Kahn 1978; Conway 1988b). [*Arrow 4b; Arrow 5; Arrow 6*]
- A condition of role stress is identified when role expectations held by the social structure (context) are incompatible with those of its role occupants and affect both parts. The occurrence of role stress results in impaired role performance (Hardy and Hardy 1988). [*Arrow 5; Arrow 6; Arrow 7; Arrow 4b*]
- The role occupant responds to the occurrence of role stress with role strain, which is the difficulty felt in meeting role requirements (Hardy and Hardy 1988). [*Arrow 8*]

The next six sections of this chapter present a detailed exploration of the concepts that compose the theoretical framework (Llahana 2005) and

their significance in relevance to the APN role performance and development.

68.3 Personal Characteristics

68.3.1 Educational Qualifications and Experience

According to Biddle (1979), roles are performed by persons, and the concept of role is confined to the behaviours of human beings. Therefore, the occupant's individual characteristics and personality shape to some extent their role performance. APNs differ in intelligence, temperament, and in the learning that they have acquired. Those differences can be reflected in their particular total behavioural repertoire. In addition, continuous and appropriate training will enhance the status of their roles, and as Biddle (1979) stated, '…not only will they [roles] be differentiated more clearly from other roles, but also their practitioners will come to be positionally designated and differentiated from others' (p. 70).

It has been recognised that initial professional education is not enough to correspond to today's complex, expanded, and advanced practice nursing activities. Meeting the needs of patients and their families demands that APNs adopt multifaceted roles which require further professional education and training (Llahana 2005). However, according to the International Council of Nurses (2008) specific practice requirements are rare, and a wide diversity in APN qualifications exists not only between different countries but also within countries. While in the USA as early as the 1980s, a master's degree level or its equivalent was recommended for APN practice (American Nurses Association 1984), in the UK the entry requirements are still vague and vary from practice to practice.

Great emphasis has been placed in recent years, especially in North America, on the doctoral preparation of APNs and the continuation of their involvement in clinical practice. A study of 20 doctorally prepared APNs demonstrated that their active involvement in clinical practice had a great impact on patient outcomes, promoting cost-effective practice and the use of clinical research (Sterling and McNally 1999).

Graduate programmes for APN preparation, although they may be divided into specific specialities, should address the common key components of theory content, clinical practice, and research. They should prepare the APN '…to think critically and abstractly, to assess care situations at an advanced level, and to use and integrate research into clinical practice' (Sparacino 2005: 419). During the postgraduate educational programmes, APNs learn to practise the integration of expert clinical judgement, management, education, and consultation skills within their role (Sparacino 2005). The graduate education provides the APN with the academic preparation and sets the scientific foundations of role components. Development of expert skills in all aspects of the role must come with experience in the practice setting following graduation.

The longer the experience in a role, the more adequately the role is performed. According to Benner (1984), clinical expertise is highly influenced by experience with similar patient populations. Expert nurses, such as APNs, with an enormous background of experience, have an intuitive grasp of each situation. They no longer rely on analytic principles (rules, guidelines, maxims) to connect their understanding of the situation to an appropriate action. Expert nurses utilise analytic problem-solving methods only when faced with a new situation or when the initial grasp of the problem proves to be incorrect. The nurse who has not seen a range of deviations from normal, although having the theoretical knowledge of the condition, has difficulties in recognising them and in teaching the patient what to expect (Llahana 2005).

68.3.2 Personal Attributes

The recommended education for a nurse to enter advanced practice is at master's level, but it can be argued that qualities of the individual are as important as qualifications in becoming an expert practitioner. Patterson and Haddad (1992) referred to attributes and characteristics which identify an advanced practitioner. These include: risk taking (trying out new ideas), vision (utilising and evaluating nursing research to guide

patient care), flexibility, articulateness (articulating and disseminating nursing knowledge by formal and informal methods), inquiring mind (participating in nursing research) self-confidence, and leadership skills (demonstrating the use of theory-based practice to other nurses).

In a study by Hamric and Taylor (1989), CNS reported that their personal attributes and skills played a significant part in the successful development and implementation of their role. These included clinical competence, self-confidence, sense of humour, motivation, flexibility, interpersonal skills, and 'a stubborn streak that would not allow failure' (p. 69). Moreover, Davis (1994) asserted that APNs should be able to practise independently and to function autonomously in order to achieve an integrated implementation of their role.

68.3.3 Skills and Competencies

Competence in practice is based on set standards, using the identified criteria of professional competency. Therefore, an agreed set of competencies needs to be developed that relates qualifications and individuals' ability to perform tasks at a given level. Confusion exists about the concept of competence, as it involves not only behaviour which can be measured, but also attributes such as attitudes, values, judgmental abilities, and personal dispositions, which present great difficulties in their evaluation. A capable practitioner, therefore, is someone who is able to draw on a broad repertoire of skills and knowledge, in different ways and in different contexts, and to perform in a way that is recognised as competent (Lillyman 1998).

Masterson and Mitchell (2003) presented three types of competence models:

- Personal competence models
- Educational competence models
- Performance outcome models

Each model has different purpose but can be used in combination to enhance the APN role performance. The personal competence models focus on individuals' personal qualities, skills, motives, and aspirations that are thought to have a direct impact on role performance. Educational competence models focus on what it is that an individual needs to know and be able to do by the end of the learning period. Finally, performance outcome models focus on the standards and criteria that the individual undertaking a particular role is expected to achieve.

The list of competencies suggested as necessary for APNs is very broad and described in detail in Chap. 67. Competence frameworks have also been developed to guide the role of the endocrine nurses caring for children and adults with endocrine disorders (Kieffer et al. 2015; Casey et al. 2013).

Other characteristics of APNs that lead to success are perseverance in their efforts to effect change by acknowledging the fact that immediate change should not be expected. They should also be able to tolerate any ambiguities or constraints of the system. Critical thinking and analysis, clinical judgement, decision-making ability, problem-solving skills, and communication and collaboration skills are also essential for advanced nursing practice (Davies and Hughes 1995). Furthermore, the ability to institute and effect change in order to improve patient care, particularly through utilising research findings, is a key component of the APN (Llahana 2005). Negotiation skill is probably the most essential dimension of organisational issues reflecting the APN's ability to facilitate and effect change. Change does not only occur at a slow pace, but can also be expensive, something which is not always attractive to management. Therefore, it is essential that APNs can provide evidence for the benefits of this change and be skilled in negotiating for its implementation (Llahana 2005).

Individuals' personal beliefs and motivation for roles are also believed to be related to the adequacy of their role performance. The same role can be perceived and experienced differently by different people, depending on how they perceive and what they expect from their role. Highly motivated individual workers produce collectively a high output for the organisation (Conway 1988b).

68.4 Context for Role Performance

Context is defined as '…any condition or state of affairs that affects behaviour' (Biddle 1979: 52). The organisational context determines to a considerable extent the role expectations held by its members, and, consequently, the role performance of APNs. In terms of expectations, in a particular setting, the role behaviour of role occupants is influenced by the expectations of others for the role. APNs work in a multidisciplinary team and with many other teams in hospital and community settings. Their role performance is, therefore, influenced by the expectations of other members of the team (Llahana 2005). An APN performs different roles in different contextual settings. For instance, when she provides education, she acts as an educator; when undertaking research, she acts as a researcher; in her personal life she might be a wife and mother.

Benner's (1984) model suggests that a practitioner can perform at an expert level in a clinical situation, given innate ability and adequate educational preparation, only when he or she (1) is highly experienced; (2) is motivated to perform well; and (3) has the available resources facilitating that situation. Should these conditions be different, the same nurse will perform at various levels of competence. More specifically, APNs, whether experienced or new to the position, have unclear ideas when entering the role and several factors discussed below affect their role development and performance.

68.4.1 Role Description

The role (job) description of APNs influences their role performance. According to Sparacino and Cooper (1990), a well-written, concise, clear and easily understood role description has the potential to increase staff and colleagues' understanding of the APN role. A generic role description should address the basic components of the role and be consistent with the philosophy of the department of nursing regarding patients' needs, institutional goals, and nursing practice. In addition, it should be specific to a defined area of specialisation and state what services APNs provide in that setting. However, although a generic job description is essential in providing guidance for role implementation, it should also allow APNs to be flexible in their role performance. Priorities should be set based on the APN attributes and the institutional and patients' immediate needs (Llahana 2005).

A clearly documented role description which is distributed to the nursing staff, administration and others facilitates the best use of the APN services (they know what type of assistance to seek from APNs and when to ask for it) and justifies the cost of their services. Vague and inexplicit role description results in incongruity in role expectations imposed on the APN from different sources within the organisation, and role conflict and ambiguity.

68.4.2 Relationships with Generalist Nurses and Other Health Professionals

Inter/intra-professional relationships also influence the role performance of the APN. Factors such as staff resistance to change, apathy, and nurses unaccustomed to consulting other nurses have been reported as barriers to the APN role implementation (Hamric and Taylor 1989). Other factors acting as barriers have been reported, such as conflicts with physicians, team members, and other health professionals. Support has been considered as one of the basic facilitators of the APN role.

The types of relationship that APN develop with general staff nurses influence their role performance either to a positive or negative extent. The fact that APNs are often in charge of evaluating patient care through clinical research and quality assurance studies sets them up as judges of the care provided. Staff nurses then may view them as a threat rather than a help, and act as an obstacle to the APN role implementation (Bousfield 1997). Therefore, a better understanding of the APN role enhances cooperation between staff nurses and APNs.

It has also been contended that APNs can deskill other nurses if they do not apply their skills and knowledge appropriately. This may create a situation in which APNs make all deci-

sions regarding a specialised and complex area of patient care. On the other hand, general nurses may be tempted to abdicate their responsibility and leave everything to APNs, and subsequently not expand their knowledge and practice (Wade and Moyer 1989; Richmond 2004).

68.4.3 Support from the Medical Profession

Gaining support from medical staff is important if the role of the APN is to survive. Traditionally, medicine has had a monopoly over other professions within the health care field. Physicians have often yearned for nurses to be their assistants and may have been upset with the autonomous route that specialist and advanced practice nursing has been taking. On the other hand, APNs are not always clear about their roles and may allow the system to misuse their abilities and skills (Castledine 1995). They are then in danger of being called or treated as medical assistants. When physicians are helped to realise that the APN role is firmly rooted in nursing and they do not wish to be seen as a new generation within the medical profession, their support will be secured. In this way, the contribution of the APN will benefit the quality of care delivered to the patient population (Bousfield 1997).

68.4.4 Administrative Support

Administrative support is essential to the adequate role performance of the APN. The APN who has administrative support can accomplish more in a shorter period of time than the one who lacks this support. This support takes many forms, such as seeking the input of APNs in administrative decision-making and in future plans, recognising their accomplishments, providing guidance, allowing autonomy and flexibility in role development and performance, and giving APNs authority in the practice setting (Hamric and Taylor 1989).

68.4.5 Peer Support and Presence of Role Models

The presence of peer support and role models is considered vital in the facilitation of the APN role performance. The opportunity to share ideas, having someone with whom to compare and contrast various methods of practice, as well as collaboration in research and writing can increase the effectiveness in creating and implementing new ideas. The distinct nature of the role makes it difficult for the APN to find someone other than another CNS to understand the problems and concerns fully and offer support, advice, and practical solutions (Hamric and Taylor 1989). Having a mentor in the institutional setting, 'someone to help you learn hospital policies and the informal power source in the system' (McFadden and Miller 1994: 31), has been cited as an essential facilitator of the APN role performance. Support by team colleagues, clinical supervision, and clinical support were some of the basic facilitators to role development identified by CNSs in the study by Newton and Waters (2001). Other supportive factors mentioned by these respondents were management support, developmental opportunities and sabbaticals, and good balance between work and home.

68.4.6 Available Time and Material Resources

Bousfield (1997) reported that CNSs often lacked structure and direction on how to manage time and justify their role activities. Moreover, the varying expectations placed upon CNSs by the organisation, medical staff, and themselves were frequently incompatible with their available time and, therefore, inhibited their role performance. Attempts to perform all the required activities at the same time often result in none of them being thoroughly and/or adequately accomplished. Therefore, it is important that realistic expectations and time-frames are agreed to assist in the accomplishment of goals and objectives.

Patient caseload was described by APNs as a 'constant stream of referrals' in a study by Newton and Waters (2001) and was made worse

by other factors such as staff shortages, poor communication with other health professionals, insecurity arising from organisational changes, lack of management support, and understanding of role. Opportunities for continuing education and services provided by professional organisations, such as position statements and standards development, can be useful.

68.4.7 Professional Autonomy and Accountability

Professional autonomy is essential in the development of the APN role and the improvement of patient care. Autonomy refers to '…the capability of existing independently, the freedom to design a total plan of care, and the opportunity to interact on an interdependent level with other professionals' (O'Rourke 1989: 130). In order for CNSs to be autonomous, accountable, and responsible, not only do they need to be skilful and competent, but they also need the authority to act or refuse to undertake any activities in each individual case (Llahana 2005).

68.5 Role Expectations

Roles never exist in isolation. The role occupants and those around them have notions about what behavioural patterns should be. Katz and Kahn (1978) viewed role expectations being determined to a considerable extent by the broader organisational context. The role expectation of a nurse is shaped by the technology of the organisation, its organisational structure, its formal policies, and its rewards and punishments. Role expectations act as evaluative standards applied to a position.

The standards of care expected from the APN are those of the competent nurse undertaking those roles. Protocols and competence frameworks can provide documentary evidence of the agreement between employer and APN (expectations of the two groups) and define roles and responsibilities. The Competence Framework for Adult Endocrinology Nurses provides an agreed framework of the areas of practice and career progression from novice to expert (Kieffer et al. 2015).

68.5.1 Role Stress and Role Strain

According to Hardy and Hardy (1988), 'when a social structure creates very difficult, conflicting, or impossible demands for occupants of positions within it, the general condition can be identified as one of role stress' (p. 159). Role stress is mainly external to the occupant and can result from interpersonal or intrapersonal sources, the location of the role in the social structure, the inadequate resources of role occupants, and the social context.

Role stress may generate role strain, which is defined as the difficulty felt in meeting one's role obligations. Role stress differs from role strain in that it refers to conditions generated from impossible, contradictory, incompatible, or excessive role expectations, while role strain refers to the incumbent's reaction to those conditions (Hardy and Hardy 1988). Therefore, role stress is a prerequisite for role strain, and they hold a linear relationship: the greater the number of stressors individuals are exposed to, the greater the role strain they experience.

Prolonged role strain places considerable burden on the person. As Hardy and Hardy (1988) suggested, if uncorrected, it may have various psychological and physiological consequences on the role occupant, such as anxiety, tension, irritation, resentment, and depression.

In health professions, including the APNs, role strain not only leads to reduced quality of care, but may even jeopardise lives. Moreover, health care workers may be drained of both energy and commitment to professional values and patient care.

It is important that role strain should not be tolerated for too long and occupants should undertake actions to deal with it. They may restructure expectations for their role, develop strategies to cope with the difficulties in overcoming role strain, or decrease the level of involvement by keeping role distance, although the latter may have detrimental effect to role performance (Llahana 2005).

Hardy and Hardy (1988) identify seven classes in the typology of role stress and define each of them as follows:

1. 'Role ambiguity—vagueness, lack of clarity of role expectations
2. Role conflict—role expectations are incompatible
3. Role incongruity—self-identity and subjective values are grossly incompatible with role expectations (role transition and poor self-role fit)
4. Role overload—too much expected in time available
5. Role underload—role expectations are minimal and underutilise abilities of role occupant
6. Role overqualification—role occupant's motivation, skills, and knowledge far exceed those required
7. Role underqualification (role incompetence)—role occupant lacks the necessary resources (commitment, skill, knowledge)' (p. 162).

From the above definitions, it can be seen that all types of role stress are directly associated with role expectations, although they originate from various sources. When role expectations are congruent with the occupants' perceptions and preferences, role stress is minimal or absent. The literature reveals that the most prevalent types of role stress regarding the role of the APN are those of role conflict, role ambiguity, and role overload (Llahana 2005).

68.5.1.1 Role Conflict

Role conflict, which Biddle (1986) defined as '… the concurrent appearance of two or more incompatible expectations for the behaviour of a person' (p. 82), is often present within the APN role. This is especially apparent due to the multifaceted role and many competencies APNs are expected to perform. For example, members of the multidisciplinary team and the clinical manager may expect the APN in endocrinology to organise educational sessions for patients with adrenal insufficiency and to run daily nurse-led clinics and, at the same time the chief nurse expects her to undertake research activities and projects as part of her job description. Being unable to conform to both expectations simultaneously, the APN is caught in a role conflict.

68.5.1.2 Role Ambiguity

Role ambiguity is one of the biggest challenges for APNs as it occurs when there is a lack of clarity of role expectations. When little information is available on expected performance or the normative expectations for the role are vague, ill defined, or unclear, the APN as the role occupant may experience role strain (Hardy and Hardy 1988).

Loudermilk (1990) identified the following sources of role ambiguity for APNs: inadequate development to the role, conflicting role expectations of administrators and staff, inconsistent job descriptions, poorly defined job qualifications, multiple accountability, inconsistent position within the bureaucratic framework, and unclear criteria for evaluation.

Role ambiguity, like role conflict, although detrimental to the incumbent's role performance when prolonged, provides the opportunity for creativity within the role and in role making. There has been great progress in the past two decades regarding clarification, structure, and continuous definition of the role of the APN (Bryant-Lukosius and Martin-Misener 2016; Hamric and Tracy 2018; ICN 2018) (please refer to Chap. 67 for more detail).

68.5.1.3 Role Overload

Role overload occurs when role expectations of equal importance are excessive relative to the time available. Although able to perform each of the role obligations competently, the role occupant is unable to complete all of them within given time limits. The occupant experiences role strain due to difficulties in deciding which expectations to comply with and which to hold off (Hardy and Hardy 1988). Evidence exists that the increased workload of APNs results in inadequate performance of all the activities and sub-roles that are expected of them. The sub-roles that are more frequently affected are those of education and research (Johns 1997; Crowley 2000; Llahana et al. 2001).

68.6 Role Development

68.6.1 Facilitators and Barriers to Role Development

According to Biddle (1979), most role theorists use the concept of *socialisation* to explain the appearance and development of roles. This is how role expectations are conveyed and roles are learned, for example how the role development takes place throughout an APN's career progression. Such roles require persons to incorporate new knowledge, alter their behaviour, and change their definition of self within the social context. Several factors already discussed can influence role development in a positive or negative way. Tables 68.1 and 68.2 present the ten most frequently reported barriers and facilitators to role development as identified by diabetes specialist nurses in a UK national study (Llahana 2005).

68.6.2 APN Role Development Process

The role development of the APN (referring mainly to the CNS role) has been discussed in a number of articles since the 1970s. A model of clinical skill acquisition broadly discussed in nursing in the past three decades has been that of Benner (1984), who described five levels of evolving expertise: novice, advanced beginner, competent, proficient, and expert. This model has been adopted by the UK competence framework for adult endocrinology nurses as a guidance on career progression through different stages of competence (Kieffer et al. 2015).

Besides the skill acquisition process, another approach to understanding CNS role development has focused on the CNS's experiences and feelings engendered as competence and confidence in practice are developed. Hamric

Table 68.1 Factors facilitating role development and the frequency of their citation by respondents ($N = 334$) (from Llahana 2005)

No.	Facilitating factors to role development of the DSN	Number of responses	
		Frequency	Percent
1	Peer support and networking with other DSNs	90	*26.9*
2	Supportive and encouraging health care team	38	*11.4*
3	Personal characteristics and attributes	35	*10.5*
4	Support for role by management/administration	31	*9.3*
5	Length of experience in the DSN post	30	*9.0*
6	Support and recognition of DSN role by medical staff	23	*6.9*
7	Flexibility and autonomy in role performance	23	*6.9*
8	Education/training related to diabetes care	15	*4.5*
9	Regular updates and ongoing education	13	*3.9*
10	Having a mentor/role model	12	*3.6*

Key: *DSN* diabetes specialist nurse

Table 68.2 Barriers to role development and the frequency of their citation by respondents ($N = 334$) (from Llahana 2005)

No.	Barriers to role development of the DSN	No. of responses	
		Frequency	Percent
1	Time pressures due to staff shortages and heavy workload	77	*23.1*
2	Lack of or constraints on resources/financial restrictions	73	*21.9*
3	Lack of support by management/administration	59	*17.7*
4	Lack of understanding of DSN role by management/health staff	38	*11.4*
5	Lack of role models and/or working alone with no peer support	14	*4.2*
6	Restraints on DSN role deriving from medical staff	14	*4.2*
7	Negative attitudes of other health professionals	13	*3.9*
8	Personal characteristics	12	*3.6*
9	Politics within the institution and organisational structure	12	*3.6*
10	Funding or time constraints for further formal education	10	*3.0*

Key: *DSN* diabetes specialist nurse

Table 68.3 Development phases based on role experiences [adapted from Hamric and Taylor (1989), Llahana (2005), and Llahana and Hamric (2011)]

Developmental phase	Description and characteristics of each developmental phase
Orientation phase	Enthusiasm, optimism, eager to prove self to setting Anxious about ability to meet self- and institutional expectations Expects to make change
Transition phase	Self-confidence, assurance, competence, and advanced level of practice Anxiety relate to new work setting rather than role knowledge base Enthusiasm, excitement, and eagerness in bringing about improvement in new area of practice when moving within the same speciality
Frustration phase	Discouragement and questioning as a result of unrealistic expectations (either self or employer); difficult and slow-paced change; resistance encountered Feelings of inadequacy in response to the overwhelming problems encountered, pressure to prove worth
Implementation phase	Returning optimism and enthusiasm as positive feedback received and expectations realigned Reorganisation of role activities is modified in response to feedback Implementing and balancing new sub-roles Regaining sense of perspective May focus on specific project(s)
Integration phase	Self-confident and assured in role Rated self at advanced level of practice Activities reflect wide recognition, influence in area of speciality Continuously feels challenged; takes on new projects; expands practice Either moderately or very satisfied with present position Congruence between personal and organisational goals and expectations
Frozen phase	Self-confident, assured in role Rated self at intermediate or advanced practice level Experiencing anger/frustration reflecting experience Conflict between self-goals and those of organisation/supervisor Report sense of being unable to move forward due to forces outside of self
Reorganisation phase	Reported earlier experiences that represent integration Organisation experiencing major changes Pressure to change role in ways that are incongruent with own concept of CNS role and/or self-goals
Complacent phase	Experiences self in role as settled and comfortable Variable job satisfaction Questionable impact on organisation

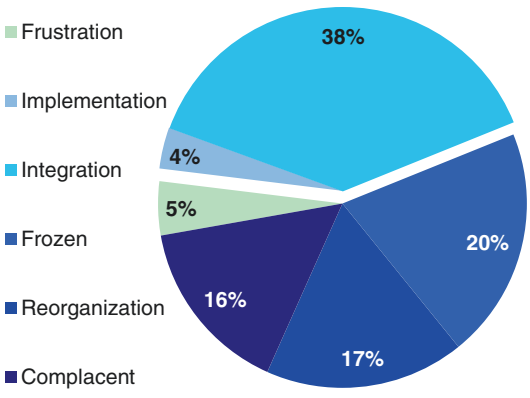


Fig. 68.2 The role developmental phase which respondents were experiencing at the time of the study ($N = 334$) (Llahana 2005; copyrights remain with the author)

and Taylor's (1989) CNS role development framework includes seven phases: Orientation, Frustration, Implementation, Integration, Frozen, Reorganisation, and Complacent. Further refinement of this model was undertaken in a national study involving 334 diabetes specialist nurses; an additional phase of transition emerged for experienced nurses moving to a different setting (Llahana 2005; Llahana and Hamric 2011). A description of the phases is presented in Table 68.3 and discussed below. Figure 68.2 presents the phase that respondents were experiencing at the time of the study.

68.6.2.1 Orientation and Transition Phases

According to Hamric and Taylor (1989), the orientation phase presents the first natural developmental step in learning a new role. It reflects the time required by APNs to become familiar with the role and the employing organisation. Llahana and Hamric (2011) in a national study of diabetes specialist nurses (DSNs) found that this phase was characterised as transition phase by respondents holding either a second, third, or fourth DSN post. This was a typical phase for experienced respondents moving into a new APN post or changing work setting within the same post.

A structured orientation plan should be organised for newly employed CNSs whether they are neophytes or experienced. It should be appropriately designed to inform the CNS not only about the role itself, but also about the organisational structure, philosophy, and policies (Hamric and Taylor 1989; Brykczynski 2009).

Bamford and Gibson (2000) identified four areas which can prepare CNSs for their role:

> 'a pre-existing educational pathway, a training post for the future CNS [APN] role, a team member to act as a role model, and a tailor-made orientation programme' (p. 286).

The first year of the CNS practice is crucial in establishing their credibility and laying the foundation for future development. Many neophyte CNSs have often the feeling that they should be 'everywhere at once' and 'all things to all people' (Llahana 2005). However, as Cameron (1994) points out, giving in to this urge could render the APN a physical wreck at best and a dabbler at worst. Therefore, it is particularly crucial to provide the neophyte CNS with help in setting limits and realistic self-expectations, in understanding how to cope with problem situations, and in maintaining a sense of perspective. The novice CNS who is taught how to work within an organisation and learns whom to consult for advice and guidance can then begin to develop a network for advancement and learning (Beecroft 2001).

During orientation phase, novice CNSs should devote the major portion of their time to direct-care activities to substantiate their role as expert practitioners. This will provide them with the competence and confidence to combine gradually other components within their practice (Llahana 2005). There is a general agreement that the CNS should attend graduate education before entering the role. The purpose of this education, as Hamric and Taylor (1989) state, should aim to prepare graduate students for the realities of the CNS role and for the possible slowness of movement through developmental phases, especially in the first year.

68.6.2.2 Positive Phases: Implementation and Integration

Implementation and integration phases have been characterised by Hamric and Taylor (1989) as positive resolution of the CNS role development. Most participants in the Llahana and Hamric (2011) study attributed the occurrence of positive phases to the opportunity to undertake new projects and introduce improvement in their area of practice. This was also attributed to further academic education and research involvement by many respondents.

During the integration phase, as the CNS has gained positive feedback and recognition relating to the effectiveness of the role, more time can be devoted to areas of scholarly interest (Llahana 2005). It is important for the CNS in this phase to have a plan to guide continued role expansion and refinement over time. Long-term projects and objectives should be organised and implemented. Hamric and Taylor (1989) suggest that the integrated CNS should be involved widely in research, writing, and other outside professional activities and act as preceptor for graduate students. Seeking appointment to key committees and taking part in the strategic decision-making process are also important in broadening the organisational impact of the CNS. Peer support was also seen as a significant facilitator of role development. The main factors, however, as contributing to the experience of implementation and integration phases came from work setting and included support, recognition, and positive feedback from management, health professionals and patients/carers (Hamric and Taylor 1989; Llahana and Hamric 2011).

68.6.2.3 Negative Phases: Frustration, Frozen, Reorganisation, and Complacent

Unlike implementation and integration, these phases share a negative and non-productive character in relation to role development (Brykczynski 2009). The prevailing factor was identified as incongruence of role expectations between respondents and other parties within their work setting, i.e. management, supervisors, health professionals, and patients/carers (Llahana and Hamric 2011).

A certain degree of role stress is inevitable in organisations and, in the short term, can often be a motivating factor for moving into positive phases. However, if uncorrected over a long-term period, role stress may be detrimental not only for CNSs but also for individuals with whom they work (Llahana 2005). The CNS, therefore, should engage in periodic self-assessment to recognise early signs of characteristics associated with these phases and take proactive steps to deal with the negative feelings (Brykczynski 2009). This is even more important during frustration phase, as CNSs have not reached an advanced level of practice and have not yet developed 'self-defence' role strategies. Neophyte CNSs are particularly vulnerable to negative role experiences and need trusted and helpful mentors/managers. Initiation of honest discussion is an important strategy in clarifying problematic role issues before they become serious (Hamric and Taylor 1989; Brykczynski 2009).

Novice CNSs can focus on short-term objectives that can be successfully implemented and provide evidence that staff and patients can benefit from their role. The resulting positive feedback and sense of achievement will increase their self-confidence and comfort within the role. Moreover, the development of good working relationships with team members and other health professionals, as well as establishment of self within the system, is essential in obtaining support and recognition.

Discussion and exchange of opinions with other CNSs who had similar experiences is helpful in relieving tension, as is having a confidant (Hamric and Taylor 1989; Brykczynski 2009). Monthly sessions for sharing concerns and planning future role objectives with a group of peers and supervisors/administrators facilitate movement through the negative phases.

Role ambiguity and lack of understanding of the role by other parties is also a contributing factor for negative phases (Llahana and Hamric 2011). This can result in lack of support, isolation, and controversial dynamics within the working environment. Bamford and Gibson (2000) reported that although CNSs can describe the key components of their role, some cannot clearly explain their role to others. It is, therefore, apparent that role clarification should be a priority, if not the most important objective, in the process of role development of a CNS. If others do not understand the benefits of the role, they will not support and accept CNSs; rather they may try to marginalise their contributions or even eliminate the role (Bigbee and Amidi-Nouri 2000; Llahana 2005).

A strategy by which CNSs can achieve this objective is the dissemination of their role description to all health professionals with whom they work. This should be well-written and concise but long enough to state exactly who CNSs are and what they provide in that particular setting. Furthermore, graduate educational programmes need to prepare CNSs to have a clear understanding of their role and to have the ability to describe it to others (Hamric and Hanson 2003).

68.7 Role Performance

Role performance refers to the differentiated behaviour or action of an occupant relevant to a specific position within a context (Hardy and Hardy 1988). Role performance represents the result of the development process (socialisation) of an individual into a role. Role performance also indicates the behaviour of a person given a set of role expectations. As already discussed, role performance is influenced by expectations, personal characteristics, and contextual factors.

The performance in a particular role is also influenced by individual behavioural tendencies, which are primarily determined by their personal attributes. These attributes include personality characteristics, intelligence, ability, knowledge level, communication skills, interpersonal skills, motivation, and prior experiences. Individuals who lack these attributes relevant to the role will not perform it successfully, although their motivation to do so is very strong (Hardy and Hardy 1988).

The structure of the social setting (context) within which a role occurs influences the occupant's performance in the particular role. Contextual factors can be individual, interpersonal, and organisational. Understanding the nature of systems in health care organisations can help health professionals to cope more adequately with problems that may arise as they attempt to perform their role (Conway 1988b). The role of the CNS is multifaceted and consists of several role components, competencies, and activities. These are discussed in detail in Chap. 67.

Finally, role expectations and role prescriptions in nursing and health professions cannot be specified in detail, because these roles are dynamic and often require unpredictable activities or behaviours. As Benner (1984) explains, although making organisational rules explicit facilitates the co-ordination and implementation of procedures with some degree of quality control, a nurse must not, for instance, follow the written nursing care plan to the letter. If changes in the patient or environment condition occur, the care plan will need to be modified accordingly. This is especially crucial for the APN as they deal with highly complex patient cases and organisational situations (Llahana 2005). Therefore, an APN must acquire the skill of situational assessment and adjustment. Moreover, APNs need to adjust the performance of a specific role to the individuality of each person. To illustrate this within endocrinology nursing, let us consider education which is a common and vital competency for the endocrine APN. Although the performed role component is education, the APN uses different approaches when educating patients, carers, or health professionals, or even when educating patients with the same condition, as each of them differs in their cognitive and physical abilities.

68.8 Conclusions

This chapter discussed the process of role development and factors that influence role performance for APNs. Personal characteristics, contextual factors, and role developmental phases contribute to the success of the APN role. Positive developmental phases maximise the potential of the CNS role performance. On the other hand, although negative experiences during role development can often be unavoidable, it is evident that CNSs should not allow themselves, nor should management tolerate them, remaining and practising in these negative phases. CNSs and their employing institutions must give attention to facilitating positive developmental phases and removing barriers to CNS role implementation throughout the course of a CNS's employment. Further research needs to focus on the relationship between the developmental phases and CNS role performance. It should also examine the effectiveness of facilitators and strategies to enhancing role development and impede negative developmental phases. Open discussion should be initiated in order to find ways of overcoming the barriers which inhibit the successful role implementation.

References

Aikin JL, Taggart JR, Tripoli CA. Evaluation and time documentation for the clinical nurse specialist. Clin Nurse Spec. 1993;7(1):33–8.

American Nurses Association. Issues in professional nursing 2: specialisation in nursing practice. Kansas City: American Nurses Association; 1984.

Bamford O, Gibson F. The Clinical Nurse Specialist: perceptions of practicing CNSs of their role and development needs. JCN. 2000;9:282–92.

Bandura A. Social learning theory. Englewood Cliffs: Prentice-Hall, Inc.; 1977.

Beecroft PC. Mentors and mentoring: editorial. Clin Nurse Spec. 2001;15(3):89.

Benner P. From novice to expert: excellence and power in clinical nursing practice. Menlo Park: Addison-Wesley Publishing Company; 1984.

Biddle BJ. Role theory: expectations, identities and behaviours. New York: Academic; 1979.
Biddle BJ. Recent developments in role theory. Annu Rev Sociol. 1986;12:67–92.
Bigbee JL, Amidi-Nouri A. History and evolution of advanced nursing practice. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced nursing practice: an integrative approach. 2nd ed. Philadelphia: W. B. Saunders Company; 2000. p. 3–32.
Bousfield C. A phenomenological investigation into the role of the clinical nurse specialist. J Adv Nurs. 1997;25:245–56.
Brink PJ, Wood MJ. Basic steps in planning research: from question to proposal. 4th ed. Boston: Jones and Bartlett Publishers; 1994.
Bryant-Lukosius D, Martin-Misener R. Advanced practice nursing: an essential component of country level human resources for health. ICN Policy Brief. 2016. http://www.who.int/workforcealliance/knowledge/resources/ICN_PolicyBrief6AdvancedPracticeNursing.pdf. Accessed 8 July 2018.
Brykczynski KA. Role development of the advanced practice nurse. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced practice nursing: an integrative approach. 4th ed. St. Louis: Saunders Elsevier; 2009. p. 95–117.
Cameron F. Models of specialist practice. In: Humphris D, editor. The clinical nurse specialist: issues in practice. London: The Macmillan Press; 1994. p. 16–28.
Casey A, Davies K, Langham S, et al. Competences: an integrated career and competency framework for children's nurse endocrine specialists. London: Royal College of Nursing; 2013. https://www.rcn.org.uk/professional-development/publications/pub-003264.
Castledine G. Will the nurse practitioner be a mini doctor or a maxi nurse? Br J Nurs. 1995;4(16):938–9.
Conway ME. Theoretical approaches to the study of roles. In: Hardy ME, Conway ME, editors. Role theory: perspectives for health professionals. 2nd ed. Norwalk: Appleton & Lange; 1988a. p. 63–72.
Conway ME. Organisations, professional autonomy, and roles. In: Hardy ME, Conway ME, editors. Role theory: perspectives for health professionals. 2nd ed. Norwalk: Appleton & Lange; 1988b. p. 111–32.
Crowley M. Education for diabetes nurses: the challenge for the new millennium. J Diabetes Nurs. 2000;4(2):61–3.
Davies B, Hughes AM. Clarification of advanced nursing practice: characteristics and competencies. Clin Nurse Spec. 1995;9(3):156–160, 166.
Davis EA. Factors influencing the implementation of the CNS role in a private practice. Clin Nurse Spec. 1994;8(1):42–7.
Georgopoulos B, Christman L. The clinical nurse specialist: a role model. Am J Nurs. 1970;70(5):1030–9.
Hamric AB, Hanson CM. Educating advanced practice nurses for practice reality. J Prof Nurs. 2003;19(5):262–8.
Hamric AB, Spross JA. The clinical nurse specialist in theory and practice. 2nd ed. Philadelphia: W. B. Saunders Company; 1989.
Hamric AB, Taylor J. Role development of the CNS. In: Hamric AB, Spross JA, editors. The clinical nurse specialist in theory and practice. 2nd ed. Philadelphia: W. B. Saunders Company; 1989. p. 41–82.
Hamric AB, Tracy MF. A definition of advanced practice nursing. In: Tracy MF, O'Grady E, editors. Hamric & Hanson's advanced practice nursing: an integrative approach: Elsevier; 2018. p. 61–79.
Hardy ME, Conway ME. Role theory: perspectives for health professionals. 2nd ed. Norwalk: Appleton & Lange; 1988.
Hardy, M. E., Hardy, W. L. (1988). Role stress and role strain. In: Hardy, M. E., Conway, M. E. (Eds.). Role theory: perspectives for health professionals, 2nd edition (pp. 241–256). Norwalk: Appleton & Lange.
ICN—International Council of Nurses. ICN Policy Brief. Advanced practice nursing: an essential component of country level human resources for health. 2018. http://www.who.int/workforcealliance/knowledge/resources/ICN_PolicyBrief6AdvancedPracticeNursing.pdf. Accessed 4 July 2018.
International Council of Nurses. The scope of practice, standards and competencies of the advanced practice nurse. ICN Regulation Series. Geneva: ICN; 2008.
Johns P. Activity analysis on the workload of the diabetes specialist nurse. J Diabetes Nurs. 1997;1(2):50–3.
Katz D, Kahn R. The social psychology of organisation. 2nd ed. New York: Wiley; 1978.
Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, Shepherd L, Yeoh P. Competency framework for adult endocrine nursing: 2nd edition. Society for Endocrinology. Endocr Connect. 2015;4:W1–W17.
Lillyman S. Assessing competence. In: Castledine G, McGee P, editors. Advanced & specialist nursing practice. Oxford: Blackwell Science Ltd.; 1998. p. 119–31.
Llahana S. A theoretical Framework for Clinical Specialist Nursing: an example from diabetes. Salisbury: Fivepin Publishing; 2005. Complete book available on line at: www.books.google.co.uk/books?isbn=1903877369.
Llahana SV, Hamric AB. Developmental phases and factors influencing role development in diabetes specialist nurses: a UK study. Eur Diabetes Nurs. 2011;8(1):18–23.
Llahana SV, Coates VE, Poulton BC. Survey: role components, functions and activities of the DSN. J Diabetes Nurs. 2001;5(6):181–7.
Loudermilk L. Role ambiguity and the clinical nurse specialist. Nursingconnections. 1990;3(1):3–12.
Masterson A, Mitchell L. Developing competence for advanced practice. In: McGee P, Castledine G, editors. Advanced nursing practice. 2nd ed. Oxford: Blackwell Publishing Ltd; 2003. p. 31–46.
McFadden EA, Miller MA. Clinical nurse specialist practice: facilitators and barriers. Clin Nurse Spec. 1994;8(1):27–33.

McGee P, Castledine G. A survey of specialist and advanced nursing practice in the UK. Br J Nurs. 1999;8(16):1074–8.
Newton J, Waters V. Community palliative care clinical nurse specialists' descriptions of stress in their work. Int J Palliat Nurs. 2001;7(11):531–40.
Nuccio SA, Costa-Lieberthal KM, Gunta KE, Mackus ML, Riesch SK, Schmanski KM, Westen BA. A survey of 636 staff nurses: perceptions and factors influencing the CNS role. Clin Nurse Spec. 1993;7(3):122–8.
O'Rourke MW. Generic professional behaviours: implications for the clinical nurse specialist role. Clin Nurse Spec. 1989;3(3):128–32.
Patterson C, Haddad B. The advanced nurse practitioner: common attributes. Can J Nurs Adm. 1992;5(3):18–22.
Richmond J. General nurses' perceptions of the role of the clinical nurse specialist in Ireland. Cancer Nurs Pract. 2004;3(6):33–9.
Robichaud AM, Hamric AB. Time documentation of clinical nurse specialist activities. J Nurs Adm. 1986;16(1):31–6.
Sarbin T, Allen VL. Role theory. In: Lindsey G, Aronson E, editors. The handbook of social psychology. 2nd ed. Reading: Addison-Wesley; 1968. p. 488–568.
Sparacino PSA. The clinical nurse specialist. In: Hamric AB, Spross JA, Hanson CM, editors. Advanced practice nursing: an integrative approach. 3rd ed. St Louis: Elsevier Saunders Inc.; 2005. p. 415–46.
Sparacino PSA, Cooper DM. The role components. In: Sparacino PSA, Cooper DM, Minarik PA, editors. The clinical nurse specialist: implementation and impact. Norwalk: Appleton & Lange; 1990. p. 11–40.
Sterling YM, McNally JA. Clinical practice of doctorally prepared nurses. Clin Nurse Spec. 1999;13(6):296–302.
Tarsitano B, Brophy E, Snyder D. A demystification of the clinical nurse specialist's role. Perceptions of clinical nurse specialists and nurse administrators. J Nurs Educ. 1986;25(1):4–9.
Wade B, Moyer A. An evaluation of clinical nurse specialists: implications for education and the organisation of care. Sr Nurse. 1989;9(9):11–6.

Key Reading

1. Tracy MF, O'Grady E. Hamric & Hanson's advanced practice nursing: an integrative approach. St. Louis: Elsevier; 2018.
2. Llahana S. A theoretical framework for clinical specialist nursing: an example from diabetes. Salisbury: Fivepin Publishing; 2005. Complete book available on line at: www.books.google.co.uk/books? ISBN = 1903877369.
3. Hardy ME, Conway ME. Role theory: perspectives for health professionals. 2nd ed. Norwalk: Appleton & Lange; 1988.
4. Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, Shepherd L, Yeoh P. Competency framework for adult endocrine nursing: 2nd edition. Society for Endocrinology. Endocr Connect. 2015;4:W1–W17.
5. Llahana SV, Hamric AB. Developmental phases and factors influencing role development in diabetes specialist nurses: a UK study. Eur Diabetes Nurs. 2011;8(1):18–23.

Research and Evidence-Based Practice: The Nurse's Role

69

Lesley Baillie, Debbie Carrick-Sen, Anne Marland, and Margaret F. Keil

Contents

69.1 **Introduction** 1322

69.2 **Introducing Evidence-Based Practice and Research** 1323
69.2.1 Types of Evidence 1323
69.2.2 Types of Research Evidence 1324

69.3 **Process for Implementing Evidence-Based Practice** 1326

69.4 **Conducting Your Own Research** 1327
69.4.1 Independent Nursing Research: Pursuing a Clinical Academic Career 1328

69.5 **Clinical Research Nursing in Endocrinology** 1330
69.5.1 Paediatric Clinical Research Nurses and Clinical Research 1332
69.5.2 Challenges for Clinical Research Nurses and the Benefits 1333
69.5.3 Clinical Research Nurse Role: A Summary 1334

69.6 **Ethics in Research Conduct** 1334

69.7 **Conclusions** 1335
69.7.1 Resources 1335

References 1336

L. Baillie (✉)
Faculty of Wellbeing, Education and Language Studies School of Health, Wellbeing and Social Care Nursing, The Open University, Milton Keynes, UK
e-mail: lesley.baillie@open.ac.uk

D. Carrick-Sen
Florence Nightingale Foundation, School of Nursing, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
e-mail: D.Carrick-Sen@bham.ac.uk

A. Marland
Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
e-mail: Anne.Marland@ouh.nhs.uk

M. F. Keil
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA
e-mail: keilm@cc1.nichd.nih.gov

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_69

Abstract

This chapter introduces evidence-based practice and research, explaining the nurse's role in accessing and appraising evidence for endocrinology nursing practice. The contribution of different types of research studies to the evidence base is discussed. The chapter considers how best evidence can be implemented in practice, with reference to quality improvement methods. Nurses are in a good position to identify gaps in the available evidence and identify new research questions. Clinical academic roles provide the opportunity for nurses to take forward their research ideas and combine clinical nursing with research. Clinical research is essential for finding new treatments and improving patient care and so clinical research nurses make a vital contribution, focusing on the care of research participants within clinical research studies. All research must be conducted in accordance with international standards for research ethics and local processes for ethical scrutiny. This chapter's sections on evidence-based practice, clinical academic roles and clinical research nursing all include application to endocrinology nursing.

Keywords

Research · Evidence-based practice · Nursing
Clinical research nurse · Endocrinology
Quality improvement · Clinical academic role

Key Terms

- **Evidence:** available facts (expert opinion, literature) used to assess or validate a belief, proposition or action.
- **Evidence based practice:** the use of the best available evidence used in clinical decision-making and practice to achieve the best outcomes.
- **Research design:** describes the type of study and methodology used to answer a (clinical) question.
- **Quality assurance:** assessment of a practice against an established standard.
- **Research:** development of new knowledge.

Key Points

- Nurses need to be able to access and appraise evidence so that they can implement best evidence in practice and continually improve patient care.
- Quality improvement methods can be used to facilitate implementation of best evidence in practice.
- Nurses are in a good position to identify gaps in the available evidence and identify important new research questions.
- Nurses who are in a clinical academic role combine clinical nursing with research; these roles benefit patients, the individual nurse, the organisation and the profession.
- Clinical research nurses focus on the care of research participants within clinical research and act as an advocate to ensure patient understanding and protection.

69.1 Introduction

All nurses need to be able to access, appraise and implement best evidence for practice to ensure that patients receive best available care and that there are continuing improvements in care quality. However, there are areas of nursing practice where there is no conclusive evidence to underpin care. These gaps can inspire you to conduct research of your own, thus creating as well as using evidence. Nurses who aspire to combine clinical nursing with research can follow a clinical academic career pathway and eventually become research leaders in their field. Clinical research is essential for finding new treatments and improving patient care. Clinical research nurses often work within large, multisite research projects and thus make a vital contribution to extending the evidence base for healthcare.

This chapter first introduces evidence-based practice and research, considering how to access and implement evidence in practice. Clinical academic roles are then considered, with explanations about the benefits and the pathways available. The role of the clinical research nurse is then explained,

with reference to the skills required and competency frameworks. Finally the chapter considers the important area of ethics within research conduct. There are examples from endocrinology research and nursing practice throughout the chapter.

69.2 Introducing Evidence-Based Practice and Research

Nurses must deliver and promote care that is based on the best available evidence and so they need the ability to access and evaluate the available evidence, and to effectively implement best evidence in practice. One of the most well-known definitions of evidence-based practice came from Dr. David Sackett, the founder of the National Health Service (NHS) Research and Development Centre for Evidence Based Medicine in Oxford, England:

> '*the conscientious and judicious use of current best evidence in conjunction with clinical expertise and patient values to guide health care decisions*' (Sackett et al. 2000: 71–72)

This definition highlights that accessing best evidence is not enough; practitioners must also understand each individual patient's perspective and what matters to them, in combination with using their clinical expertise to make professional judgements. As well as applying best evidence in the care of individual patients, best evidence needs to be used when developing care guidelines, designing new services and improving care.

69.2.1 Types of Evidence

Evidence can be defined as 'the available body of facts or information indicating whether a belief or proposition is true or valid' (Oxford Living Dictionaries 2017). Evidence is produced in various ways through research, clinical audit and service evaluation/improvement. Although they all provide evidence, their purpose and method differs (see Box 69.1). All include the collection of data in a rigorous manner, which could be through measurements, questionnaires, observation or analysing documents such as healthcare records.

Box 69.1 The Purpose of Research, Audit and Service Evaluation (Adapted from Health Research Authority 2017)

Research: Attempts to derive generalisable new knowledge by addressing clearly defined questions with systematic and rigorous methods

Clinical Non-Financial Audit: Designed and conducted to produce information to inform delivery of best care

Service evaluation: Designed and conducted solely to define or judge current care: 'What standard does this service achieve?' Measures current service without reference to a standard

(Source: www.hra.nhs.uk)

Up-to-date textbooks produced by experts in the field are a helpful resource for you to access best evidence but there are many other resources available too: see Box 69.2 for examples. Endocrinology websites include information for the public and professionals and can be a useful medium to share evidence. In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) guidelines and standards and the Cochrane library systematic

Box 69.2 Sources for Best Evidence for Endocrinology: Some Examples

- American Diabetes Association: http://www.diabetes.org/
- Diabetes UK: https://www.diabetes.org.uk/
- The Pituitary Foundation website: http://www.pituitary.org.uk/
- The British Thyroid Society website: http://www.btf-thyroid.org/
- American Thyroid Association website: http://www.thyroid.org/
- The British National Formulary: https://www.bnf.org
- Endocrine Society : http://press.endocrine.org/journal/endo

- The National Institute for Health and Care Excellence (NICE) evidence-based guidelines and quality standards (see www.nice.org.uk)
- The NICE evidence search website: http://www.evidence.nhs.uk/
- The Cochrane Library: online resource that provides systematic reviews of research on different topics. http://www.cochranelibrary.com/
- Expert practitioners, e.g. pharmacists can advise on side effects of medication and drug interactions
- Journal papers identified through a literature search using keywords

reviews are regularly updated and will help you to access the most current available evidence. The NICE website has an intuitive search engine and is highly recommended. You can also conduct your own literature search for research articles, by using databases and then appraising the evidence you find in journal articles.

69.2.2 Types of Research Evidence

Table 69.1 presents examples of research designs, which have been used to investigate different research questions, and contribute to the evidence base for people with endocrinology disorders.

The quality of evidence is often presented as a hierarchy in a pyramid, with meta-analyses and systematic reviews of high-quality individual RCTs at the top, followed by individual high-quality RCTs, and then other types of individual studies (non-randomised trials, surveys, qualitative studies) further down, case reports and expert opinion presented at the bottom of the pyramid. As meta-analyses and systematic reviews are considered the highest level of evidence, these make a valuable contribution to evidence-based guidelines. Systematic reviews follow a precise methodology to ensure the review is rigorous enough to provide high-quality evidence. In Table 69.1, Attridge et al.'s (2014) study is an example of a systematic review. They identified 33 RCTs of sufficient quality for inclusion, of which 28 provided data that could be entered into a meta-analysis, leading to much more powerful evidence set than that provided by an individual study alone.

An RCT uses an experimental approach to determine the effectiveness of an intervention (e.g. a medicine or a method of giving patient information). Key features of an RCT are randomisation and having a control group. As an example, in Martínez-Momblán et al.'s (2016) study (see Table 69.1), patients were randomised, which means that each person taking part had an equal chance of being in the intervention group and receiving the educational programme, or being in the control group, who did not receive this intervention. The effects of the intervention (the educational programme) were studied through pre- and post-intervention questionnaires, which included measurements of health-related quality of life, clinical parameters, level of pain and physical activity, patterns of rest, and use of health resources. RCTs are set up to control as far as possible any other factors that might affect the results, so the sample included in an RCT must meet specific inclusion and exclusion criteria. Exclusion of individuals in order to achieve control has however led to certain groups of people being under-researched, which has ethical implications as well as affecting generalisability. For example, people with learning disabilities have often been excluded from drug trials, and people who have diabetes have often been excluded from trials of wound care products.

In nursing, the notion that systematic reviews and RCTs should always be at the top of the hierarchy of evidence has attracted some criticism, as nursing practice requires multiple ways of knowing (Barker 2013). There are also many nursing topics for which there is no conclusive evidence, based on systematic reviews of RCTs. Petticrew and Roberts (2003) argue instead for a matrix of evidence rather than a hierarchy, with types of research design rated according to the research question of interest. For example, if, as in Strong et al.'s (2014) study (see Table 69.1), the research question pertains to what knowledge practice nurses have about diabetes, then a survey is an appropriate study design as it will answer the question of interest. In contrast, an RCT would

Table 69.1 Examples of endocrinology studies using different research designs

Research design	Author and title	Summary of study design
Systematic review	Attridge et al. (2014) Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus	The objective was to assess the effectiveness of culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. They selected randomised controlled trials (RCTs) of culturally appropriate health education for people over 16 years of age with type 2 diabetes mellitus from named ethnic minority groups residing in upper-middle-income or high-income countries. The review included 33 trials involving 7453 participants. 28 trials provided suitable data for entry into meta-analysis
Randomised controlled trial	Martínez-Momblán et al. (2016) A specific nursing educational program in patients with Cushing's syndrome	The study aim was to assess the effectiveness of an educational nursing programme in patients with Cushing's syndrome, on health-related quality of life, clinical parameters, level of pain and physical activity, patterns of rest, and use of health resources. In a randomised controlled trial, 61 patients were divided into 2 groups: an 'intervention' group where educational sessions were performed over 9 months and a 'control' group, without these sessions. Specific questionnaires were used at the beginning and end of the study, with results statistically compared
Controlled trial without randomisation	Follin et al. (2010) Cardiovascular Risk, Cardiac Function, Physical Activity, and Quality of Life with and without Long-Term Growth Hormone Therapy in Adult Survivors of Childhood Acute Lymphoblastic Leukemia	The study aim was to evaluate growth hormone (GH) therapy on cardiovascular risk, cardiac function, physical activity, and quality of life in Acute Lymphoblastic Leukaemia (ALL) patients, treated with cranial radiotherapy and chemotherapy. The study was a non-randomised prospective study with two groups of GH-deficient ALL patients and matched population controls. One ALL group received GH for 5 years and the other ALL group did not. The outcome measures were: prevalence of CV risk factors and metabolic syndrome, cardiac function, quality of life and physical activity
Non-experimental study: survey	Strong et al. (2014)	The study surveyed practice nurses to ascertain whether they are adequately equipped with knowledge, skills and resources, to provide nutrition education to people with type 2 diabetes. A self-administered questionnaire was used
Qualitative study	Gurel et al. (2014) Patient perspectives on the impact of acromegaly: results from individual and group interviews.	The study aimed to understand the impact of acromegaly on disease-related concerns and treatment choices from the patient perspective. In Phase I, 10 patients participated over the course of 5 days in a moderated online discussion board. In Phase II, a separate nine-patient cohort participated in face-to-face interviews

not be an appropriate study design to answer this research question. If your research question concerns people's experience of living with an endocrine disorder or exploration of acceptability of its treatment, then a qualitative research approach is more appropriate, as it enables the gathering of in-depth data about people's experiences or feelings. In Table 69.1, Gurel et al.'s (2014) study is an example of a qualitative study that used online discussions and individual interviews to study experiences from people's perspectives of living with acromegaly.

The application of the results of a systematic review must take into account the individual and the context of care. For example, from a critical appraisal of an extensive set of high-quality RCTs, the authors of a systematic review may conclude there is good evidence for a particular patient education device for diabetes self-management. However, for any individual patient, the use of the device in practice could be affected by another health condition (e.g. visual impairment or rheumatoid arthritis), their cognitive ability (e.g. they could have dementia or a learning disability), their literacy level or their social situation. Critics of evidence-based practice argue that generalised evidence-based guidelines detract from a person-centred approach (Barker 2013) although Sackett et al.'s (2000) definition of EBP does

include the patient's values and preferences as part of the decision-making process.

A collaborative group that supports EBP and has a strong nursing focus with a broad approach is the Joanna Briggs Institute (JBI) (see http://joannabriggs.org/). The JBI was established in Australia but has now been adopted as a global enterprise. The Cochrane library (http://www.thecochranelibrary.com) aims to provide high-quality, independent evidence to inform healthcare decision-making. The library contains databases of systematic reviews on an increasing number of topics. There is a useful section entitled 'Endocrine and metabolic' with current subtopics that include: Diabetes, High cholesterol, Neuroendocrine cancer, Nutritional deficiencies; Obesity and overweight; Other endocrine disorders and Parathyroid disorders. Attridge et al.'s (2014) study (see Table 69.1) is an example of a systematic review, accessed via the Cochrane library. Most of the systematic reviews in the 'Endocrine and metabolic' section are, like Attridge et al.'s review, diabetes related, rather than other endocrine disorders; this could indicate there are gaps in endocrinology research. There are also relatively few reviews in the Cochrane library that are focused on nursing practice and this indicates potential gaps in the nursing-related research evidence base.

69.3 Process for Implementing Evidence-Based Practice

Box 69.3 summarises the process for implementing evidence-based practice, which starts with accessing and appraising the available evidence. The key to a good literature search is to formulate the search topic into an answerable question. The most frequently used framework is PICO (population or patient problem, intervention, comparison or context, and outcome). Use of a framework like PICO is helpful to develop a good, focused research question, but it can also assist in compiling the search terms to use for identifying available evidence (Norris 2010). The 'comparison' component is optional as there may not be a comparison intervention available. Instead, the context or setting might be more relevant for some topics. As an example of using PICO, your research topic area might be to investigate ways of increasing adherence with medication for a pituitary disorder in young adults. Your research question formulated using PICO might be:

- For young people with hypopituitarism on growth hormone replacement (P), are daily reminder text messages (I) more effective than usual care (C) for achieving adherence with medication?

Box 69.3 Implementing Evidence-Based Practice

- Formulate a question to focus the evidence gathering, using the PICO format (patient/population, intervention, comparison/context, outcome)
- Identify keywords and plan how they will be combined (and/or) and any other search parameters such as publication date range, terms to exclude
- Identify the search-engines and databases to use, for example, CINAHL (Cumulative Index to Nursing and Allied Health Literature), MEDLINE, PsycINFO, BNI (British Nurse Index) and SCOPUS
- Review the database search results and select articles by rejecting irrelevant articles first on title and then, from those remaining, by reviewing the abstracts for relevance, and then finally, by reviewing the remaining articles in full.
- Critically appraise the selected research studies to make a judgement about their quality. There are many useful appraisal guidelines available; see the UK Critical Appraisal Skills Programme (CASP) at http://www.casp-uk.net, which includes checklists for appraising different types of research;
- Apply the evidence you have identified to the context of care delivery, drawing on clinical expertise and with consideration of patient values and preferences.

You can then identify your keywords from this PICO formed question. Keep records of the results of your searches and the process you followed so that you can justify your selection of papers. If you identify few relevant research studies and a critical appraisal of these reveal that the study designs are weak and the results are inconclusive, you have then identified that further research is necessary. Identifying gaps in the evidence may inspire you to conduct your own research; see later section 'Independent nursing research: pursuing a clinical academic career'.

Once you identify the evidence relating to your question, your goal is to implement evidence in practice. However, what may appear to be small changes to implement evidence-based practice can be more complex than they first appear and involve many different disciplines and changes to whole systems. Quality improvement methodology can be used to implement best evidence, through mapping current processes and then planning, trying out, evaluating and refining evidence-based changes on a small scale in repeated Plan-Do-Study-Act cycles (Langley et al. 2009). Let us consider our earlier example, of using daily text messages with young people with growth hormone deficiency to improve medication adherence. If you found high-quality evidence about this intervention from your literature review and wanted to implement this in practice with your patients, Plan-Do-Study-Act cycles could work in the following way:

1. **Plan**: You would need to first collect some baseline data about medication adherence with your service user group. You would need to conduct detailed planning and should involve colleagues and service users to co-design how you will approach the improvement. For example: who will send the text message and at what time? If it is a clinical nurse specialist, do they provide 7-day cover and is there a cost implication? You would need to plan who you will pilot the text messaging with and for how long, and what data you need to collect and how, so you can measure the improvement. You might start with just one service user, for 1 week perhaps.
2. **Do:** At this stage you will try out the text messaging as planned, while collecting the data.
3. **Study**: You will measure the effects of the text messaging by comparing the data before the improvement with the data collected at the 'Do' stage. You can use for example self-reported adherence questionnaires, biochemical markers, i.e. insulin-like growth factor 1, prescription use and stock check for their growth hormone use and patient feedback on new intervention.
4. **Act**: You next act on the results, reviewing these with your colleagues and service user group.

After this first PDSA cycle you will move into a second PDSA cycle, with planning based on the first cycle. You might next try out the text messaging with a few more service users and for a longer timeframe. You might identify other data you need to collect and review as part of the cycle. You would continue with small scale projects using PDSA cycles to continually improve how the intervention is working in practice with your service user group, before widespread rolling out of the evidence-based improvement.

69.4 Conducting Your Own Research

Some nurses working in endocrinology may be interested in creating evidence as well as using existing evidence. To conduct your own research you need to have a sound understanding about research methods, data collection methods and data analysis. One way to acquire and utilise these skills AND continue to work as a clinical nurse is through the development of a clinical academic role.

In the next section we will explain what a clinical academic is, the key benefits, describe national and local initiatives that support the development of a clinical academic, explore how you can develop your role as a clinical academic and finally we provide an example of a case study of an endocrinology clinical academic.

69.4.1 Independent Nursing Research: Pursuing a Clinical Academic Career

69.4.1.1 What Is a Clinical Academic?

A clinical academic is a registered health professional who works concurrently in a healthcare clinical setting as well as an academic (usually a university) setting (Carrick-Sen et al. (2016). The role is relatively new within the UK; however, Australia and the United States of America (USA) have established senior clinical academic roles for the last two decades. Within the UK, medicine introduced the role of the medical Academic Clinical Fellow (ACF) in 2005 (UK Clinical Research Collaboration and Modernising Medical Careers 2005). The role in medicine is now well established and valued. The research-focused clinical academic role within the UK has been developed to support and create roles within nursing, midwifery and allied health professions.

69.4.1.2 What Are the Benefits?

The benefits of a clinical academic are plentiful. Beneficiaries include patients, the individual health professional, the organisation and the profession. High quality of care is associated with continual service improvement (Care Quality Commission [CQC] 2016). Patients involved in research report increased monitoring, treatment options, care contacts and improved clinical outcomes. In the pursue of being a clinical academic, the individual gains extensive knowledge, skills and confidence relating to research methodology, advanced critical thinking and decision-making, reporting outcomes and findings and are likely to feel valued and appropriately challenged and utilised. Benefits to the organisation include increased provision of evidence-based care, increased reputation, efficiency and clinical outcomes, potentially reduced complaints and increased staff morale as well as attracting and retaining high-quality staff. The profession benefits from increased evidence-based care and treatment options and the creation of valued and appropriately developed and utilised healthcare professionals.

69.4.1.3 Initiatives That Support the Development of a Clinical Academic

In 2000, a UK-wide group was set up under the Association of UK University Hospitals (AUKUH) Director of Nursing sub-group (AUKUH 2018). The AUKUH focus on the important integration and development of service, research and education within the healthcare provider setting. The group, founded and chaired by Professor Debbie Carrick-Sen, works in close partnership with other key UK organisations, which include: the National Institute for Healthcare Research (NIHR), Health Education England (HEE), NHS Improvement, NHS England, the Royal College of Nursing (RCN) and the Royal College of Midwives (RCM). The group have been successful in achieving a number of high-quality outputs including a national career framework, identified required competences and example job descriptions, to name but a few. It has also successfully influenced this agenda including the aspiration of national clinical academic roles within HEE national mandate as well as being the focus of a number of important national strategies and initiatives. The latest output launched in October 2016 is an online healthcare provider organisation guide to support the transformation of care through research-focused clinical academic roles (Carrick-Sen et al. 2016). The guide has been endorsed by national key partners and early evaluation suggests it is extremely helpful to individuals and organisations aspiring to develop clinical academic roles. The individual and organisation case studies are reported to be particularly helpful and insightful.

Although it is possible to develop as a clinical academic without organisational support, it is highly recommended that you gain organisation/line management support. Doing so, will assist you to make the most of available opportunities in a timely way and ensure that the research you focus on is aligned to local and national service priorities.

There are a number of recognised training steps in the development of a clinical academic (Fig. 69.1). These include a number of new

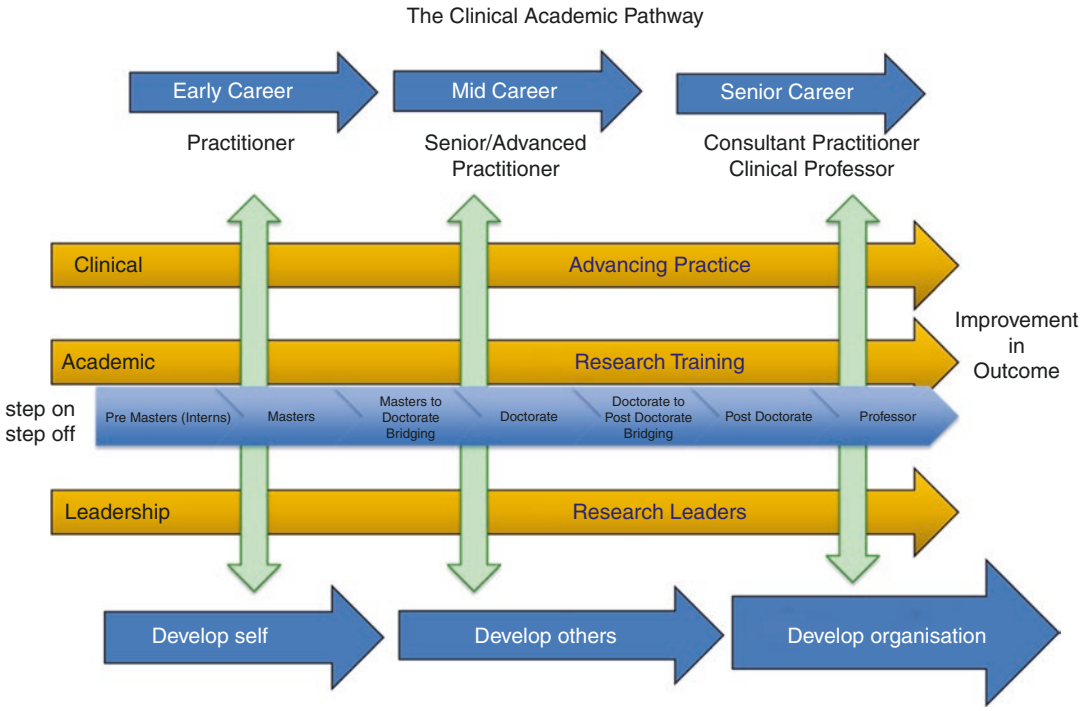


Fig. 69.1 Training steps in the development of clinical academics (developed by D. Carrick-Sen)

opportunities called 'bridging programmes'. These new bridging opportunities bridge between formal recognised qualifications and are excellent opportunities to enable you to stay on and continue to progress to a senior clinical academic. The aspiration is to develop clinical academic leaders who not only create high-quality research but also encourage and inspire others to commence and stay on the clinical academic career pathway.

Figure 69.1 represents the clinical academic pathway model that was developed by AUKUH and, in partnership with DH/NHS England, has developed and defined an embedded clinical and training pathway. This model is cross cutting and highlights early, mid and senior career. Within the career trajectory, the healthcare professional continues to develop in clinical practice, leadership and scholarship, developing self, through others and at organisation level with the purpose of improved outcome, impact, capacity and environment. Although these are important first steps, a number of challenges remain.

69.4.1.4 Developing Your Role as a Clinical Academic

It is complex to develop into a clinical academic; however, persistence and determination are key required attributes. It takes 10 years to develop and sustain a major organisational culture shift and it is important that we continue to pursue this goal globally. In times to come, it is hoped that clinical academic roles will be the norm and accepted as a valid and attractive career option. Meanwhile, there are a number of models that may work for you; one of the most common models is the 50/50 split. This is where you are likely to be currently 100% funded and employed by a healthcare provider organisation and you apply for funding to undertake research activity (+/− a formal qualification) for 50% of your time. If successful, the research funding provides finance to backfill 50% of your role and you therefore commence as a clinical academic spending some of your time doing clinical work and some of your time doing research activity. One of the current challenges is what you do at the end of that funding. Our sugges-

tion would be to apply for bridging funding, which is likely to be less hours than your formal training research funding (see Fig. 69.1) and use this time to publish and prepare for the next stage.

Working within a good multidisciplinary research team is critical to success. Another very important aspect is to identify mentors who understand your role and professional perspective, and who have the required time and commitment you need from a successful mentoring relationship. It is likely that you will need to identify and approach your mentor/s. You can have more than one and it is often beneficial if they are outside your own organisation as they can often articulate a more objective viewpoint. Mentors are often successful people who have successfully negotiated the role you are aspiring to. Box 69.4 provides an example of an endocrinology clinical academic.

Box 69.4 A Case Study of an Endocrinology Clinical Academic

Lisa Shepherd is an endocrinology clinical nurse specialist at Heart of England NHS Foundation Trust in England. Lisa's prime goal is to improve and further understand how we can help patients with primary adrenal insufficiency and to reduce the risk of developing an adrenal crisis. She has successfully completed her Masters qualification and published the findings. She was successful in attaining a place on the West Midlands HEE funded Masters to Doctorate bridging programme. During this time, she worked with an academic mentor and created a solid effective research multidisciplinary team to work with her and guide her. During the 18-month bridging programme she published two further papers to enhance her publication profile and submitted five funding applications for small amounts to undertake pilot projects that helped and increased understanding of knowledge and evidence gaps. She was successful in attaining three of these and these then further increased her research profile. She also enhanced her current national and international profile, to further build her role esteem factors. The pilot project and publications were all aligned to her research topic and therefore further building her personal storyline and creditability within the field. The publications included her supervisors and academic mentor demonstrating effective and supportive supervision. Lisa has recently submitted a high-quality NIHR clinical academic doctorate funding application to undertake a large study focused on behaviour change and technology. She is clearly dedicated, able and determined to pursue a clinical academic role and I am sure will be one of our endocrinology research leaders of the future.

69.5 Clinical Research Nursing in Endocrinology

It is important to first differentiate between a nurse conducting nurse-led research and a clinical research nurse. Nursing research is a systematic, objective process of analysing phenomena of importance to nursing. Clinical research nursing is nursing practice with a specialty focus on the care of research participants. This section will explain the role of the nurse in clinical trials, rather than other types of research.

Clinical research nursing roles may be varied. Clinical research nurses (CRNs) support study implementation within the context of a care delivery setting in primary or secondary care. Research Nurse Coordinators (RNC) are nurses primarily responsible for study coordination and data management, with a central focus on managing subject recruitment and enrolment, consistency of study implementation, data management and integrity, and compliance with regulatory requirements and reporting.

Although there are many definitions of clinical trials, they are generally considered to be

biomedical or health-related research studies in human beings that follow a pre-defined protocol. They are conducted in four phases (see Box 69.5). Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.

Box 69.5 The Four Phases of Clinical Trials

- Phase I tests a new drug or treatment in a small group of healthy volunteers.
- Phase II expands the study to a larger group of volunteers and patients.
- Phase III studies are conducted with an even larger group of patients and are often randomised to confirm therapeutic effect.
- Phase IV consists of formal post-marketing surveillance studies, which may include other population groups and surveillance for interaction with other drugs.

Competency frameworks have been developed in order for CRNs to benchmark their practice and maintain high standards of care. One example is a competency framework which has been adopted by the UK's National Institute of Health Research (NIHR) and is used extensively by CRNs working in varied clinical settings (Gelling 2011). The framework promotes patient safety and the achievement of quality data, by bringing together the knowledge and skills of the CRN. The framework is designed to be comprehensive, giving an overview of the current expectations of the work of a CRN and at various levels of seniority. It consequently also provides clear structure for career development. One of the strengths of a competency framework is that it is adaptable to meet local requirements within all research settings.

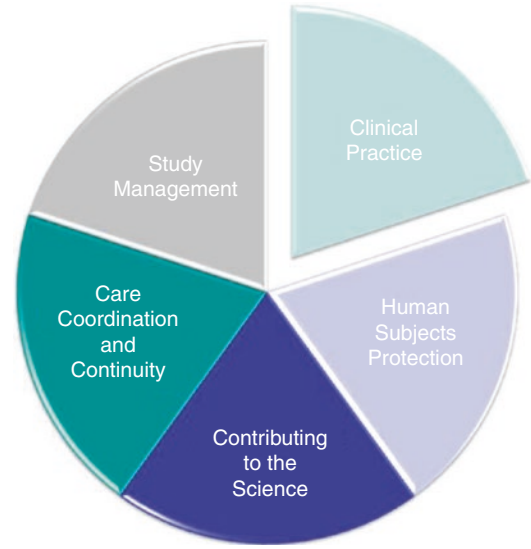


Fig. 69.2 Clinical research nursing domain dimensions (CRN 2010 Domain of Practice Committee 2009: Figure 2, p.4)

In 2009 the National Institutes of Health (NIH) CRN task force started a 4 year strategic plan to lead an international effort in order to define the specialty practice of clinical research nursing (CRN 2010 Domain of Practice Committee 2009). The domain of practice for the CRN specialty encompasses five dimensions (see Fig. 69.2), each of which houses a cluster of activities which together describe the specialty practice.

Let us now examine in more detail each of the domains.

Study management: Managing clinical research support activities: assuring patient safety, addressing clinical needs, assuring protocol integrity, accurate data collection and compliance with Good Clinical Practice guidelines (GCP).

Care Coordination and Continuity: Facilitating the education of the interdisciplinary teams, coordinating study visits, providing nursing leadership within the interdisciplinary teams and effectively communicating the impact of study procedures on the participants.

Contributing to the science: Participating as a research team member in the development of

new ideas for studies, serving as an expert in specialty areas, participating in the query and analysis of research data, mentoring junior staff, students and new investigators as members of the research team.

Human subject's protection: Facilitating the initial and ongoing informed consent process, acting as the research and development liaison, coordinating research activities to minimise patient risk and managing potential ethical and financial conflicts of interest.

Clinical practice: Providing direct nursing care to research participants, teaching using advanced practice skills and monitoring the patient, recording research data in accordance with GCP.

Professional development and career progression is essential for all CRNs and revalidation requirements expect CRNs to show engagement with evidence based continuing professional development. The 'Competency framework for research nurses' (Gelling 2011) illustrates the skills and behaviours, and knowledge and understanding, for identified clinical research nurse competencies, across the career pathway.

69.5.1 Paediatric Clinical Research Nurses and Clinical Research

Children differ from adults and have distinct healthcare needs related to anatomic, physiologic, developmental, psychological, cognitive and behavioural characteristics. A challenge for paediatric nurses is to develop and integrate best research evidence to improve the quality of care for children, adolescents and their families. Utilising findings from research with adults is not always appropriate or optimal to develop best practices for paediatric care. Paediatric clinical research nurses and nurse scientists endeavour to incorporate best practices that integrate the developmental level and health needs of the child and in the context of family-centred care.

Advocacy is an important role of the paediatric nurse working with children research participants. Although a parent or guardian must provide consent for their child to participate in a research study, children should have a voice in the decision to participate. Typically, children from age 7 years are capable of understanding basic information if it is presented at the appropriate developmental level. Nurses should be aware of the legal age of consent under the applicable law of the jurisdiction in which the research will be conducted as well as who is authorised under applicable state or local law to consent on behalf of a child to participate in research (i.e. parent, guardian, legal authorised representative). The priority of human subject's research is protection from undue harm and burden from the research and to support participants (children and their parent/guardian) to make informed decisions about participation in a research study. Children are considered a vulnerable population and special regulatory requirements provide additional protection for the inclusion of children in clinical research. The paediatric nurse must be vigilant to identify possible ethical concerns that may arise in the research process. Also, the paediatric research nurse has a key role to address and monitor safety issues and implement pain prevention or reduction strategies (e.g. blood drawing volumes, exposure to imaging studies involving radiation exposure, use of anaesthesia and procedure-related pain reduction strategies (Refer to Chap. 5)).

Translational research is also needed to develop intervention strategies to improve paediatric nursing practice (i.e. standards of paediatric nursing practice, competencies), which will promote the health of children and adolescents (Christian 2018). In 2014 the American Academy of Nursing endorsed the 'Health Care Quality and Outcomes Guidelines for Nursing of Children, Adolescents, and Families' as a framework for nurse-directed services and intervention development and testing, as well as a model for paediatric nurse education programmes. In addition, a priority to create practice-based child health nursing research networks (PBRN) which are described as 'a network of practice sites that have formed a collaboration with the express purpose to identify, investigate, and disseminate findings associated

with health problems and clinical management and treatment' is promoted in academia as well as in clinical and research settings (Betz 2013). There are child health and nursing based PBRN registered with the Agency for Healthcare Research and Quality (AHRQ) (United States of America (USA)), and this model can be expanded to facilitate the development of evidence-based paediatric nursing practice (https://pbrn.ahrq.gov/about).

69.5.2 Challenges for Clinical Research Nurses and the Benefits

Many challenges face the CRN; however, career defining skills and knowledge are gained, bringing numerous rewards and benefits. Let us review some of these challenges first.

69.5.2.1 Challenges for CRNs

Complex studies: Some challenging studies will certainly require creative thinking and problem solving.

Cross networking: Working with different multidisciplinary teams who all have their own way of doing things requires patience and flexibility.

Time management: Research nurses juggle many different aspects of work and it can be challenging to manage your time efficiently and effectively.

Skills and knowledge gained as a CRN:

Organisational: You will develop your organisational skills and adopt a flexible and adaptable approach.

In-depth knowledge: You will gain a comprehensive understanding of the specialty in which you are working and extensive knowledge of the research process and research-related legislation.

Management: This includes many different aspects of the research study, preparing trial protocols and other trial related documentation, submitting study proposals for regulatory approval and coordinating the initiation, management and completion of the research.

Attention to detail: You will develop a meticulous approach and a high level of integrity for randomisation and for collecting and recording data.

Leaders of research: Research nurses may also act as teachers, mentors and advisers to other health professionals. Some research nurses go on to develop their own research studies and undertake doctoral study.

69.5.2.2 Rewards and Benefits for CRNs

The role is varied and interesting—every day is different from the one before. CRNs take part in a study from start to finish; they hear and learn about a completely new study, enrol patients and are there to see the results that will make a difference to the patient and their families in the future. CRNs are at the frontline of improving patient care, building and maintaining personal effective relationships with patients on a long-term basis; a lot of time is spent with patients one-on-one adding value to interpersonal relationships. CRNs can develop a career pathway, accessing training and supervision within research nursing, to suit their developmental needs. As well as maintaining and building on your existing skills, you will learn many new skills that are transferable too.

Box 69.6 provides an example of endocrinology research phase 11, 111, 1V trials; all these trials include CRN involvement.

Box 69.6 Example of Endocrinology Research Trials

Phase 11 example (Halse et al. 2014)

This study's objective was to identify a dose of MK-5442 that produces osteoanabolic effects without excessive hypercalcemia. The design was a randomised, double-blind, placebo-controlled, parallel-group trial of private or institutional practice. The trial participants were 383 postmenopausal women with osteoporosis who were administered daily oral MK-5442 (2.5, 5, 7.5, 10 or 15 mg) or placebo.

Phase 111 example (Kulke et al. 2016)

This study evaluated telotristat ethyl, a tryptophan hydroxylase inhibitor, to reduce bowel movement frequency in patients with carcinoid syndrome. Patients ($N = 135$) experiencing four or more bowel movements per day, despite stable-dose somatostatin analogue therapy, received (1:1:1) placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg three times per day orally during a 12-week double-blind treatment period.

Phase 1V example (Beck-Peccoz et al. 2015)

The PATRO Adults study is a large, multi-centre, longitudinal surveillance study of the diabetogenic potential and overall long-term safety of Omnitrope® for adults with growth hormone deficiency in real-life clinical practice. By January 2015, 855 patients had been recruited to the study; data is collected at each routine visit for treatment with Omnitrope®.

69.5.3 Clinical Research Nurse Role: A Summary

Clinical research is vital for finding new treatments and improving patient care. The CRN requires a thorough understanding of the research process and terminology, and of the specialty under investigation. The CRN acts as an advocate for patients, ensuring they are protected and supported throughout the research study. The CRN requires a wide range of skills, including management and organisation, teaching and mentoring, communication and technology. Working with other researchers and the multidisciplinary team is crucial for successful research.

The role of the CRN is diverse, rewarding and challenging. Managerial tasks and communication with participants, colleagues and study funders must be undertaken alongside the more familiar tasks of patient care and data collection. Assertiveness, determination and commitment are required to maintain high standards of clinical research, patient care and job satisfaction. The competency frameworks bring together the knowledge and skills of the CRN and are designed to be comprehensive, giving an overview of the current expectations of the work of the CRN and at various levels of seniority, and consequently providing a clear structure for career development.

69.6 Ethics in Research Conduct

The principles for conducting research ethically, in particular, that there should be voluntary consent, were established following the adoption of the World Medical Association's Declaration of Helsinki in 1964. This was the first international standard for biomedical research and led to the setting up of processes for research ethics scrutiny. Frameworks for research ethics, and therefore research ethics application documents, are based on the well-established bioethical principles: respect for autonomy, non-maleficence, beneficence and justice (Beauchamp and Childress 2013). Table 69.2 presents these principles with examples applied to research.

Each country has its own systems for research ethics scrutiny, so a nurse involved in research should be familiar with these processes. Although healthcare is devolved in the UK, there is now a UK-wide governance framework (Department of Health (England), the Department of Health (Northern Ireland), the Scottish Government Health and Social Care Directorates and the Department for Health and Social Services (Wales) 2017) The Health Research Authority (HRA) is a national body responsible for governance of research in the National Health Service (NHS). The organisation defines research and provides a decision tool to assist project leads in deciding whether their project is research, from an NHS research ethics perspective or whether it is audit, surveillance, public health or service evaluation, which the HRA states may include service improvement or quality improvement (HRA 2017). If the project does not meet the identified criteria for research, from a governance perspective (randomisation, use of treatment/care

Table 69.2 Bioethical principles (summarised from Beauchamp and Childress 2013)

Ethical principle	Explanation related to research
Respect for autonomy	The right of individuals to make decisions about taking part in research for themselves without coercion or any pressure from others. This principle underpins the necessity for informed consent in research conduct
Non-maleficence	The duty to avoid harm to others. Researchers must identify any potential harm and explain what steps will be taken to prevent, reduce or mitigate potential harm. Any potential harm must be justifiable, balanced against potential benefits of the research
Beneficence	The duty of researchers to conduct studies that are worthwhile and, where possible, to do good. Researchers must therefore justify the need for the research and demonstrate that the study's design is of a high quality, to maximise potential benefits
Justice	Upholding the rights of research participants and ensuring fairness. This principle requires inclusivity, for example, not excluding participants (e.g. those who cannot speak English) without good justification

different from usual standard, intention to derive generalisable new knowledge), then it will not require an NHS research ethics committee review although other local governance processes may be needed within the NHS (HRA 2017). The HRA website includes useful resources about all aspects of preparing a research ethics application, including informed consent, templates for consent forms and patient information sheets and processes to follow when including adults who cannot consent for themselves.

There can be blurring between research and quality improvement and so what ethical processes are necessary is not always clear-cut. The World Health Organisation (2013) recommended independent ethical oversight wherever more than minimum risk is identified, pointing out that no matter how the activity is labelled, whether research or quality improvement, what is important is that people are not subjected to risk, as risks can generally be anticipated and strategies planned to deal with them. Flaming et al. (2009) reported that the Alberta Research Ethics Community Consensus Initiative (ARECCI) network has developed ethics guidelines for quality improvement projects with six considerations; see http://www.aihealthsolutions.ca/arecci/guidelines/ for an online tool with points to consider for each question to assist with screening of level of risk based on responses. Flaming et al. (2009) suggested that anyone conducting quality improvement should use the guidelines from the start of planning their project.

69.7 Conclusions

In this chapter, we introduced evidence-based practice and research, explaining how to access and appraise evidence for endocrinology nursing practice. We discussed the nature of research evidence and the contribution of different types of research studies to the evidence base for practice. We considered how best evidence can be implemented in practice, with an example of applying quality improvement methods in practice. Nurses are in an ideal position to identify gaps in the available evidence and propose new research questions. Clinical academic roles provide the opportunity for nurses to address gaps in the evidence base and combine clinical nursing with research. We explained the benefits of clinical academic roles and the career and training pathways available for nurses. Clinical research is vital for finding new treatments and improving patient care. The role of the clinical research nurse is diverse, rewarding and challenging, and requires assertiveness, determination and commitment to maintain high standards of clinical research and patient care. All research must be conducted in accordance with international standards for research ethics and follow local processes for ethical scrutiny.

69.7.1 Resources

Cochrane library: http://www.thecochranelibrary.com

Critical Appraisal Skills Programme (CASP): http://www.casp-uk.net

Joanna Briggs Institute: http://joannabriggs.org/

Institute for Healthcare Improvement: http://www.ihi.org

NHS Improvement: https://improvement.nhs.uk/

National Institute for Health and Care Excellence (NICE): www.nice.org.uk

International Association of Clinical Research Nurses: https://www.iacrn.org

Children and Clinical Studies: http://www.childrenandclinicalstudies.org

References

Agency for Healthcare Research and Quality. PBRN networks. https://pbrn.ahrq.gov/about. Accessed 20 June 2018.

Association of UK University Hospitals UKUH. National clinical academic roles development group for nurses, midwives and allied health professionals. 2018. http://www.aukuh.org.uk/index.php/affiliate-groups/nmahps. Accessed 18 Mar 2018.

Attridge M, Creamer J, Ramsden M, Cannings-John R, Hawthorne K. Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2014;(9). Art. No.: CD006424. https://doi.org/10.1002/14651858.CD006424.pub3.

Barker J. Evidence-based practice for nurses. 2nd ed. London: Sage; 2013.

Beauchamp TL, Childress F. Principles of biomedical ethics. 7th ed. Oxford: Oxford University Press; 2013.

Beck-Peccoz P, Höybye C, Murray RD, Simsek S, Leal-Cerro A, Zabransky M, Gunter Stalla G. The PATRO adult study of Omnitrope[reg] for the treatment of adult patients with GH deficiency: latest results. In: Endocrine abstracts, 17th European Congress of Endocrinology. 2015. https://www.endocrine-abstracts.org/ea/0037/ea0037EP665. Accessed 27 May 2018.

Betz CL. Practice-based child health networks. J Pediatr Nurs. 2013;28(3):211–2.

Care Quality Commission. The state of care in NHS acute hospitals: 2014 to 2016 findings from the end of CQC's programme of NHS acute comprehensive inspections. 2016. http://www.cqc.org.uk/sites/default/files/20170302b_stateofhospitals_web.pdf. Accessed 12 Jan 2018.

Carrick-Sen D, Richardson A, Moore A, Dolan S. Transforming healthcare through clinical academic roles in nursing, midwifery and allied health professions: a practical resource for healthcare provider organisations. London: AUKUH. 2016. https://www.medschools.ac.uk/media/2325/aukuh-transforming-healthcare.pdf. Accessed 12 Jan 2018.

Christian BJ. Translational research—the stress and uncertainty of hospitalization and strategies for paediatric nurses to improve the quality of care for children and families. J Pediatr Nurs. 2018. https://doi.org/10.1016/jpedn2018.05.012.

CRN 2010 Domain of Practice Committee. Building the foundation for clinical research nursing: domain of practice for the specialty of clinical research nursing. 2009. National Institutes of Health Clinical Center, Nursing and Patient Care Services. 2009. https://clinicalcenter.nih.gov/nursing/about/whatwedo.html. Accessed 23 May 2018.

Department of Health (England), the Department of Health (Northern Ireland), the Scottish Government Health and Social Care Directorates and the Department for Health and Social Services (Wales). UK policy framework for health and social care research. 2017. http://www.research.hscni.net/sites/default/files/uk-policy-framework-health-social-care-research_0.pdf. Accessed 18 March 2018.

Flaming D, Barratt-Smith L, Brown N. Ethics? But it's only quality improvement. Healthc Q. 2009;12(2):52–7.

Follin C, Thilén U, Österberg K, BjÖrk J, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metabol. 2010;95(8):3726–35.

Gelling L. Competency framework for clinical research nurses. 2011. https://cambridge.crf.nihr.ac.uk/wp-content/uploads/2015/04/Research_Nurse_Competency_Framework_-_Version_2_-_Full_-_Oct_20111.pdf. Accessed 24 May 2018.

Gurel MH, Bruening PR, Rhodes C, Lomax KG. Patient perspectives on the impact of acromegaly: results from individual and group interviews. Patient Prefer Adherence. 2014;8:53–62.

Halse J, Greenspan S, Cosman F, Ellis G, Santora A, Leung A, Heyden N, Samanta S, Doleckyj S, Rosenberg E, Denker AE. A phase 2, randomised, placebo-controlled, dose ranging study of the calcium-sensing receptor antagonist MK-5442 in the treatment of postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2014;99(11):E2207–15.

Health Research Authority. Defining research. 2017. http://www.hra.nhs.uk/documents/2016/06/defining-research.pdf. Accessed 18 Mar 2018.

Kulke MH, Horsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, Welin S, Warner RRP, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2016;35:14–23.

Langley G, Moen R, Nolan K, Nolan T, Norman C, Provost L. The improvement guide: a practical approach to enhancing organizational performance. San Francisco: Wiley; 2009.

Martínez-Momblán MA, Gómez C, Santos A, Porta N, Esteve J, Úbeda I, Halperin I, Campillo B, Guillaumet M, Webb SM, Resmini E. A specific nursing educational program in patients with Cushing's syndrome. Endocrine. 2016;53(1):199–209.

Norris N. How to ….carry out a literature search. Educ Prim Care. 2010;21:124–5.

Oxford Living Dictionaries. Evidence. Oxford: Oxford University Press; 2017. https://en.oxforddictionaries.com/definition/evidence. Accessed 18 Mar 2018.

Petticrew M, Roberts H. Evidence, hierarchies, and typologies: horses for courses. J Epidemiol Community Health. 2003;57:527–9.

Sackett DL, Straus SE, Richardson WS, Rosenburg W, Haynes RB. Evidence-based medicine: how to practise and teach EBM. London: Churchill Livingstone; 2000.

Strong PA, Lyon J, Stern K, Vavasour C, Milne J. Five-year survey of Wellington practice nurses delivering dietary advice to people with type 2 diabetes. Nutr Diet. 2014;71(1):22–7.

UK Clinical Research Collaboration and Modernising Medical Careers. Medically- and dentally-qualified academic staff: recommendations for training the researchers and educators of the future. 2005. http://www.ukcrc.org/wp-content/uploads/2014/03/Medically_and_Dentally-qualified_Academic_Staff_Report.pdf. Accessed 12 Jan 2018.

World Health Organisation. Ethical issues in patient safety research: interpreting existing guidance. Geneva: WHO; 2013.

World Medical Association. Declaration of Helsinki. 1964. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 18 Mar 2018.

Key Reading

1. Aveyard H. Doing a literature review in health and social care: a practical guide. Maidenhead: Open University; 2014.
2. Baillie L, Maxwell E, editors. Improving healthcare: a handbook for practitioners. Abingdon: Routledge; 2017.
3. Kieffer V, Davies K, Gibson C, Middleton M, Munday J, Shalet S, Yeoh P. Society for endocrinology competency framework for adult endocrine nursing: 2nd edition. Endocr Connect. 2015;4(1):W1–W17. https://doi.org/10.1530/EC-14-0134.
4. Schmidt NA, Brown JM. Evidence-based practice for nurses: appraisal and application of research. 3rd ed. Burlington: Jones and Bartlett Learning; 2015.

Correction to: ACTH Producing Adenomas: Cushing's Disease

Raven McGlotten

Correction to:
S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6

The original version of Chapter 21 was inadvertently published without the author names "Daphne T. Adelman" and "Margaret F. Keil". These author names were included in the Acknowledgments text on Page 412 which has been removed and the author names have been included in the chapter.

Daphne T. Adelman
Northwestern University
Chicago, IL, USA
e-mail: d-adelman@northwestern.edu

Margaret F. Keil
Eunice Kennedy Shriver National Institute of Child Health and Human Development,
National Institutes of Health
Bethesda, MD, USA
e-mail: keilm@nih.gov

The updated online version of this chapter can be found at
https://doi.org/10.1007/978-3-319-99817-6_21

S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_70