Nutrition and Health
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Glenn M. Chertow *Editors*

Nutrition in Kidney Disease

Second Edition

Humana Press

Nutrition and Health

Adrianne Bendich, Ph.D., FACN, FASN, Series Editor

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Nutrition in Kidney Disease

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Laura dedicates this book to her husband, Steven, and her daughters, Erin and Jillian. Jerrilynn dedicates this book to the thousands of patients with kidney disease who will benefit from the information embedded in these pages. The goal is to improve the health and well-being of patients with kidney disease through optimal nutritional practices.

Foreword

Nutrition in Kidney Disease is a book that truly fills a gap as both a desk reference and guide to practice. Dietitians, nurses, and physicians who wish to practice state-of-the-art clinical nutrition therapy for renal patients will benefit from it. Two dietitians with special expertise in renal nutrition and one of the best and brightest nephrologists of this generation have edited the book. All three are active practitioners and researchers and are deeply knowledgeable about both the science and practice of treating renal disease. They have assembled a superb set of authors, each authority one for specific chapters that best show off the writer's expertise.

The book has five parts. It begins with six chapters that introduce kidney disease as a worldwide problem, review the relevant renal physiology and tools for assessing nutritional status. The authors of the chapters are all experts in their own right on the topics they are covering. Each chapter includes an abstract that provides a succinct survey followed by learning objectives, which are thoroughly covered in the ensuing text, accompanied by liberal use of charts, tables, and figures. It concludes with practical suggestions for managing patients.

The second part of the book focuses on chronic kidney disease in adults. Here dietary approaches to managing hypertension, diabetes mellitus, and obesity are considered.

Part III considers the problems of patients receiving renal replacement therapies such as dialysis and transplantation and also the treatment of acute renal injury. Management of protein energy malnutrition and wasting, bone and mineral metabolism and disease, and physical activity and exercise are discussed at length.

Part IV deals with kidney disease among those with special physiological needs due to pregnancy, infancy, childhood and adolescence, and advanced age. Special morbidity-related risks such as nephrotic syndrome and nephrolithiasis are also considered.

Part V is a potpourri of additional considerations on nutrition and kidney disease. The chapters include the use of dietary supplements, micronutrient needs in chronic kidney disease, and more cultural issues such as what is needed in public policy. In addition, it covers cultural issues that may slow dietary adherence and counseling approaches to improve it. A plea is made for more outcomes research. The book concludes with a full chapter on resources for renal experts to consult.

All in all, this is a book full of up-to-date science with progressive and sympathetic approaches to treating renal patients. It is a long overdue and very much welcome addition to my bookshelf, and I suspect it will also be to yours.

Boston, MA — Johanna Dwyer

Preface

The field of kidney disease has evolved over the years to encompass a broad and sophisticated knowledge base. There has been a proliferation of scientific information and technical advances in the field. The clinician involved in the care of patients with kidney disease must have a vast knowledge of nutrition management of the disease. The purpose of this book is to provide a comprehensive reference on the practice of Nutrition in Kidney Disease. It is our belief that this book will become a useful reference and tool for practicing clinicians in the fields of nutrition and nephrology, as well as other disciplines whose research, practice, and education includes nutrition and kidney disease. This book will also be a current resource for undergraduate and graduate level nutrition and allied health profession students, medical students and residents, nutrition and allied health clinicians, including general practitioners, nephrologists, educators, and researchers.

Organization and Content

Nutrition in Kidney Disease is organized into five sections with a variable number of chapters based on breadth and depth of information. Part I addresses kidney function in health and disease and it defines and forecasts healthcare trends and outcomes in kidney disease. A comprehensive review of the components of the nutrition assessment is also provided. In Parts II and III, in-depth information on the prevention of common disorders associated with chronic kidney disease, current treatment options based on the latest scientific evidence, and management of comorbidities such as protein–energy malnutrition/wasting, obesity, and bone disease are covered. Part IV presents the nutrition concerns of special needs populations such as through the life cycle—pregnancy, infancy, childhood, adolescence, and the elderly, and nutrition management of disorders such as acute kidney injury, nephrotic syndrome, and nephrolithiasis. Part V addresses additional nutritional concerns in kidney disease such as complementary and alternative medicine, cultural issues affecting dietary adherence, and outcomes research.

In an attempt to make this textbook as practical as possible, a wide variety of tables, resources, practical tools, clinical practice guidelines, and Internet websites are compiled into one chapter.

Features

The chapters in this textbook have been designed with special features to enhance learning. Each chapter begins with keywords and ends with a summary. Up-to-date references for more in-depth review are included at the end of each chapter. This list provides the clinician and student with an

extensive source of reading for continued study. In addition, several chapters end with a case study, which can be used to assess knowledge of the content area within the context of the didactic curricula. They provide thought-provoking, illustrative questions that will add to the student's learning and clinical application of the material. The answers to the case studies are provided at the end of the book. The problems posed in these chapters enable the clinician and the student to apply the chapter material to "real-life" nutrition-related problems.

The chapters have been written by a collaborative group of distinguished dietitians and physicians in the specialized field of kidney disease and clinical nutrition, and who have devoted their careers to the care of patients with kidney disease. This collaborative effort is a testament to the interdisciplinary approach that is used to provide care to this unique patient population. It is our belief that this book will be used to guide and enhance the care of the patients we serve.

Stratford, NJ — Laura D. Byham-Gray
Brookville, NY — Jerrilynn D. Burrowes
Stanford, CA — Glenn M. Chertow

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patients as well as health professionals' questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice-oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Nutrition in Kidney Disease, Second Edition" edited by Laura D. Byham-Gray, Jerrilynn D. Burrowes, and Glenn M. Chertow is a very welcome addition to the Nutrition and Health Series and fully exemplifies the Series' goals. The first volume was published in 2008 and was given excellent reviews by health professionals in both the nephrology and clinical nutrition health professional communities. Over the past 5 years, there have been major changes in the treatment of individuals with kidney disease and especially those with chronic kidney disease who require dialysis and/or transplantation. Likewise, research on the nutritional requirements of kidney disease patients has expanded and reflects the changes in demographics, technical advances, and further emphasis on the interactions among a number of disease states that increase the risk of kidney disease. This Second Edition volume is therefore especially timely as over 10% of the global adult population currently suffers from kidney disease and the number is increasing as the major comorbidities, obesity and diabetes, continue to increase around the world. As indicated in the Foreword to this volume, written by Dr. Johanna Dwyer, Director of the Frances Stern Nutrition Center, Tufts Medical Center and Professor of Medicine, Tufts University School of Medicine: "All in all, this is a book full of up-to-date science with progressive and sympathetic approaches to treating renal patients. It is a long overdue and very much welcome addition to my bookshelf, and I suspect it will also be to yours."

The three editors of this volume, Laura D. Byham-Gray, Jerrilynn D. Burrowes, and Glen M. Chertow, are internationally recognized leaders in the fields of clinical nutrition and renal disease

research, treatment, and management. Each has extensive experience in academic medicine and collectively, they have over 500 peer-reviewed publications and numerous awards for their efforts to improve the care of those with kidney disease. The editors are excellent communicators and they have worked tirelessly to develop a book that is destined to continue as the benchmark in the field of nutrition and kidney disease. Over the past 5 years, the editors have grown in their prominence in their fields and it is of benefit to the reader that these are the same editors who developed the first edition as they have remained committed to providing readers with the most up-to-date practice-oriented chapters as in their first edition.

Laura D. Byham-Gray, Ph.D., R.D. is an Associate Professor in the Department of Nutritional Sciences, School of Health Related Professions at Rutgers University in Newark, New Jersey. Dr. Byham-Gray practiced in the field of clinical nutrition, with specialty practice in nutrition support, kidney disease, and home care for over 20 years. She has held numerous elected and appointed positions at the national, state, and local levels of the National Kidney Foundation (NKF), the American Society of Parenteral and Enteral Nutrition (ASPEN), and the American Dietetic Association (ADA). Dr. Byham-Gray has been appointed to the *Clinical Standards Committee* for ASPEN because of her expertise in kidney disease, outcomes research, and evidence-based practice guideline development. She also serves as the Associate Editor for the *Journal of Renal Nutrition*. Presently, Dr. Byham-Gray is a consultant for the Academy of Nutrition and Dietetics (AND) as an evidence analyst for the *Evidence Analysis Library* recently launched by the Association. She has authored the self-study publication entitled *Medical Nutrition Therapy in Renal Disease*, *Second Edition* with Wolf Rinke Associates, and she has co-edited the AND publication, *A Clinical Guide to Nutrition Care for Kidney Disease*. Dr. Byham-Gray has received numerous awards, including the *Outstanding Service Award* by the AND-Renal Dietitians dietetic practice group and the Joel D. Kopple Award of the Council on Renal Nutrition of the National Kidney Foundation.

Jerrilynn D. Burrowes, Ph.D., R.D. is Professor of Nutrition in the School of Health Professions and Nursing at Long Island University (LIU) Post in Brookville, NY. Dr. Burrowes was the research coordinator for the NIH-funded Hemodialysis (HEMO) Study and she practiced as a renal dietitian for over a decade. Dr. Burrowes is currently the Editor-in-Chief of the *Journal of Renal Nutrition* and a Contributing Editor for the Clinical Column in *Nutrition Today*. Dr. Burrowes has held several leadership positions in the National Kidney Foundation (NKF) Council on Renal Nutrition (CRN). She was a member of the NKF Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Nutrition Work Group and a member of the NKF-KDOQI Advisory Board. Dr. Burrowes was recently appointed to the Research Committee of the Academy of Nutrition and Dietetics (AND). She has been the recipient of the Recognized Renal Dietitian Award and the Joel D. Kopple Award from the NKF-CRN and the *Outstanding Service Award* from the AND Renal Dietitians Practice Group.

Glenn M. Chertow, M.D., M.P.H. is the Norman Coplon/Satellite Healthcare Professor of Medicine and Chief, Division of Nephrology at Stanford University School of Medicine. Dr. Chertow has authored over 300 peer-reviewed articles on Stage 5 chronic kidney disease, acute kidney injury (AKI), mineral metabolism, nutrition, and costs and outcomes of dialysis therapy. Dr. Chertow currently leads or participates in several clinical trials and cohort studies sponsored by the National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases. He is Co-Editor of Brenner & Rector's *The Kidney*, ninth and tenth editions, Dr. Chertow was vice-chair of the NKF-KDOQI Nutrition Work Group in 1998–2000, and also a member of the KDOQI Bone and Mineral Metabolism Work Group from 2000 to 2002. Dr. Chertow has been elected to the American Society of Clinical Investigation and has been a recipient of the President's Award from the National Kidney Foundation and the National Torchbearer Award (2007) and Nephrologist of the Year Award (2011) from the American Kidney Fund.

This updated text, containing 28 practice-oriented chapters, continues to include many unique features, such as highly relevant case studies that help to illustrate the complexity of treating the patient with kidney disease and/or reduced kidney function. The volume is also relevant for

non-practicing healthcare providers as there are in-depth discussions of the basic functioning of the kidney; demographics of the different kidney diseases, and disease conditions that affect the kidney. There are also clear, concise recommendations about dietary intakes and use of drugs and supplements across the stages of kidney disease. Thus, this volume provides the broad knowledge base concerning kidney anatomy, physiology, and pathology required by the practicing health professionals and will also be appreciated by health professionals, students, and faculty who have an interest in the latest, up-to-date information on the consequences of loss of kidney function, treatment of kidney disease, and disease-related morbidity and mortality.

This volume serves a dual purpose of providing in-depth focus on the nutritional aspects of treating individuals throughout the lifespan who have lost some or all of their kidney function as well as examining the current clinical modalities used in treating kidney disease and the consequences of the treatments on nutritional status. The book is organized as a stand-alone resource text that provides the historic beginnings of nutritional interventions in patients and reflects upon the necessity of these historic practices even today in developing countries where dialysis and/or kidney transplants, expensive drugs, and other disease management tools are not readily available and medical nutritional support remains the primary care available to patients with kidney disease. The volume includes extensive, in-depth chapters covering the most important aspects of the complex interactions between kidney functions, diet, obesity, cardiovascular disease, autoimmune disease, and diabetes as examples, and the impact of loss of kidney function on other disease states. Additionally, the nutritional consequences of loss of kidney function in infancy, children, pregnant women, and the aged are examined in depth in separate chapters that also include potential solutions to the nutritional deficits specific for patients with impaired kidney function.

"Nutrition in Kidney Disease, Second Edition" is organized into five relevant sections. The six introductory chapters in the first part, entitled "Foundations for Clinical Practice and Overview" provide readers with the basics so that the more clinically related chapters can be easily understood. The first chapter describes the functions of the kidney and the consequences of decreased kidney function including AKI, chronic kidney disease, nephrotic and nephritic syndromes, tubulointerstitial diseases, vascular diseases of the kidney and diabetic nephropathy. There is a detailed review of the functions of the kidney. Kidneys control the composition and volume of the body fluids and maintain acid-base balance as well as blood pressure. The kidneys remove various nitrogenous metabolic end products and control the contents of the urine. We learn that the kidneys are critical endocrine organs that synthesize hormones including renin, erythropoietin, and the active form of vitamin D. The next chapter examines the global care available for patients with kidney disease and indicates that currently there is a wide range in availability of care throughout the world: as an example, there are no nephrologists in 27 African nations. In the USA and Europe, approximately 10% of the adult population has been diagnosed with kidney disease and usually the patients did not know they had kidney disease prior to diagnosis. The chapter details the statistics, in relevant tables and figures, of the global prevalence of kidney disease and the use of dialysis.

The next four chapters (Chaps. 3–6) provide descriptions of the assessment methodologies available to determine the nutritional status of the patient with kidney disease. The next chapter, containing 120 up-to-date references, describes the process of dietary assessment in healthy individuals and the many tools available for collecting individual and/or population data on intakes. However, as described in detail, the recommended dietary intake of people with kidney disease differs for some nutrients from that of healthy individuals. Guidelines for dietary intake of key nutrients, such as protein for patients with kidney disease, are based on the level of kidney function and the types of treatments. Certain assessment methodologies are recommended for use in patients with kidney diseases. Chapter 4 describes the methods of anthropometry methodologies and the standards used to determine the potential effects of kidney disease on the body's composition. Nutritional status influences kidney disease progress and its potential comorbidities. Kidney failure and its management can affect diet and nutritional status especially of electrolytes. Thus, the routine monitoring of nutritional status and

body composition is a key component of the management of CKD and the chapter details the measurements that can provide guidance in determining the nutritional needs of the patient. The next chapter identifies and tabulates the biochemical parameters that are critical for the evaluation of patient with kidney disease and reviews the importance of each of these measurements. The chapter includes the recommended frequency of measurement suggested in the Kidney Disease Outcome Quality Initiative (KDOQI) nutrition guidelines and International Society of Renal Nutrition and Metabolism consensus conference for routine, confirmatory, and screening testing. The final chapter in Part I reviews the role of the renal nutrition specialist in performing nutrition-focused physical assessments as suggested by federal, KDOQI, Joint Commission, and the Academy of Nutrition and Dietetics. The detailed and well-referenced chapter includes the Nutrition Physical Exam as the standard used in chronic kidney disease patients for comprehensive physical examination of both micro- and macronutrient status. A unique feature of this chapter is the inclusion of comprehensive nutrient overviews of niacin, vitamin B6, and zinc that summarize nutrient disposition, dietary sources, drug/nutrient interactions, laboratory evaluation, medical comorbidity data, and nutrient-based lesions/functional deficits that are frequently seen in this patient population. Detailed figures illustrating these nutrient deficiencies are included.

Part II, containing four chapters, describes risk factors and consequences of CKD in adults. The first chapter examines the adverse effects of chronic hypertension on kidney function. There are also important descriptions of dietary components as well as diet strategies that have been shown to reduce hypertension in populations that are not affected by CKD; potential alterations targeted to these diets that are of value to the patient with CKD are reviewed. Diabetes mellitus can also affect kidney function. In fact, as indicated in the next chapter, diabetes mellitus is the leading cause of kidney failure in the USA. The chapter reviews the effects of diabetic nephropathy and identifies nutrition recommendations for patients with concurrent comorbidities including diabetes, CKD, hypertension, and/or cardiovascular disease. This detailed, comprehensive chapter, containing over 200 references and relevant case studies clearly sensitizes the reader to the complexities of treating the unique nutritional needs of the patient with diabetes mellitus, whether on insulin or other drugs who is being treated for CKD. Patients with CKD often have hyperlipidemia, described in the next chapter. Included are descriptions of nutritional and pharmacological interventions to help control abnormal lipid levels in the Stage 1 through Stage 5 CKD patient. The last chapter in this section reviews the implications and management of obesity in the CKD patient. The chapter provides the reader with an overview of the epidemiology, basic science, and clinical aspects of obesity as these relate to patients with kidney disease including those on dialysis as well as patients undergoing transplantation. The chapter includes over 200 references, case studies, and helpful tables and figures.

Part III examines the nutritional consequences in adult patients who are being treated with renal replacement therapies. Dialysis is described in the first chapter and includes relevant case studies and a full description of the medical nutrition therapy used to treat patients with end-stage renal disease. The chapter reviews the different types of renal replacement therapies including hemodialysis, peritoneal dialysis, nocturnal home hemodialysis, short daily hemodialysis and describes the corresponding dietary recommendations for calories, protein, sodium, fluid, potassium, calcium, phosphorus, lipids, vitamins, and trace minerals. The next chapter emphasizes the importance of nutrition counseling for kidney transplant recipients. Three phases of nutrition consultations are described including pre-transplantation, acute, posttransplantation, and long-term nutrition counseling. Transplantation-related immunosuppression, effects on bone mineral density, electrolyte handling by the allograft, obesity-related factors such as glucose intolerance and new onset diabetes are reviewed and case studies are included. Protein-energy wasting or uremic malnutrition is described in the next chapter that includes practice-based guidelines for identifying the patient with this serious condition. Assessment strategies of the status of chronic inflammation and other relevant indices as well as current recommendations for improving appetite and caloric intake are reviewed.

AKI can be a temporary condition or may result in permanent damage to the kidneys. Critically ill patients may develop AKI due to comorbid factors including severe illness, surgical stress, injury such as trauma and burns, or the result of multiple organ damage. As a result, the AKI is often related to existing conditions that may already require specialized nutrition support. AKI may also result in the need for specialized medical nutrition therapy. Enteral nutrition may be required to meet the nutritional requirements of the patient with AKI. There may also be patients who cannot absorb nutrients through their gastrointestinal tract and parenteral nutrition is required. This informative chapter reviews all of the potential nutritional needs of the patient with AKI. The chapter also describes the intensive care staging of kidney injury and consequences including both pathological and nutritional effects.

Chronic kidney disease has significant effects on bone and mineral metabolism that are described in the next chapter. Over the last decade, there has been extensive clinical research into the role of electrolyte imbalance and other physiological losses seen in CKD. The chapter defines the terms Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) and Renal Osteodystrophy (RO) and includes discussions of the calcium-sensing receptor, the phosphaturic hormone, fibroblastic growth factor 23, the vitamin D receptor, and the regulation of 1, 25-dihydroxy-vitamin D production and metabolism. Evidence-based clinical practice guidelines to help prevent, ameliorate, and/or treat bone and mineral abnormalities in CKD are outlined for the reader. Manifestations of serious abnormal bone and mineral metabolism are tabulated and specific nutritional guidelines are included. Related to this chapter is the final chapter in this section that examines the role of physical activity and exercise in the determination of the nutritional requirements in the patient with advanced CKD. The author provides case studies and reviews the clinical studies that associate low levels of physical activity in the dialysis patient with poor outcomes associated with muscle atrophy, decreased lung function, and frailty.

Part IV contains five chapters that examine the importance of nutrition in the CKD patient with special needs. The first chapter reviews the intensive interdisciplinary efforts required to treat women with CKD who become pregnant. As outlined by the chapter's author, women who become pregnant during early stages of the disease, while undergoing maintenance dialysis or after kidney transplantation are all considered to be at high risk for complications. Care of the pregnant dialysis patient presents a challenge to the renal healthcare team, and requires a multidisciplinary team approach including coordination with a high-risk obstetrics team. More intensive dialysis therapy, modifications in oral and intravenous medications, and emphasis on increased intake of protein, calories, and specific vitamins and minerals are discussed in detail and case studies are included. The next chapter reviews the major causes, treatments, and unique nutritional needs of infants, children, and adolescents with CKD. The most common causes of CKD in children are congenital, hereditary, acquired, or metabolic disorders. Congenital causes include abnormally developed kidneys and obstructive uropathy. The second most common cause is acquired conditions. A major focus of nutritional care is the provision of sufficient protein, calories, and electrolytes and other essential nutrients to help assure the child's growth during dialysis and/or transplantation. The chapter includes ten informative tables, detailed discussions of physical and biochemical assessment methodologies as well as tube feeding options. The effects of aging on the major body systems, including the kidney, are reviewed in the next chapter. Seniors over the age of 65 have reduced kidney function compared to young adults and also have decreases in related functions including thirst signals. In the senior population, CKD typically occurs in individuals with chronic conditions such as diabetes mellitus (as discussed in detail in Chap. 8). More than 20 % of seniors in the USA have three comorbid conditions that impact kidney function: CKD, diabetes, and congestive heart failure or other aspects of cardiovascular disease. The management of the senior patient with CKD and potential consequences of comorbidities including bone effects, body weight, and muscle loss are described and case studies are included.

The last two chapters in this section discuss damages specific to the kidney. Nephrotic syndrome, the topic of the next chapter, results from excessive urinary losses of albumin and other plasma proteins and is characterized by edema, hyperlipidemia, and hypoalbuminemia. The causes, diagnosis,

complications, and treatments including nutritional and pharmacological are reviewed in detail. The chapter on nephrolithiasis also describes the diagnosis, risk factors, complications, and nutritional recommendations for the treatment of patients that develop kidney stones. There are 11 helpful tables that provide details for patient assessment and treatment.

Additional nutritional considerations are included in the final seven chapters of this comprehensive volume. There is an historical perspective that reviews the evolution of public policies and renal nutrition practice guidelines development. It was not until 1972 that Medicare eligibility was extended to individuals under 65 with long-term disabilities and to individuals with end-stage renal disease (ESRD). In 2002 renal patients who were not receiving dialysis were provided Medicare coverage for medical nutrition counselling with a physician referral. Another chapter examines the role of complementary and alternative medicine's use by patients with CKD and concentrates on nonessential nutrient containing dietary supplements. Traditional Chinese medicines are reviewed and a list of relevant websites is provided for the reader. The next chapter reviews the essential vitamin and mineral supplements that may be of value to CKD patients. There is a review of the function, recommended intake, and potential effects of CKD on the nutritional status for each specific nutrient. Gaps in the knowledge-base and areas for future research are identified.

Medical nutrition treatment for the patient with kidney disease requires adherence to complex dietary instructions that change with the level of severity of the kidney disease. A number of factors can influence a patient's ability to follow the recommended dietary instructions. The next chapter reviews the major factors that can improve adherence as well as inhibitors of dietary adherence. The following chapter provides practical approaches to implement behavioral changes that can improve the level of patient adherence. Assessment of the stage of change of each patient, in accordance with the Transtheoretical Model, is recommended. Cognitive behavioral therapy and motivational interviewing in patients who have dietary restrictions are also discussed. Of great importance to the care of CKD patients is the data from well-controlled outcomes research studies. The standards for conducting clinical, patient-oriented, and economic outcome studies in CKD patient populations are reviewed. Practice guidelines for different stages of CKD are also described. The final chapter contains numerous suggested resources, references, and ten valuable tables for the practicing health provider who is treating the patient with KD. The topics covered include information on CKD, nutrition, diabetes mellitus, bone mineral disorders, and other related areas.

The above descriptions of the volume's 28 chapters attest to the depth of information provided by the 39 well-recognized and respected chapter authors. Each chapter includes complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include the numerous case studies provided in the relevant chapters. The volume includes over 125 detailed tables and informative figures, an extensive, detailed index and more than 1,900 up-to-date references that provide the reader with excellent sources of worthwhile information. Moreover, the final chapter contains a comprehensive list of resources in print as well as via the Internet including a complete listing of the practice guidelines that have been developed under the auspices of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI); protocols from the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) concerning nutrition therapy for the non-dialysis patient; tables of general as well as specific nutrient contents of foods for individuals with different stages of kidney disease; extensive list of reliable Internet sites as well as examples of relevant assessment tools for the health provider.

In conclusion, "Nutrition in Kidney Disease, Second Edition" edited by Laura D. Byham-Gray, Jerrilynn D. Burrowes and Glenn M. Chertow provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of maintaining the nutritional status of the patient with decreased kidney function regardless of cause and the critical value of medical nutrition evaluation, treatment support, and management for patients with CKD and other kidney diseases. This volume will serve the reader as the benchmark in this complex area of interrelationships between diet, nutritional and non-nutritional supplements, specific nutritional

products for maintaining kidney function, and the functioning of all organ systems that are intimately affected by renal disease. Moreover, these physiological and pathological interactions are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Unique chapters that examine the effects of CKD from infancy through the aging process are included along with resources for enhancing behaviors that can increase patient adherence to nutritional therapies. The editors are applauded for their efforts to develop the most authoritative resource in the field of "Nutrition in Kidney Disease" to date and this excellent text is a very welcome addition to the Nutrition and Health Series.

Morristown, NJ, USA

Adrianne Bendich, Ph.D., FACN, FASN
Series Editor

About Series Editor

Dr. Adrianne Bendich, Ph.D., FACN, FASN has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 100 editors that have developed the 50+ well respected and highly recommended volumes in the Series.

In addition to "Nutrition in Kidney Disease, Second Edition edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes and Dr. Glenn M. Chertow"—major new editions in 2012–2013 include:

1. *Handbook of Food Fortification and Health, volume I* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
2. *Handbook of Food Fortification and Health, volume II* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
3. *Diet Quality: An Evidence-Based Approach, volume I* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
4. *Diet Quality: An Evidence-Based Approach, volume II* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
5. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, M.D., F.A.C.P., F.A.C.N., FACG, 2013
6. *Nutrition in Infancy, volume I* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013

7. *Nutrition in Infancy, volume II* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013
8. *Carotenoids and Human Health*, edited by Dr. Sherry A. Tanumihardjo, 2013
9. *Bioactive Dietary Factors and Plant Extracts in Dermatology*, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
10. *Omega 6/3 Fatty Acids*, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
11. *Nutrition in Pediatric Pulmonary Disease,* edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
12. *Magnesium and Health*, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012
13. *Alcohol, Nutrition and Health Consequences*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
14. *Nutritional Health, Strategies for Disease Prevention, Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
15. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
16. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

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Part I
Foundations for Clinical Practice and Overview

Chapter 1
Kidney Function in Health and Disease

Alluru S. Reddi and Kishore Kuppasani

Key Points

- Describe the gross and microscopic structure of the kidney.
- Discuss the various functions of the normal kidney.
- Define and discuss the various renal syndromes, such as acute kidney injury, chronic kidney disease, nephrotic and nephritic syndromes, tubulointerstitial diseases, vascular diseases of the kidney, and diabetic nephropathy.

Keywords Nephron • Glomerulus • Renal function • Chronic kidney disease • Nephrotic syndrome • Nephritic syndrome • Diabetic nephropathy

Introduction

The kidneys perform three major functions. As regulatory organs, the kidneys precisely control the composition and volume of the body fluids and maintain acid–base balance as well as blood pressure by varying the excretion of water and solutes. As excretory organs, the kidneys remove various nitrogenous metabolic end products in the urine. In general, the kidneys filter plasma in the glomerulus to form a protein-free ultrafiltrate. This ultrafiltrate passes through the various tubular segments where reabsorption of essential constituents and secretion of unwanted products occur. As endocrine organs, the kidneys produce important hormones, such as renin, erythropoietin, and active vitamin D_3 (calcitriol). In addition, the kidneys participate in the degradation of various endogenous and exogenous compounds. To understand these functions, it is essential to examine the gross and microscopic structure of the kidneys.

Anatomy of the kidney: The kidneys are paired, bean-shaped structures located retroperitoneally in the lumbar region, one on either side of the vertebral column [1–3]. The lateral edge of the kidney is convex, while the medial aspect is concave with a notch called the hilum. The hilum receives the

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blood and lymphatic vessels, the nerves, and the ureter. The hilum contains a cavity, the renal sinus, where the ureter expands to form the renal pelvis. The normal adult kidney is about 10–12 cm long, 5–7 cm wide, and 2–3 cm thick, and it weighs 125–170 g.

Each kidney is composed of the parenchyma and the collecting system. The parenchyma consists of an outer cortex and an inner medulla. The medulla is divided into an outer (toward the cortex) and an inner medulla (toward the pelvis). The collecting system includes the calyces, renal pelvis, and ureters. The major calyces unite to form the renal pelvis. The renal pelvis drains into the ureter, which connects the kidney to the bladder.

The basic structural and functional unit of the kidney is the nephron. There are about 600,000 (range 300,000–1,400,000) nephrons in each kidney. Each nephron contains specialized cells that filter the plasma, then selectively remove, reabsorb, and secrete a variety of substances into the urine. The nephron consists of a renal corpuscle, the proximal tubule, the loop of Henle, and the distal tubule. The collecting duct is not part of the nephron because it is embryologically derived from the ureteric bud, whereas the nephron is derived from the metanephric blastema. However, the collecting duct is commonly included in the nephron because of its related function.

Renal corpuscle: The renal corpuscle consists of the glomerulus and Bowman's capsule. Generally the term "glomerulus" is widely used for the entire corpuscle. The glomerulus is composed of a capillary network lined by an inner thin layer of endothelial cells, a central region of mesangial cells surrounded by collagen-like mesangial matrix, and an outer layer of visceral epithelial cells. The endothelial and epithelial cells are separated by the glomerular basement membrane (GBM).

The GBM is a dense fibrillar structure, which is the only anatomical barrier between blood and urine. Biochemical studies of the GBM showed that it contains predominantly type IV collagen, proteoglycans, and laminin. Collagen provides the structural framework, whereas proteoglycans, such as heparan sulfate, confer a negative charge to the GBM. Because of this negative charge, filtration of albumin is curtailed. The Bowman's capsule, which is a double-walled cup surrounding the glomerulus, consists of an outer layer of parietal epithelial cells. Between the visceral epithelial and parietal epithelial cells is a space called Bowman's space. The glomeruli are located exclusively in the cortex, which undergo pathologic changes in several disease conditions.

The endothelial cells line the glomerular capillaries and separated by large (70 nm) fenestrations. These fenestrations limit filtration of only cellular elements such as erythrocytes but not water or proteins. The epithelial cells, also called podocytes, represent the visceral layer of the Bowman's capsule. The podocytes have foot processes that cover the GBM. These foot processes are separated by a thin diaphragmatic structure called the slit diaphragm or slit pore.

The renal corpuscle is responsible for the ultrafiltration of the blood, which is the first step in urine formation. In this process, medium- and small-sized molecules are allowed to pass through into the Bowman's space, while large-sized molecules, such as proteins, are left behind. To enter the Bowman's space, the ultrafiltrate must pass through the fenestrae of the endothelial cells, the layers of the basement membrane, and the slit diaphragms of the foot processes.

Proximal tubule: The Bowman's capsule continues as the proximal tubule, which is lined by cuboidal or columnar cells with a brush border on their luminal surface. The brush border consists of millions of microvilli, which markedly increase the surface area available for the absorption of solutes and water through cells (transcellular transport) or between cells (paracellular transport) or both. The proximal tubule reabsorbs about 60 % of the ultrafiltrate. Several electrolytes (Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, HPO_4^{3-}), amino acids, glucose, and water are reabsorbed in the proximal tubule. Also, secretion of organic acids and bases occurs in the proximal tubule. The proximal tubule is susceptible to insults such as renal ischemia and nephrotoxins, resulting in altered kidney function.

Thin limb of Henle's loop: The proximal tubule continues into the medulla as the thin descending limb of Henle's loop. The loop then bends back and becomes the thin ascending limb of Henle's loop.

The thin descending limb is more permeable to water and less permeable to NaCl. As a result, water moves into the interstitium and makes the ultrafiltrate more concentrated than in the proximal tubule. In contrast, the thin ascending limb is impermeable to water, but permeable to NaCl. Therefore, the ultrafiltrate becomes dilute and the medullary interstitium hypertonic. Thus, the thin descending and ascending limbs participate in the countercurrent multiplication of the urinary concentration process.

Distal tubule: The distal tubule includes the thick ascending limb of Henle's loop and the distal convoluted tubule. The thick limb runs from the medulla into the cortex up to its parent glomerulus, where it forms the macula densa, a component of the juxtaglomerular apparatus that secretes renin. The thick ascending limb of Henle's loop is responsible for the reabsorption of Na^+, K^+, and Cl in the ratio of 1:1:2. The reabsorption of these electrolytes is dependent on the Na/K ATPase located in the basolateral membrane. NaCl reabsorption also occurs in the distal convoluted tubule. Both segments of the distal tubule are normally impermeable to water, and thus the fluid formed in the distal tubule is hypotonic. The impermeability of the distal tubule to water, combined with active transport of Na^+ and Cl out of the thick ascending limb, makes the medullary interstitium hypertonic. The distal tubule is connected to the collecting duct by the connecting tubule.

Collecting duct: Depending on its location in the kidney, the collecting duct can be divided into the cortical, outer medullary, and inner medullary portions. The epithelium of the collecting ducts contains two types of cells: principal (65 %) and intercalated (35 %) cells. In addition, the presence of a third cell has been recently described [3]. The principal cell is the predominant type of cell lining the collecting duct system. In the cortical collecting duct, principal cells are responsible for K^+ secretion and Na^+ reabsorption. This function is only partly regulated by aldosterone, because some of the cells are capable of K^+ secretion in the absence of this hormone. Intercalated cells are involved in H^+ ion and HCO_3 secretion. Transport of water occurs in all segments of the collecting duct in the presence of the antidiuretic hormone or vasopressin. Figure 1.1 summarizes the functions of various segments of the nephron.

Interstitium: The renal interstitium, a space between tubules, is comparatively sparse. It increases from the cortex to the medulla. In humans, the fractional volume of the cortical interstitium ranges from 12 % in younger individual to 16 % in older subjects. In the medulla, the interstitial volume increases from the outer to the inner medulla in the range of 4 to approximately 30 %.

Two types of interstitial cells have been described in the cortex: type 1 cortical interstitial cell, which resembles a fibroblast, and type 2 interstitial cell with mononuclear or lymphocyte-like structure. Between the cells is a space that contains collagen and fibronectin. It is believed that the peritubular fibroblast-like interstitial cells secrete erythropoietin. Type 2 interstitial cells are believed to represent bone marrow-derived cells. Three types of interstitial cells have been described in the medulla. None of these cells is the site of erythropoietin; however, some cells (type 1 medullary interstitial cell) contain lipid droplets, which are believed to have hypotensive effects. All medullary interstitial cells synthesize proteoglycans that are present in the interstitium.

Blood supply: Each kidney is usually supplied by one renal artery arising from the abdominal aorta. After or before entering the hilum, the renal artery divides into an anterior and a posterior branch; both of them give rise to a total of 5 segmental arteries. The segmental arteries are end arteries, and occlusion of a single artery results in infarction of the area supplied. These segmental branches form the interlobar arteries in the renal sinus, which follow the curvature of the kidneys to form arcuate arteries. From these arteries arise interlobular arteries that course radially through the cortex toward its surface. The interlobular arteries give rise to the afferent arterioles, which divide into 5–8 lobules and form the glomerular capillaries. The loops of these capillaries reunite to form the efferent arteriole of the glomerulus. The efferent arteriole leaves the glomerulus as a short unbranched segment before it branches into capillaries. These capillaries, which supply blood to the proximal and distal tubules of the cortex, are known collectively as the peritubular capillary network. The efferent arterioles of

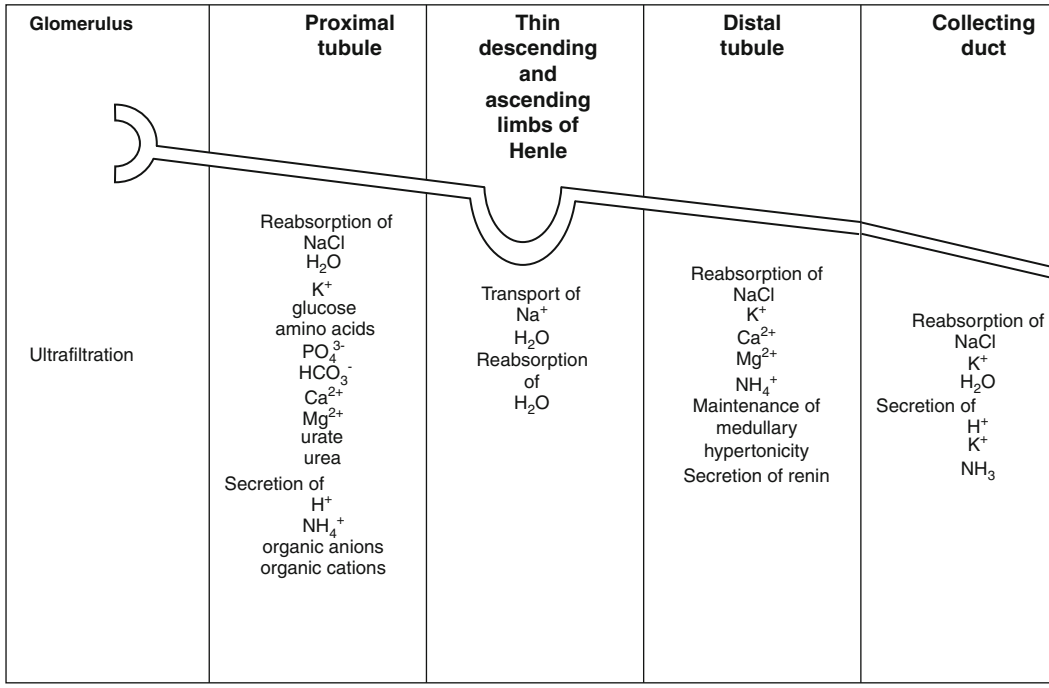

Fig. 1.1 Schematic representation of nephron segments showing the structural-functional relationships

glomeruli located in the juxtamedullary cortex and near the medullary region not only supply blood to their own tubules but also run deep into the medulla. These long, thin vessels are called arteriolae rectae, or straight arterioles. They form a loop with straight venules or venulae rectae of the medulla to form the vasa recta of the kidney. Thus, the blood supply to the medulla is entirely derived from the efferent arterioles of the juxtamedullary glomeruli. The capillaries of the outer cortex converge to form the stellate veins which drain into the interlobular veins, then into the arcuate and interlobar veins, and finally into the renal vein.

Clinical Evaluation of Kidney Function

Currently, determination of serum creatinine and blood urea nitrogen (BUN) concentrations, and estimation of glomerular filtration rate (GFR) remain the most important tests to assess the kidney function in clinical practice. GFR can be measured directly by radioisotope methods or indirectly from serum creatinine concentration as estimated GFR (eGFR), using the Modification of Diet in Renal Disease formula. Although serum creatinine concentration of 0.8–1.2 mg/dL and a BUN concentration of 10 mg/dL are considered normal, their values vary with muscle mass and protein intake as well as the functional status of the liver. Therefore, an eGFR is recommended for evaluation of kidney function. Most clinical laboratories provide both serum creatinine and eGFR to the physician for assessment of kidney function. An eGFR of 60 mL/min/1.73 m^2 or less is considered chronic kidney disease (CKD). In addition to eGFR, urinalysis provides an assessment of glomerular, tubular, and interstitial functions of the kidney. The presence of albuminuria, hematuria, and red blood cell (RBC) casts in a well-performed urinalysis indicates significant glomerular disease. Determination of urine pH and urine

osmolality is helpful in assessing the kidney's ability to acidify as well as concentrate or dilute the urine. A renal biopsy is needed to assess the pathology of the kidney in disease states.

Kidney Function in Disease States

When GFR is decreased due to functional or structural damage to the kidney, a variety of functions and also the structure of the kidney are altered. These functional and structural disturbances are briefly discussed below.

Fluid, electrolyte and acid–base disturbances: When GFR is below normal but not low enough, the kidneys try to maintain relatively normal fluid, electrolyte, and acid–base balance. However, when GFR is severely decreased, the kidneys retain Na^+, water, K^+, Mg^{2+}, PO_4^{3-}, and H^+ ions, resulting in edema, either hyponatremia or hypernatremia, hyperkalemia, hypermagnesemia, hyperphosphatemia, and severe metabolic acidosis. Hypocalcemia results from decreased calcitriol production by the kidney. These patients also develop hypertension due to retention of Na^+ and water. Anemia and bone disease are commonly seen in patients with low GFR.

Acute kidney injury (*acute renal failure*): Acute kidney injury (AKI) is defined as an abrupt decrease in renal function, resulting in accumulation of nitrogenous (creatinine and BUN) and nonnitrogenous waste products. Based on the increase in serum creatinine and urine output, the Acute Dialysis Quality Initiative group recently proposed the RIFLE system, which classifies AKI into three severity categories (R = risk; I = injury; F = failure) and two clinical categories (L = loss; E = end-stage renal disease). According to this classification, AKI is described as an abrupt (within 48 h) reduction in kidney function defined as an absolute increase in serum creatinine level of 0.3 mg/dL, a 50 % increase in serum creatinine level from baseline, or a reduction in urine output of <0.5 mL/kg/h for >6 h [4].

Studies have shown that even a small increase in serum creatinine levels is associated with increased morbidity and mortality. For example, it was reported that an increase in serum creatinine by ≥0.5 mg/dL was associated with a 6.5-fold increase in hospital mortality, while an increase in serum creatinine of 0.3–0.4 mg/dL was associated with only 70 % increase in mortality risk. Even the length of the hospital stay was prolonged by AKI [5].

The causes of AKI are divided into three major categories: prerenal, renal, and postrenal. Prerenal AKI is due to decreased renal perfusion, caused by hypovolemia, decreased effective arterial blood volume, renal artery disease, and/or altered intrarenal hemodynamics. These patients are usually volume depleted. A variety of intrinsic renal disorders due to an acute insult to the renal vasculature, glomerulus, tubules, or interstitium can cause AKI. Acute tubular necrosis remains the major form of AKI due to renal ischemia and exposure to nephrotoxins, such as drugs or contrast material. Postrenal AKI is due to obstruction to the urinary system either by intrinsic or extrinsic masses.

Treatment of AKI includes volume repletion in hypovolemic conditions and elimination of the causative agent or disease process. Some patients may require hemodialysis or other renal replacement therapies, such as continuous venovenous hemodialysis. AKI is usually a reversible process; however, it is a risk factor for progression to CKD in a small percentage of patients.

Chronic kidney disease (*chronic renal failure*): CKD is defined as a gradual decrease in renal function over a period of several months to years. Diabetes, hypertension, glomerulonephritis, cystic kidney diseases, and tubulointerstitial diseases (TIDs) are the major causes of CKD. Approximately 6.2 million people are estimated to have a serum creatinine level ≥1.5 mg/dL. Unlike in AKI, serum creatinine level does not represent the extent of renal disease in subjects with CKD. Therefore, either actual determination of GFR by radioisotope methods or eGFR is used to assess the severity of kidney

Table 1.1 Stages of chronic kidney disease and proposed actions [6]

Stage	Description	GFR (mL/min/1.73 m^2)	Action	Related terms
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Slow progression of CKD Treat comorbidities Cardiovascular disease risk reduction	Albuminuria, proteinuria, hematuria
2	Kidney damage with mild ↓ GFR	60–89	Estimate progression	Albuminuria, proteinuria, hematuria
3a[a]	Moderate ↓ GFR	45–59	Treat complications	Chronic renal insufficiency, early renal insufficiency
3b[a]	Moderate ↓ GFR	30–44	As above	As above
4	Severe ↓ GFR	15–29	Prepare for renal replacement therapy	Chronic renal insufficiency, late renal insufficiency, pre-ESRD
5	Kidney failure	<15 (or dialysis)	Renal replacement therapy	Renal failure, uremia, ESRD

[a]Recently subdivided; *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate

disease in a CKD patient. Based on these methods of GFR, a staging system and action plan for CKD was developed (Table 1.1).

There are several risk factors for the progression of CKD, including hypertension, diabetes, hyperlipidemia, excessive protein intake, smoking, anemia, and genetic predisposition to kidney disease. CKD is one of the major risk factors for cardiovascular disease. Conservative management of CKD includes (1) control of blood pressure (<130/80 for patients with no proteinuria and <120/80 for those with proteinuria >1 g/day), using dietary sodium restriction <100 mEq/L, and antihypertensive agents such as angiotensin converting enzyme-inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) as well as a low-dose diuretic; (2) maintenance of HbA_{1c} <7 % in type 2 diabetic patients; (3) restriction of protein intake <0.8 g/kg/day; (4) maintenance of LDL <100 mg/dL; (5) maintenance of hemoglobin ~10–12 g/dL and control of bone disease; and (6) smoking cessation. Dialysis or kidney transplantation is required if the patient progresses to ESRD (end-stage renal disease).

Nephrotic syndrome: This syndrome is characterized by proteinuria >3.5 g/day, hypoalbuminemia, edema, hyperlipidemia, and lipiduria. The nephrotic syndrome is caused by (1) either primary (idiopathic) or secondary (known) glomerular diseases; (2) drugs, such as nonsteroidal antiinflammatory drugs, heroin, and gold; and (3) bacterial, viral, and parasitic infections. Among secondary glomerular diseases, diabetes is the leading cause of nephrotic syndrome in adults. The primary glomerular diseases that cause nephrotic syndrome are minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

Proteinuria is caused by losses of charge and size in the GBM. Also, a decrease in protein (nephrin, podocin, α-actinin) or mutation in genes that encode these proteins in slit diaphragm and cytoskeleton of podocytes can cause proteinuria. Hypoalbuminemia is due to renal loss of albumin and increased catabolism. Both hypoalbuminemia and increased salt and water retention lead to edema formation. Recently, it has been proposed that an increase in Na^+ reabsorption by the epithelial sodium channel (ENaC) located in the late distal convoluted tubule and cortical collecting duct is responsible for accumulation of Na^+ and edema formation in nephrotic syndrome. Hyperlipidemia is secondary to increased hepatic synthesis and decreased degradation of lipoproteins.

The patients with nephrotic syndrome are at risk for thrombotic complications, infections, cardiovascular disease, and skeletal abnormalities. Management of nephrotic syndrome includes salt and water restriction in edematous patients, ACE-Is or ARBs for proteinuria and control of hypertension, low protein diet to improve serum albumin level, proteinuria and renal function, vaccination to prevent infection from encapsulated organisms, prevention of thrombosis by avoiding prolonged immobilization

and volume depletion, and control of hyperlipidemia. Anticoagulation is recommended in patients whose serum albumin levels are <2.0 g/dL and high risk for thromboembolic complications (e.g., patients with membranous nephropathy). Immunosuppressive therapy is reserved for patients with primary renal diseases. Elimination of the secondary cause usually improves nephrotic syndrome.

Nephritic syndrome: The nephritic syndrome, also called glomerulonephritis, is characterized by hematuria, RBC casts, hypertension, renal insufficiency, and varying degrees of proteinuria. Based upon the etiology and pathogenic mechanisms, this syndrome can present as (1) asymptomatic hematuria or proteinuria, (2) acute nephritis to rapidly progressive glomerulonephritis (RPGN), and finally (3) chronic sclerosing glomerulonephritis. There are several primary (e.g., RPGN) and secondary (e.g., systemic lupus erythematosus) causes of nephritic syndrome. Treating the underlying cause by conservative (acute nephritis) or aggressive (RPGN) management and control of blood pressure remain the main stay of therapy in patients with nephritic syndrome. A substantial number of patients presents with renal insufficiency, requiring renal replacement therapy.

Tubulointerstitial diseases (TIDs): Tubulointerstitial diseases are a group of clinical disorders that affect principally the tubules and interstitium. Pathologically, TIDs are characterized by tubular epithelial injury, atrophy, hyperplasia or hypertrophy, and fibrosis. Initially, the glomeruli and blood vessels are usually spared. The tubulointerstitium is affected in all forms of renal disease [7]. Based upon the morphologic changes and the rate of deterioration of renal function, TIDs can be classified into acute TID or acute interstitial nephritis or chronic TID or chronic interstitial nephritis. Acute TID manifests as sudden onset of renal failure within days to weeks (1 day to 2 months), hematuria, mild proteinuria, WBC casts, and at times eosinophiluria or eosinophilia. The accurate diagnosis is made by renal biopsy. Acute TID is caused by drugs, infections, or immune disorders. Treatment includes removing the causative agent or in some cases steroids. Renal replacement therapy may be necessary in some patients.

Chronic TIDs are caused by a variety of drugs, infections, vascular, metabolic, immune, hematologic diseases, urinary tract obstruction, and heavy metals. In some cases, the cause is unknown. Clinical manifestations include hypertension, renal insufficiency, hyperkalemia, anemia (both hyperkalemia and anemia are disproportional to the degree of renal insufficiency), inability to concentrate urine, and Fanconi syndrome. Urinalysis shows mild proteinuria and absence of RBC cats. Glomeruli are affected secondarily. Pathologic findings of the kidney include progressive scarring of the interstitium, tubular atrophy, and infiltration with lymphocytes and macrophages. Removal of the offending agent or treatment of the underlying cause, control of blood pressure with dietary sodium restriction and antihypertensive agents, and correction of anemia as well as bone disease remain the main stay of therapy in patients with chronic TIDs.

Vascular diseases: Renal artery stenosis, hypertensive nephrosclerosis, vasculitis affecting the medium and small renal arteries, renal vein thrombosis as a complication of nephrotic syndrome, and several microangiopathic diseases such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are some of the vascular diseases that cause altered kidney function. Appropriate management is required to prevent the progression of kidney disease.

Diabetic Nephropathy: As stated previously, diabetes is the leading secondary cause of nephrotic syndrome in adults and deserves special attention. About 35–44 % of all patients diagnosed with diabetes eventually develop ESRD. To prevent the progression of kidney disease and also delay the onset of ESRD, it is essential to follow the natural history and clinical course of diabetic nephropathy. It appears that there are two pathways for progression of diabetic nephropathy: One is proteinuric and the other is non-proteinuric pathways. In the majority of patients with type 1 and possibly type 2 diabetes, the kidney disease progresses (proteinuric pathway) through five distinct stages. Stage 1 (early hypertrophy–hyperfunction) corresponds to the onset of diabetes, which is characterized by enlarged kidneys and increased GFR. These changes can be reversed by good glycemic control. Stage 2 (normoalbuminuria) develops 2–5 years after onset of the disease and involves an increase in

GFR and the development of some structural changes in the kidney. GFR improves with good glycemic control. Stage 3 (incipient nephropathy) takes 6–15 years to develop and is characterized by the presence of microalbuminuria (30–300 mg/day), which is the first clinical sign of diabetic nephropathy. There are progressive changes in the kidney, and patients develop hypertension. In addition to glycemic control, lowering blood pressure to <130/80 mmHg with an ACE-I or ARBs has been proven to be extremely beneficial in preventing the progression of kidney disease to other stages of diabetic nephropathy. Stage 4 (overt nephropathy) occurs 15–20 years later and is characterized by clinically detectable proteinuria. Patients develop nephrotic syndrome, and hypertension becomes worse, resulting in gradual decrease in GFR (GFR decreases by 1 mL/min/month). Some patients with type 1 and type 2 diabetes develop CKD without any microalbuminuria or proteinuria. These patients are usually referred to as non-proteinuric subjects with CKD. The progression of CKD in these patients follows non-proteinuric pathway. How CKD progresses in non-proteinuric subjects is unclear at this time. Strict blood pressure control with 2–4 antihypertensives, if needed, stabilizes GFR in both proteinuric and non-proteinuric patients. Despite good glycemic and blood pressure control, some patients invariably progress to stage 5 (ESRD), requiring either maintenance dialysis or kidney transplantation for survival. Restriction of protein, Na^+, and phosphate in the diet has been shown to be beneficial in patients with CKD stages 3–5. Thus, glucose control, blood pressure control, and low protein diet play a significant role in the management of diabetic nephropathy.

Summary

This chapter has provided a brief review of gross and microscopic anatomy of the kidney, and its functions in health and disease. A variety of commonly seen renal abnormalities have been discussed that require nutritional and pharmacologic intervention alone or in combination for management.

References

1. Reddi AS. Structure and function of the kidney. In: Reddi AS, editor. Essentials of renal physiology. New Jersey: College Book; 1999. p. 21–43.
2. Kriz W, Elgar M. Renal anatomy. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive clinical nephrology. 4th ed. St. Louis: Elsevier Saunders; 2010. p. 3–14.
3. Nielsen S, Kwon I-H, Fenton RA, Praetorious J. Anatomy of the kidney. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, editors. Brenner and rector's the kidney, vol. 1. 9th ed. Philadelphia: Elsevier Saunders; 2012. p. 31–93.
4. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16:3365–70.
5. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiologic principles. Intensive Care Med. 2004;30:33–7.
6. Levey AS, Coresh J, Balk E, Kausz T, et al. National Kidney Foundation guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137–47.
7. Kelly CJ, Neilson EG. Tubulointerstitial diseases. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, editors. Brenner and rector's the kidney, vol. 1. 9th ed. Philadelphia: Elsevier Saunders; 2012. p. 1332–55.

Chapter 2
Global Perspective of Kidney Disease

Shuchi Anand, Masuma Akter Khanam, and Fredric O. Finkelstein

Key Points

- The prevalence of CKD in economically developing nations is approaching that of developed nations.
- A large proportion of patients living in economically developed regions who approach end-stage renal disease (ESRD) likely die without accessing therapy. This gap in care is as yet unquantified.
- Most nations offer some form of renal replacement therapy, but its expense and scarcity limit universal access. Expansion of peritoneal dialysis and transplantation may be potential strategies for improving access.
- Traditional risk factors for the development of CKD and ESRD include diabetes and hypertension; these are increasing in prevalence across the world. Moreover relatively novel risk factors including low birth weight and metabolic syndrome are now recognized to play a role. Managing the extremes of nutrition—i.e., malnutrition and obesity—can play an important role in cost-effective prevention of ESRD.

Keywords Global epidemiology of chronic kidney disease • Global epidemiology of renal replacement therapy • Low birth weight • Metabolic syndrome

Introduction

The demographic shift towards an older population [1] and urbanization with subsequent change in diet and physical activity patterns [2] are resulting in rise of chronic noncommunicable diseases across the world. A majority of patients suffering from diabetes and hypertension—primary risk

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factors for development of chronic kidney disease (CKD)—now reside in economically developing nations [3, 4].

In this context, more nations are investigating the burden of CKD, although few are looking at strategies for management. CKD not only multiplies the risk for cardiovascular disease—a leading cause of morbidity and mortality worldwide—but also leads to the development of end-stage renal disease (ESRD). Care for patients with ESRD requires costly dialysis or transplant; even nations with established economies struggle to finance this therapy.

In this chapter we review available data on the prevalence and incidence of CKD and ESRD, with emphasis on studies from economically developing nations. We then detail the challenges in provision of renal replacement therapy (RRT) in low-resource settings. Finally, we examine associated risk factors, highlighting the role of the extremes of nutrition (i.e., both malnutrition and obesity).

Epidemiology of CKD and ESRD

In the USA, data on epidemiology of CKD are made available through National Health and Nutrition Examination Survey (NHANES) and periodically updated. The NHANES is a cross-sectional survey sampled to be representative of the overall US population [5]. The latest available estimate of a CKD prevalence of 13 % spans 1988–2004, includes 28,721 individuals over 20 years of age, and defines CKD as persistent albuminuria >30 mg/g and/or estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 by the Modification Diet in Renal Disease (MDRD) formula. Restricting to individuals with eGFR below 60 mL/min/1.73 m^2 yields a prevalence of about 5 %. Other population-based studies from established economies also present estimates close to 5 % for eGFR below 60 mL/min/1.73 m^2. In Norway the estimated prevalence using the NHANES definition was 10 % among adults over 20 years of age, with a 4.7 % prevalence of individuals with eGFR below 60 mL/min/1.73 m^2 [6]. Another population-based, nationally representative survey from Taiwan detected 7 % prevalence for individuals with eGFR below 60 mL/min/1.73 m^2 [7]. Studies from the UK [8], Japan [9], and Australia [10] confirm similar or higher prevalence. Among economically developing nations, a few nationally representative studies are available. Table 2.1 provides a summary of available research from large population-based studies (note: not all studies use a nationally representative sampling strategy) [11–18].

Studies examining awareness of diagnosis among persons living in economically developing coutnries reported that fewer than 10 % of patients with CKD knew of their disease [12, 13, 18]. We can postulate then few patients are seeking health care for CKD regions. Discerning what proportion of these patients reach ESRD and are able to access RRT is a further challenge. In the USA and other economically developed countries, a centralized agency manages reimbursement of the majority of RRT, e.g., Medicare in the USA and Australia, and the National Health Services in the UK. A majority of eligible and willing patients can access therapy, either through the safety net of the centralized agency or through private insurance. Thus, data on RRT prevalence and incidence is assumed to approximate the prevalence and incidence of ESRD [19].

This assumption does not hold true in most economically developing countries (Fig. 2.1). First some countries have extremely limited access to RRT. In Africa, 27 countries reported almost no availability of nephrologists, at fewer than one per million population [20]. In a survey returned by 31 of the 53 African countries, 13 reported fewer than 100 patients on dialysis [21]. Only ten countries perform transplantation. This scarcity in care likely reflects competing social and economic national priorities rather than lack of need—particularly given the high rates of malignant hypertension among young Africans [22].

Even in countries which have developed health care strategies related to ESRD, access to therapy is constrained by timely detection of ESRD [23]. The Brazilian Ministry of Health has committed to financing dialysis or transplant therapy via its public insurance; 90 % of patients on dialysis receive

Table 2.1 Chronic kidney disease epidemiology studies from economically developing countries

Study	Country	Sample size and methodology	Method of eGFR estimation	Prevalence of eGFR < 60 mL/min/1.73 m^2 (%)
Chen et al. [11]	China	Population-based study representative of China (n = 15,540)	MDRD	2.5
Zhang et al. [12]	China	Population-based study representative of Beijing residents (n = 13,925)	MDRD	1.7
Ingsathit et al. [13]	Thailand	Population-based study representative of Thailand (n = 3,459)	MDRD	8.6
Escobar et al. [14]	Chile	Population-based study representative of Chile (n = 3,619)	Cockcroft-Gault	5.9
Amato et al. [15]	Mexico	Primary care clinic-based study representative of Morelia (an urban area), Mexico (n = 3,564)	Cockcroft-Gault	8.5
Sumaili et al. [16]	Congo	Screening in 10 of 35 health zones of Kinhasa, not representative (n = 503)	MDRD	8
Cepoi et al. [17]	Romania	Voluntary participants of a national health screening program from Iasi county, Romania (n = 60,969)	MDRD	6.7
Singh et al. [18]	India	Population-based study representative of New Delhi and surrounding areas (n = 6,101)	MDRD	4.2

public health funding [24]. Despite this, experts from the country speculate that a large proportion of patients with ESRD die without diagnosis due to lack of early detection programs [25].

In South Africa, although wealthier patients have access to private dialysis units, those seeking care through the public hospitals undergo a selection process based on guidelines established by the National Department of Health [26]. From a rare single-center analysis from Cape Town, Moosa and Kidd report that the proportion of patients accepted for RRT actually declined as the number of patients presenting with advanced CKD increased over a 15-year period [26]. Overall, the unit accepted 53 % of presenting patients. The authors asserted that "poverty related" factors—such as unemployment or illiteracy—accounted for a majority of the reasons for rejection (Fig. 2.2). Younger patients, patients with nondiabetic kidney disease, and those living closer to the dialysis center were more likely to be accepted. Similarly only about 5–10 % of the Indian ESRD population is estimated to be "accepted" for RRT [27].

Complex factors underlie access to RRT in economically developing countries: government commitment to ESRD care, concentration of nephrologists and dialysis or transplant centers, and ability to detect CKD. Not surprisingly, provision of RRT may be divorced from the actual incidence of ESRD and tracks more closely with a country's income (Fig. 2.3) [28].

Provision of Renal Replacement Therapy

Not only do we know little about the characteristics of patients with CKD who die with ESRD in economically developing countries, but data on the even smaller proportion of patients who reach ESRD *and* are able to access RRT are scanty as well. In most developed countries, national registries

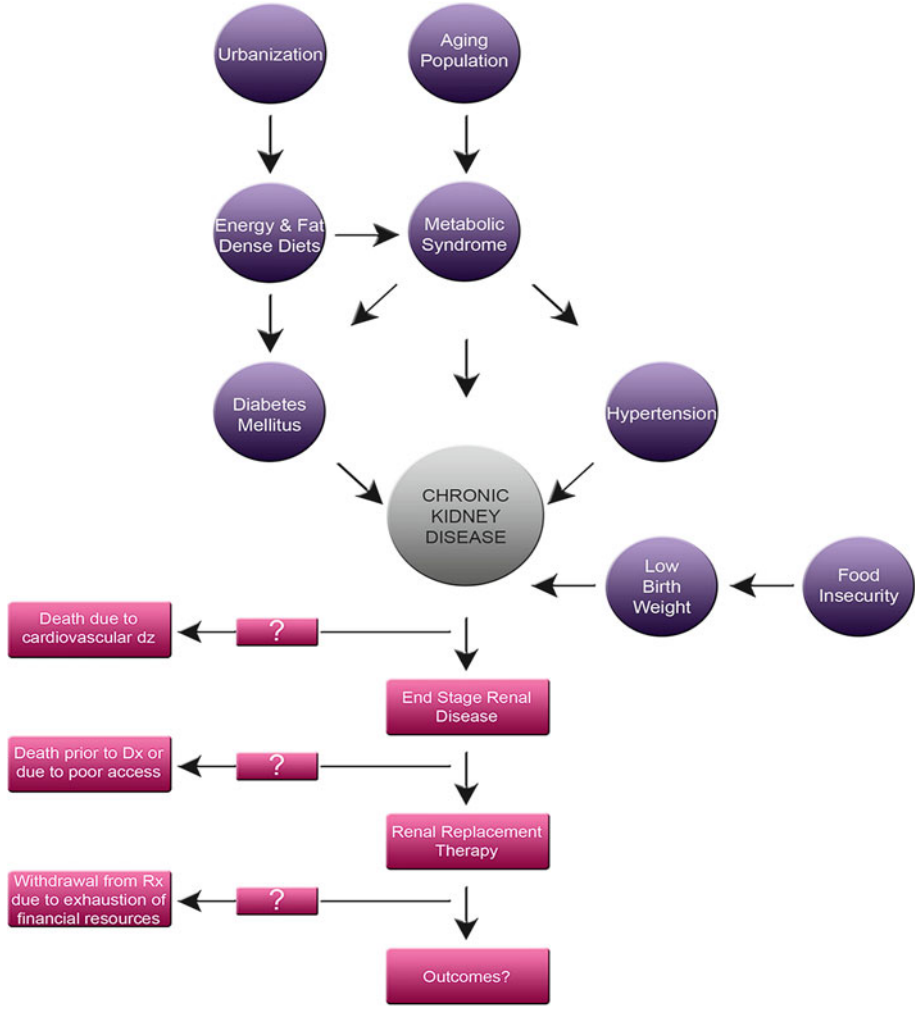

Fig. 2.1 A schematic of the risk factors (related to both malnutrition and obesity) linked with chronic kidney disease, also highlighting data gaps in morbidity and mortality related to chronic kidney disease and end-stage renal disease in low- and middle-income countries. *Dx* diagnosis, *Rx* treatment

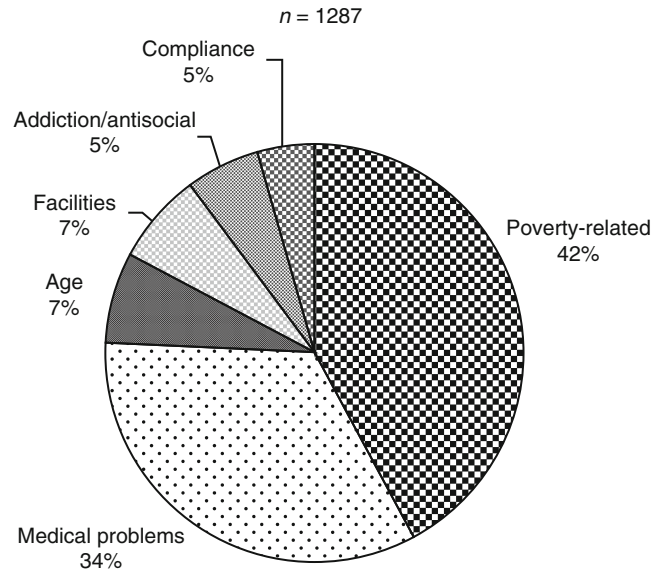

Fig. 2.2 Reasons for nonacceptance of patients for renal replacement therapy in a single center in Cape Town, South Africa. From Moosa, M.R. and M. Kidd, The dangers of rationing dialysis treatment: the dilemma facing a developing country. Kidney Int, 2006. 70(6): p. 1107–14. Reprinted with permission from Nature Publishing Group

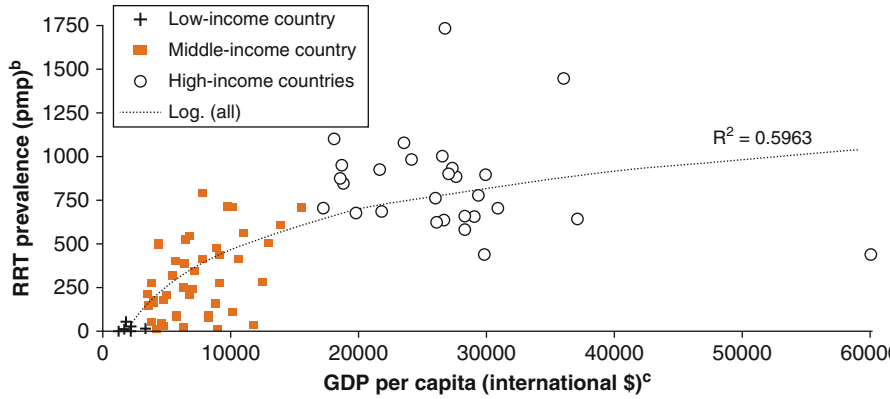

Fig. 2.3 Association between use of renal replacement therapy and gross domestic product of a country. From White, S.L., et al., How can we achieve global equity in provision of renal replacement therapy? Bull World Health Organ, 2008. 86(3): p. 229–37. Accessed at: http://www.who.int/bulletin/volumes/86/3/07-041715.pdf. June 26, 2013. Reprinted with permission from World Health Organization

gather data on dialysis and transplant provision and patient outcomes, e.g., the United States Renal Data System (USRDS), the European Renal Association-European Dialysis and Transplant Association (representing more than 20 European countries), and the Australia and New Zealand Dialysis and Transplant Registry. The USRDS has collected data since 1978, with detailed information on etiology of renal disease and patient outcomes including hospitalizations and mortality [29]. Based on its most recent report, about 450,000 (1,738 per million population) people are dialyzing or living with a transplant in the USA, and about 100,000 (355 per million population) people begin therapy annually. Provision of this therapy incurred a cost of $29 billion to Medicare (the primary payer). Cause of ESRD was attributed to diabetes or hypertension in three-fourths of the individuals starting RRT. Japan and Taiwan report the highest prevalence of RRT at more than 2,000 per million population, potentially due to a higher life expectancy allowing older patients with CKD to reach ESRD as well as improved survival while on dialysis therapy [30]. Interestingly, the incidence and prevalence of ESRD in Western European countries is well below that of Caucasians in the USA for reasons that are not clear. Whether this truly reflects a lower incidence of ESRD or the limited provision of ESRD services to selected patients (such as the elderly or those with multiple comorbidities) in Western European countries is not certain.

Very few systems of data collection exist in economically developing regions. Often patients are splintered between public institutions and a vast network of private providers. Registries of RRT are rare. One exception is the Latin American Society of Nephrology and Arterial Hypertension's Dialysis and Transplant Registry [31]. The registry received data from 18 of the 20 member nations in 2004, noting that 230,901 patients were on therapy (prevalence rate of 447 per million population). As noted by the report authors, member countries have not adopted uniform data collection methods. Typically the registry receives aggregate (not patient level) estimates from a participating country. The ERA-EDTA registry also captures aggregate data from some middle-income countries with burgeoning dialysis practices, including Russia, Romania, Latvia, Croatia, and Poland [32]. Most of these countries report a prevalence of 400–700 per million population, with the exception of Russia where prevalence rate was lowest at 170 per million population. No regional registries exist for South Asia, East Asia, Africa, or the Middle East.

A handful of economically developing countries submit aggregate RRT estimates to the USRDS [29]. The trends reported here offer an interesting perspective. Thailand, for example, reported a prevalence rate of 220 per million population in 2005; this number had doubled to 553 per million population in 2009. Similarly rapid gains were noted in Bangladesh, Mexico, and Romania. China and India have

Table 2.2 Estimated prevalence of renal replacement therapy worldwide

	Prevalence values (p.m.p.)		
	ESRD	Dialysis (HD+PD)	Transplant
Global	280	215	65
North America	1,505	1,030	470
Europe (thereof EU)	585 (850)	400 (550)	185 (295)
Japan	2,045	1,945	100
Asia (excluding Japan)	70	60	10
Latin America	380	320	65
Africa	70	65	5
Middle East	190	140	55

From Grassmann, A., et al., ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant, 2005. 20(12): p. 2587–93. Reprinted with permission from Oxford University Press

also likely experienced rapid increases in patients on RRT although data from these two countries are particularly sparse. In 1999, the Chinese Dialysis and Transplantation Registry Group sent out a questionnaire to dialysis centers across China but received responses from less than half. Based on these, the prevalence of patients on dialysis was a rather low 33 per million population with an incidence of 15 per million population [33]. However, more recent estimates from Beijing and Shanghai are more in-line with the Latin American region [34, 35]. The Shanghai Dialysis Registry reported a prevalence of around 200 per million population in 1999 with a rise to 400 per million population by 2005 [34]. This steep difference may reflect a large gradient between dialysis availability in an urban setting, compared with a rural one [36].

Grassmann et al. have attempted a worldwide estimate of RRT (Table 2.2) [37]. Their data are gathered through questionnaires distributed to in-county experts—with assistance from Fresenius Medical Care, one of the largest suppliers of dialysis equipment worldwide. According to their analysis, Asia and Africa have some of the lowest prevalence of RRT. More than half of the patients on RRT reside in North America or Europe.

Thus, from the limited data that are available from economically developing countries, we can conclude that the prevalence of RRT in ears about a quarter or less of the USA. Africa in particular lags behind in provision of RRT overall. Most middle-income countries have experienced a steep rise in RRT prevalence over the past 5 years but its provision may be concentrated around urban centers.

Modality Use

Hemodialysis is the primary modality used worldwide, even in economically developing regions. Based on the estimate by Grassmann et al., 77 % of patients on RRT are on dialysis with 89 % of this subgroup undergoing hemodialysis [37]. Use of peritoneal dialysis is proportionally greater in economically developing regions however (Fig. 2.4).

Specific countries within Latin America—Mexico, Guatemala, El Salvador, Nicaragua, and Dominican Republic—and Hong Kong are rare regions that rely more heavily on peritoneal dialysis than on hemodialysis [31]. The extent of peritoneal dialysis use is often influenced by government policy and relative costs of obtaining supplies. Nearly a quarter of the world's peritoneal dialysis population resides in Mexico [38]. After its relatively early introduction to Mexican physicians in the 1970s, the widespread use of peritoneal dialysis has also been encouraged by local manufacturing of required solutions, dissemination of simple techniques to primary care physicians, and government reimbursement policy [38]. In Hong Kong, nephrologists first initiate peritoneal dialysis in patients

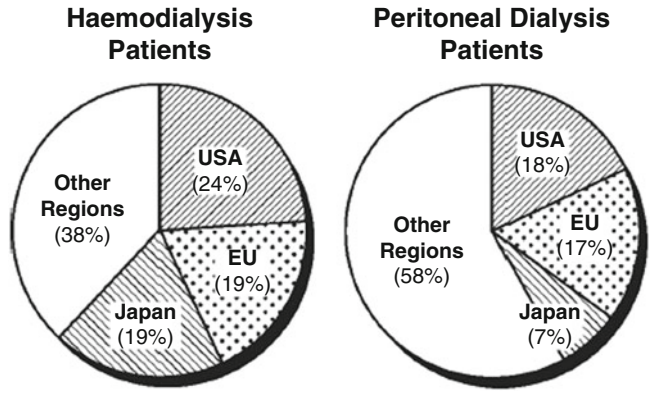

Fig. 2.4 Proportion of patients undergoing hemo- and peritoneal dialysis in various regions; a majority of patients live in North America, Europe, or Japan. From Grassmann, A., et al., ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant, 2005. 20(12): p. 2587–93. Reprinted with permission from Oxford University Press

with ESRD and use hemodialysis only in patients who experience modality failure, resulting in the use of peritoneal dialysis in more than half of patients with ESRD [39]. In Thailand, the government has instituted a similar policy as in Hong Kong, and there has been a recent, rapid growth of peritoneal dialysis. Economic evaluations carried out in the developed economy context have confirmed lower payer costs of peritoneal dialysis with no difference in survival, compared with hemodialysis [40]. Large studies from Brazil and Mexico have shown low rates of peritonitis (e.g., one episode every 24–30 months [41, 42]). Acceptable rates of peritonitis have also been reported from African countries such as Sudan [21].

Despite the expectation that peritoneal dialysis should be the favored modality—it is a low technology and infrastructure modality, and published data to date indicate acceptable outcomes and low rates of peritonitis—hemodialysis remains the predominant modality used in most economically developing countries. Paradoxically, one reason may be the cheaper labor costs involved in having nurses perform dialysis, compared with the more expensive use of imported solutions and supplies [43]. As well, nephrologists working in economically developing countries perceive several barriers to peritoneal dialysis and sometimes do not discuss the modality as an option. For example, in a single center from an Indian state-run hospital, only 30 % of patients on chronic hemodialysis were aware of peritoneal dialysis as a modality [44]. The nephrologists identified lack of an organized program and doubtful patient compliance as some of the barriers to peritoneal dialysis therapy [44]. Similarly in a survey of 68 Filipino nephrologists—another country with low peritoneal dialysis utilization rates—about 40 % of nephrologists surveyed stated that they would preferentially recommend hemodialysis over peritoneal dialysis [45]. They cited poor patient hygiene, visual impairment, and lack of manual dexterity as potential reasons for hemodialysis preference.

To overcome some of these obstacles to wider adaptation of peritoneal dialysis, governments would need to prioritize infrastructure building for peritoneal dialysis, ensure a steady supply of the low-cost dialysate solution, and organize physician training. Only then would patient volumes reach a level large enough to sustain a successful peritoneal dialysis strategy (Table 2.3).

Of the three modalities, transplant offers the best survival [40]. In developed countries, rates are limited by availability of organs. Approximately 30 % of patients with ESRD are living with a transplant in the USA, with a majority (>60 %) having received deceased donor transplants [29]. Somewhat higher proportions of prevalent transplant patients (between 40 and 50 %) are reported in European countries including France, the UK, Norway, and Sweden [32], but deceased donor

Table 2.3 Key ingredients for establishing a successful peritoneal dialysis (PD) program in a developing country

1. Developing a chronic kidney disease identification and education program
2. Developing a healthcare policy addressing the problems of end-stage renal disease therapy
3. Integrating PD into the program
4. Developing a viable financial model to support the program
5. Having appropriate individuals (nurses, physicians, etc.) trained in the details of PD therapy
6. Developing strategies to monitor the outcomes of the therapy to permit adjustments and modifications to be made to ensure the success of the program
7. Maintaining communication with groups/individuals outside the country to provide support as needed for focused problems

From Finkelstein et al. Peritoneal Dialysis In The Developing World: Recommendations From A Symposium At The ISPD Meeting 2008. Peritoneal Dialysis International. 2009;(29):618–622. Reprinted with permission

transplantation predominates here as well. Japan is one exception; overall rates of transplantation are lower and living donation predominates, partly due to a societal and organizational reluctance to accept organs from brain-dead donors [46]. Although the cost of therapy is high for the first year, costs drop off steeply after this time, resulting in an overall favorable cost-benefit ratio in comparison with dialysis therapy [40].

The provision of transplants varies widely in economically developing countries. Some countries report a thriving and successful transplantation program. For example, Iran reports that with government support and regulation of a *paid-donation* program, the number of transplantation centers rose from 2 to 25 over a 2 decade period [47, 48]. Living unrelated donation predominates, both donors and patients were young (under 40 years of age on average), and 3-year graft survival rates were over 85 %. Similarly the Brazilian government helps coordinate transplantation, particularly procurement of deceased organs and supply of immunosuppressive medications [49]. There are 138 transplant centers in Brazil, resulting in a prevalence of 123 per million population (comparable number in the USA: 528 per million population) [29, 31]. The proportion of patients receiving deceased donor transplantation is increasing.

In other regions, particularly East and South Asia, transplantation activity is harder to track. In China, a practice of organ procurement from deceased prisoners has been widely denounced [50]. After the government announced its intention to prohibit such procurement, a steep rise in the black market sale of organs was expected. India is widely known to have a thriving black market, with an estimated 2,000 kidneys sold each year [47]. Pakistan's Sindh Institute—a large, partially governmentally funded hospital—reported that foreigners received up to two-thirds of the renal transplants performed. Thus, although the reported number of renal transplants is around 3,000 per year in India, the number of native Indian patients who are able to access this therapy is likely much lower [51]. Similar practices have been reported in the Philippines.

The expense of therapy not only deters widespread use of RRT, it also forces nephrologists in economically developing countries to modify dialysis and transplantation practice. Although data on outcomes are rare, single-center studies have reported significant reliance on two times per week hemodialysis as well as reuse of older cellulosic membranes. In a report of 259 patients on hemodialysis at an Indian tertiary care center, 14 % were not able to adhere to the prescribed thrice weekly schedule [52]. Single-pool *Kt*/*V*–a marker of dialysis adequacy – was less than 1 in half of the patients. A majority of patients who started dialysis discontinued therapy when financial resources ran out within the first year; and early mortality due to uremic complications was high. Twenty-eight percent of registered Beijing patients were undergoing two times per hemodialysis in 2002 [35]. To save on costs, the number of peritoneal dialysis exchanges performed may be suboptimal as well, and immunosuppressive medication use may be tapered quickly for patients with transplants. Programs rely more on older medications such as cyclosporine and azathioprine (as compared with tacrolimus and

mycophenolate mofetil). The Sindh Institute in Pakistan ascribes to an aggressive tapering of immunosuppression, for example, discontinuing cyclosporine altogether in individuals with fully matched kidneys who are rejection-free at 1 year post-transplant [53].

In summary, despite data on the improved cost-effectiveness and survival of transplantation (compared with any dialysis) and the very valid hypothesis that peritoneal dialysis carries several advantages in resource-constrained settings, hemodialysis dominates these modalities. A concerted governmental effort is likely required to prioritize the use of peritoneal dialysis and transplantation; example programs exist in Mexico and Brazil, respectively. Data on outcomes of therapy are sparse, but its collection is particularly important since a majority of individuals are likely receiving suboptimal care and/or withdraw from therapy upon exhaustion of personal resources.

Nutrition as a Risk Factor and Key Intervention

With these challenges in provision of RRT, economically developing countries should focus on prevention of CKD and ESRD. Thus tackling risk factors for CKD is a key area of intervention. Nutrition in particular can play an important role.

Obesity and subsequent development of metabolic syndrome or frank diabetes and hypertension likely drove the largest part of the rise in ESRD rates we have seen in the USA and other developed nations. A similar pattern is repeating now in economically developing regions. As previously noted, the prevalence of diabetes and hypertension will rise proportionally more in economically developing countries. Increasing obesity and declining physical activity, corresponding to the rapid urbanization and aging of the population, are felt to underlie this accelerating rate of metabolic syndrome, diabetes, and hypertension.

Obesity has skyrocketed worldwide, tripling in prevalence in economically developing nations where the Western lifestyle has come into vogue [54]. Using data gathered from the United Nations Food and Agriculture Organization and the Chinese Health and Nutrition Survey, Popkin and Drewnowski have documented a "nutrition transition" [55]. With the advent technological efficient manufacturing of edible oils, a greater proportion of households living in developing countries can access this cheaper version of fat, even at low household incomes (Fig. 2.5). The same survey in China demonstrated a shift away from vegetable and grain intake and towards animal protein intake,

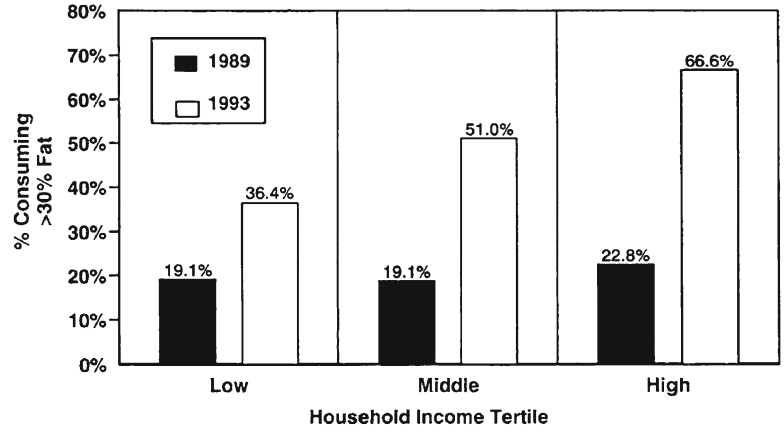

Fig. 2.5 Fats have become a larger portion of diets around the world over time. Data from the China Health and Nutrition Survey. From Drewnowski A, Popkin BM. The nutrition transition: new trends in the global diet. Nutr Rev. 1997 Feb;55(2):31–43. Reprinted with permission from John Wiley and Sons

resulting over time in a higher energy content per gram of food consumed in both urban and rural areas—although the shift was more dramatic for urban areas. Urban diets rely more on caloric sweeteners than previously [56].

Food retail has changed substantially as well. Animal meat prices have declined over time, allowing for its greater consumption. Supermarket retailers—who have an advantage in prices when selling dry processed goods or frozen prepared foods—now dominate the landscape in many economically developing countries. For example, Reardon et al. describe that over the 2-decade period spanning 1980–2000, supermarkets have grown from occupying a 10–20 % share to 50–60 % share of the food retail market in Latin America [57]. Foreign direct investment in developing country economies is felt to be driving this phenomenon. Similarly, in Indonesia the fast food chain industry has boomed, going from fewer than 10 chains in 1980s to over 70 chains in the 1990s [58]. Potentially due to influx of women into the labor force, the average Indonesian spends 30 % more on prepared foods each year.

The outlined dietary changes, coupled with decline in strenuous physical activity as the service sector employs a greater proportion of the rapidly growing urban population, have led to an increase in the average body mass index in many economically developing countries. Initially this change was felt to be confined to individuals with higher socioeconomic status, but newer data demonstrates that as a country's overall income increases, individuals of lower socioeconomic status experience a higher burden of obesity, than their "richer" counterparts [59].

The adverse impact of this obesity—i.e., the end organ damage in the form of development of coronary heart disease or CKD—may be more powerful among certain populations. A tendency towards central adiposity and insulin resistance explains this phenomenon among South Asians, who are widely recognized to be at increased risk for coronary heart disease. In a case–control study of healthy Canadians, South Asians carried a significantly higher percentage of their total body fat in the visceral fat compartment [60]. Another study demonstrated an increased insulin resistance among South Asians, even after adjusting for abdominal and generalized obesity [61]. Studies within India have demonstrated a high prevalence of metabolic syndrome, affecting up to one-third of the urban population (compared with about a quarter of the population in the USA) [62, 63]. A cross-sectional evaluation in the UK identified South Asian migrants as having the highest prevalence for metabolic syndrome, compared with Caucasians and African Caribbeans [64]. The association of coronary heart disease with metabolic syndrome was strongest among the South Asians.

Thus, not only is obesity rising at a rapid pace due to the consumption of high-energy, processed foods, its impact on chronic diseases including CKD may be proportionally more among select ethnicities. A change in the demographics of patients on dialysis in part reflects the increasing burden of obesity. For example, Brazil reports that 8 % of its patients on dialysis were considered to have diabetic nephropathy in the 1980s, but among patients more recently begun on dialysis, 18 % were considered to have diabetic nephropathy [65].

The other side of the coin—protein-energy wasting—may carry its own detrimental consequences for CKD. Children with oligonephronia with bilateral renal hypoplasia develop proteinuria and ESRD by adolescence [66]. Several large-scale epidemiology studies in the USA have demonstrated a 1.5–2.5-fold increase in odds for CKD among individuals with low birth weight [67, 68]. Biological plausibility is suggested by the hypothesis that growth and development of the kidneys is sacrificed in favor of heart and brain development in the child with low birth weight [69]. Decreased glomerular number at birth leads to an increase in glomerular size in compensation, with resulting intraglomerular hypertension predisposing to glomerulosclerosis. This link between low glomerular number and low birth weight has been confirmed in autopsy series. Another proposed mechanism emphasizes rapid weight gain post-delivery as a critical bell weather for weight gain in adulthood [70]. Researchers also invoke the "thrifty gene" hypothesis—in which the fetus creates adaptations to conserve energy when developing in an undernourished environment [71].

For countries with a large burden of food-insecure mothers as well as vulnerability to natural disasters including famine, this correlation between low birth weight and CKD as well as other chronic diseases carries important policy implications. It is no surprise then that both the United Nations and the World Health Organization have been developing strategies to correct this "nutrition paradox" of undernutrition and obesity facing economically developing countries [72]. They promote consumption of home prepared, fruits- and vegetable-rich, and low-sodium diet [72]. A focus on maternal nutrition and exclusive breast-feeding may help correct the undernutrition of infants in particular.

Summary

In summary, we are seeing that prevalence of CKD in economically developing regions is approaching that of developed ones. More and more persons living in these resource-constrained settings will likely be affected by CKD with the rise of metabolic syndrome, diabetes, and hypertension—risk factors tied chiefly to obesity and a nutrition transition. Currently a large proportion of patients with CKD in economically developing countries who approach ESRD likely die without accessing therapy; the limited few who are able to access therapy are potentially receiving suboptimal care. Emphasizing peritoneal dialysis and transplantation over hemodialysis as modalities of choice for treatment of ESRD may make provision of RRT more sustainable.

References

1. Department of Economic and Social Affairs. World population ageing 2009. New York: United Nations; 2009.
2. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012;70(1):3–21.
3. Wild S, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
4. Kearney PM, et al. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
5. Coresh J, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038–47.
6. Hallan SI, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006;17(8):2275–84.
7. Hsu CC, et al. High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey. Am J Kidney Dis. 2006;48(5):727–38.
8. Stevens PE, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int. 2007;72(1):92–9.
9. Imai E, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11(2):156–63.
10. Chadban SJ, et al. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. J Am Soc Nephrol. 2003;14(7 Suppl 2):S131–8.
11. Chen J, et al. Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years. Kidney Int. 2005;68(6):2837–45.
12. Zhang L, et al. Prevalence and factors associated with CKD: a population study from Beijing. Am J Kidney Dis. 2008;51(3):373–84.
13. Ingsathit A, et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. Nephrol Dial Transplant. 2010;25(5):1567–75.
14. Escobar C, et al. Renal health in Chile. Ren Fail. 2006;28(8):639–41.
15. Amato D, et al. Prevalence of chronic kidney disease in an urban Mexican population. Kidney Int Suppl. 2005;97:S11–7.
16. Sumaili EK, et al. Prevalence of chronic kidney disease in Kinshasa: results of a pilot study from the Democratic Republic of Congo. Nephrol Dial Transplant. 2009;24(1):117–22.

17. Cepoi V, et al. The prevalence of chronic kidney disease in the general population in Romania: a study on 60,000 persons. Int Urol Nephrol. 2012;44(1):213–20.
18. Singh NP, et al. Prevalence of low glomerular filtration rate, proteinuria and associated risk factors in North India using Cockcroft-Gault and modification of diet in renal disease equation: an observational, cross-sectional study. BMC Nephrol. 2009;10:4.
19. Gilbertson DT, et al. Projecting the number of patients with end-stage renal disease in the United States to the year 2015. J Am Soc Nephrol. 2005;16(12):3736–41.
20. El Matri A, et al. Renal replacement therapy resources in Africa. Arab J Nephrol Transplant. 2008;1(1):9–14.
21. Abu-Aisha H, Elamin S. Peritoneal dialysis in Africa. Perit Dial Int. 2010;30(1):23–8.
22. Naicker S. End-stage renal disease in sub-Saharan Africa. Ethn Dis. 2009;19(1 Suppl 1):S1-13-5.
23. Barsoum RS. Chronic kidney disease in the developing world. N Engl J Med. 2006;354(10):997–9.
24. Lugon JR. End-stage renal disease and chronic kidney disease in Brazil. Ethn Dis. 2009;19(1 Suppl 1):S1-7-9.
25. Zatz R, Romao Jr JE. End-stage renal failure and national resources: the Brazilian experience. Ren Fail. 2006;28(8):627–9.
26. Moosa MR, Kidd M. The dangers of rationing dialysis treatment: the dilemma facing a developing country. Kidney Int. 2006;70(6):1107–14.
27. Jha V. End-stage renal care in developing countries: the India experience. Ren Fail. 2004;26(3):201–8.
28. White SL, et al. How can we achieve global equity in provision of renal replacement therapy? Bull World Health Organ. 2008;86(3):229–37.
29. US Renal Data System. USRDS 2011 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2011. p. 2011.
30. Tsukamoto Y. End-stage renal disease (ESRD) and its treatment in Japan. Nephrol Dial Transplant. 2008;23(8):2447–50.
31. Cusumano A, et al. End-stage renal disease and its treatment in Latin America in the twenty-first century. Ren Fail. 2006;28(8):631–7.
32. ERA-EDTA Registry. ERA-EDTA registry annual report 2009. Amsterdam: Academic Medical Center, Department of Medical Informatics; 2011.
33. Dialysis and Transplantation Registration Group. The report about the registration of dialysis and transplantation in China 1999. Chin J Nephrol. 2001;17:77–8.
34. Yao Q, Zhang W, Qian J. Dialysis status in China: a report from the Shanghai Dialysis Registry (2000–2005). Ethn Dis. 2009;19(1 Suppl 1):S1-23-6.
35. Zuo L, Wang M. Current status of hemodialysis treatment in Beijing, China. Ethn Dis. 2006;16(2 Suppl 2):S2-31-4.
36. Zhang W, et al. Clinical characteristics and outcomes of rural patients with ESRD in Guangxi, China: one dialysis center experience. Int Urol Nephrol. 2010;42(1):195–204.
37. Grassmann A, et al. ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant. 2005;20(12):2587–93.
38. Riella MC, Locatelli AJ. History of peritoneal dialysis in Latin America. Perit Dial Int. 2007;27(3):322–7.
39. Ho Y-W, et al. Hong Kong registry report 2004. Hong Kong J Nephrol. 2005;7(1):38–46.
40. Winkelmayer WC, et al. Health economic evaluations: the special case of end-stage renal disease treatment. Med Decis Making. 2002;22(5):417–30.
41. Fernandes N, et al. The Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD): characterization of the cohort. Kidney Int Suppl. 2008;108:S145–51.
42. Paniagua R, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13(5):1307–20.
43. Just PM, et al. Reimbursement and economic factors influencing dialysis modality choice around the world. Nephrol Dial Transplant. 2008;23:2365–73.
44. Mahajan S, Tiwari S, Karla V, Bhowmik D, Agarwal S. Factors affecting the use of peritoneal dialysis among the ESRD population in India: a single-center study. Perit Dial Int. 2004;24(6):538–41.
45. Cruz DN, Troidle L, Danguilan R, Padilla B, Frando L, Sebastian E, Sy-Lim A, Luz V, Finkelstein F. Factors influencing dialysis modality for end-stage renal disease in developing countries: a survey of Filipino nephrologists. Blood Purif. 2011;32(2):117–23.
46. Fukuhara S, et al. The organization and financing of end-stage renal disease treatment in Japan. Int J Health Care Finance Econ. 2007;7(2–3):217–31.
47. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available information. Bull World Health Organ. 2007;85(12):955–62.
48. Einollahi B, Taheri S. Renal transplantation practice in Iran and the Middle East: report from Iran and a review of the literature. Ann Transplant. 2008;13(1):5–14.

49. Medina-Pestana JO. Organization of a high-volume kidney transplant program—the “assembly line” approach. Transplantation. 2006;81(11):1510–20.
50. Foster P. China admits organs removed from prisoners for transplants. The Telegraph. 2009. London.
51. Sakhuja V, Sud K. End-stage renal disease in India and Pakistan: burden of disease and management issues. Kidney Int Suppl. 2003;83:S115–8.
52. Rao M, et al. Haemodialysis for end-stage renal disease in Southern India—a perspective from a tertiary referral care centre. Nephrol Dial Transplant. 1998;13(10):2494–500.
53. Rizvi SA, et al. Renal transplantation in developing countries. Kidney Int Suppl. 2003;83:S96–100.
54. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. N Engl J Med. 2007;356(3):213–5.
55. Drewnowski A, Popkin BM. The nutrition transition: new trends in the global diet. Nutr Rev. 1997;55(2):31–43.
56. Popkin BM. Using research on the obesity pandemic as a guide to a unified vision of nutrition. Public Health Nutr. 2005;8(6A):724–9.
57. Reardon T, et al. The rise of supermarkets in Africa, Asia, and Latin America. Am J Agr Econ. 2003;85(5):1140–6.
58. Chowdhury S, et al. The rise of supermarkets and vertical relationships in the Indonesian food value chain: causes and consequences. Asian J Agric Dev. 2005;2(1 & 2):30–48.
59. Monteiro CA, et al. Socioeconomic status and obesity in adult populations of developing countries: a review. Bull World Health Organ. 2004;82(12):940–6.
60. Lear SA, et al. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. Obesity (Silver Spring). 2007;15(11):2817–24.
61. Chandalia M, et al. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J Clin Endocrinol Metab. 1999;84(7):2329–35.
62. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. Metab Syndr Relat Disord. 2009;7(6):497–514.
63. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care. 2004;27(10):2444–9.
64. Tillin T, et al. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and White Europeans: a UK population-based cross-sectional study. Diabetologia. 2005;48(4):649–56.
65. Oliveira MB, Romao Jr JE, Zatz R. End-stage renal disease in Brazil: epidemiology, prevention, and treatment. Kidney Int Suppl. 2005;97:S82–6.
66. Drukker A. Oligonephropathy: from a rare childhood disorder to a possible health problem in the adult. Isr Med Assoc J. 2002;4(3):191–5.
67. Li S, et al. Low birth weight is associated with chronic kidney disease only in men. Kidney Int. 2008;73(5):637–42.
68. White SL, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. Am J Kidney Dis. 2009;54(2):248–61.
69. Hoy WE, et al. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol. 2005;16(9):2557–64.
70. Stettler N, et al. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. Circulation. 2005;111(15):1897–903.
71. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr. 2004;23(6 Suppl):588S–95.
72. Caballero B. A nutrition paradox—underweight and obesity in developing countries. N Engl J Med. 2005;352(15):1514–6.

Chapter 3
Dietary Assessment in Kidney Disease

Linda W. Moore

Key Points

- An overview of the Dietary Reference Intakes and suggestions that these new approaches to dietary intake assessment may have applicability to kidney diseases.
- Historical approaches to dietary intake assessment have provided only moderate correlation to biomarkers of dietary intake.
- Multiple methods and multiple days of dietary intake assessment should be considered when evaluating dietary intake in an individual as well as in groups.

Keywords Dietary intake assessment • Dietary record • Food Frequency Questionnaire • Recommended dietary allowance • Chronic kidney disease • Acute kidney injury • Hemodialysis • Kidney transplantation • Biomarkers

Abbreviations

AI	Adequate intake
AMDR	Acceptable macronutrient distribution range
AMPM	Automated Multiple-Pass Method
ASA24™	Automated self-administered 24-h recall
BMI	Body mass index
BMR	Basal metabolic rate
CKD	Chronic kidney disease
DEI	Dietary energy intake
DHQ	Diet History Questionnaire
DPI	Dietary protein intake
DRI	Dietary Reference Intakes
EAR	Estimated average requirement
EBPG	Evidence-based practice guideline
EER	Estimated energy requirement

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EI	Energy intake
ELMP	Exchange Lists for Meal Planning
FFQ	Food Frequency Questionnaire
FNDDS	Food and Nutrient Database for Dietary Surveys
IOM	Institute of Medicine
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/*V*	Dialyzer solute clearance (*K*), time on dialysis (*t*), volume of solute distribution (*V*)
NCDS	National Cooperative Dialysis Study
NHANES	National Health and Nutrition Examination Survey
OPEN	Observing protein and energy nutrition
PCR	Protein catabolic rate
RDA	Recommended dietary allowance
REE	Resting energy expenditure
TEE	Total energy expenditure
UL	Tolerable upper intake level
USDA	United States Department of Agriculture

Introduction

Understanding the dietary intake of people with kidney disease is fundamental to addressing their treatment or for the prevention or progression of disease. Several recent guidelines on chronic kidney disease (CKD) vary on recommendations for assessing the dietary intake of patients (Table 3.1) [1–8]. Whether the approach to assessing dietary intake is considered warranted is not discussed in these guidelines, so perhaps it is not an issue of the reliability of dietary intake assessment methods but rather one of the origin of the guidelines. For example, the guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) on nutrition [1] are written to be multidisciplinary and include guidelines for dietitians. The guidelines for CKD that were produced by the Academy of Nutrition and Dietetics are written specifically for dietitians [4]. However, many of the other guidelines for CKD are physician specific, and obtaining the dietary record is not included in their guidelines, perhaps because physicians do not normally collect this information. In contrast, assessment of dietary intake is a significant practice of dietetics, and they routinely evaluate dietary intake in assessing the nutritional status of patients.

Purpose and Utility of Dietary Intake Assessment

The intent of dietary intake assessment is to aid in understanding the eating patterns and practices of individuals or groups for education, for nutritional status assessment and disease risk, and for research. As an educational tool, the dietary intake assessment serves as a type of evaluation pre- and post-education or pre- and post-event evaluation (e.g., the diagnosis of disease, occurrence of an acute injury). Soliciting dietary intake information prior to the time of a disease diagnosis (the diet history) forms a baseline understanding for the educational session—a sort of pretest. Once the education sessions begin, additional dietary intake assessments provide a status of individual or group understanding and food opportunity (the ability to obtain or interest in obtaining or consuming the recommended foods). Fundamental to behavior change is understanding the difference between a food or a food pattern previously practiced and the one being recommended. Dietary intake records help to reinforce the education.

Table 3.1 Assessment of dietary intake recommended in practice guidelines for chronic kidney disease

Guideline	Publication year	Target population	Targeted nutrients	Recommended methodology
KDOQI Nutrition [1]	2000	Adults with GFR ≤25 mL/min and children	Protein, energy	Interviews and diaries; 24-h recall, 3-day food record (including 1 weekend day and/or 1 dialysis day, if applicable)
EBPG guideline on nutrition [2]	2007	Adults requiring maintenance hemodialysis	Protein, energy	Dietary records (24-h recall, 3- or 7-day food record) or food questionnaires
KDOQI Guideline for Diabetes and CKD [7]	2007	People with diabetes having CKD stages 1–5	Protein for CKD stages 1–4	Not specified
US Department of Veterans Affairs [5]	2008	Adult incident or prevalent patients (not requiring dialysis or transplant) with eGFR 30–60 mL/min having evidence of kidney damage	Protein, potassium, sodium, phosphorus	Food recall records for patients with malnutrition
Medical Services Commission, British Columbia [6]	2008	Adults ≥19 years of age at increased risk for CKD (diabetes, hypertension, family history of kidney disease, or ethnicity as First Nations, Pacific Islanders, African descent, Asian) or already have CKD	Not specified	Not specified
Chronic Kidney Disease, National Collaborating Centre for Chronic Disease [8]	2008	People with CKD not requiring dialysis or transplant, ≥16 years of age	Potassium, phosphate, protein, calorie, salt intake (unspecified amounts)	Not specified
KDOQI Pediatric Nutrition [3]	2009	Children, stages 2–5 CKD	Protein, energy, vitamins (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, cobalamin, ascorbic acid, retinal, α-tocopherol, vitamin K, vitamin D, folic acid), minerals (copper, zinc, calcium and phosphorus), and amino acids (carnitine)	Not specified
Academy of Nutrition and Dietetics [4]	2010	Adults, eGFR <50 mL/min	Protein, energy, phosphorus, calcium, sodium, potassium	Diet history, 24-h recall, 3–7-day record

KDOQI Kidney Disease Outcomes Quality Initiative, *GFR* glomerular filtration rate, *EBPG* evidence-based practice guideline, *CKD* chronic kidney disease, *US* United States, *mL/min* milliliters per minute

Eating practices and patterns are related to nutritional status and disease risk. The discovery of most vitamins and essential nutrients came about as certain foods were demonstrated to be antidotes to common diseases. For example, citrus fruits for treatment or prevention of scurvy resulted in the knowledge that foods missing from the diet resulted in disease and, ultimately, the discovery of ascorbic acid (vitamin C) as the essential missing nutrient [9, 10]. These discoveries resulted in the assessment of dietary intake as a surrogate for nutritional status. In contrast to missing nutrients, examining dietary intake also provided information on dietary excesses for understanding how foods consumed in excess were contributing to disease conditions (e.g., overweight/obesity, heart disease, diabetes, kidney disease).

Methodology of Dietary Intake Assessment

Dietary intake assessment is performed in different ways. A recollection of food intake may be obtained for either a previous 24-h period (e.g., the 24-h recall) or over a longer period of time (e.g., the Food Frequency Questionnaire (FFQ)). Both of these methods require the person to remember what foods they consumed. Alternatively, a food diary is a prospective food record and may be collected for a period of days or longer. Each method has advantages and disadvantages as well as applicability. Comparing dietary intake to recommended intake will be different with each instrument.

Recently, the Food and Nutrition Board of the Institute of Medicine (IOM) joined with Canadian scientists to establish reference values for nutrient intakes of healthy US and Canadian individuals and populations [11, 12]. These reference values replace the previous publications of Recommended Dietary Allowances (RDA) used in the USA and Recommended Nutrient Intakes used in Canada and are now referred to as the Dietary Reference Intakes (DRIs). The DRIs are intended for dietary planning [13] and assessment [14] of both individuals and groups and take into account the distribution of nutrient requirements and usual intake. According to the DRIs, the RDA is the dietary intake that would meet the needs of almost all healthy individuals (97–98 %) of a particular age or sex. The RDA is based on the estimated average requirement (EAR) and is two standard deviations above the EAR. The EAR is the average daily nutrient intake required to meet the needs of half of the healthy population of a particular age or sex and provides insight into the proportion of a group that will experience inadequate nutrient intake [15]. Assessment of estimated energy requirement (EER) is different from EAR in that the EER is the estimated energy intake (EI) that would be required to maintain body weight (e.g., the body weight of someone who has a body mass index [BMI] between 18.5 and 25 kg/m^2) according to their life stage, sex, and activity level. The adequate intake (AI) is the mean intake of a nutrient or food component in a group of healthy people and is used as a reference when no RDA is available (e.g., dietary fiber or omega-3 fatty acids). The tolerable upper intake level (UL) of a nutrient has been described as the highest average nutrient intake that is likely to cause no health risk. Another consideration in dietary assessment is the distribution of nutrients. An Acceptable Macronutrient Distribution Range (AMDR) for adults is available for individuals for carbohydrate (45–65 % of energy), protein (10–35 % of energy), and fat (20–35 % of energy). Together, these terms represent the DRIs and provide more than one assessment of dietary intake. For example, assessing whether an individual or a group meet the AI level but exceed the UL is a new opportunity for dietary intake assessment. These terms and definitions represent current guidance on dietary assessment and will be referred to in subsequent sections of this chapter. A description of the tools currently used in dietary intake assessment, how they are analyzed, and where they are applied to DRIs are reviewed below.

24-h Recall

Typically used as a quick assessment of dietary intake, the 24-h recall requires that the patient be able to remember what was consumed on the day prior to the interview day. Memory can be aided by the presence during the interview by the presence of another family member or someone residing with the patient. The interviewer who is leading the recall also utilizes prompts to aid in the recall of foods (e.g., time of day, the setting during which the food was consumed) and portion sizes (e.g., visuals such as food models, measuring tools, or representative serving utensils). The 24-h recall is easy to implement and quick to analyze. It is often used in the clinic or research setting for individuals and for groups.

Data from the 24-h recall are analyzed by using proprietary nutrient analysis software (see a list of examples in "Diet Record or Diary" section), by entering foods into the free online Nutrient Data Laboratory service from the US Department of Agriculture's Agricultural Research Library [16], or by using Exchange Lists for Meal Planning (ELMP) from the Academy of Nutrition and Dietetics [17]. An example of the use of the AND's Exchange Lists is shown in Tables 3.2 and 3.3. The ELMP is a crude estimate of macronutrient distribution across foods by grouping the foods into categories (e.g., starch, fruit, dairy, non-starchy vegetables, meats and meat substitutes, and fats). Combination foods (e.g., lasagna, casseroles, desserts) are accounted for by including all the food groups represented by the combination food. Another method of collecting and analyzing the 24-h recall is the new automated, self-administered 24-h recall (ASA24™) reviewed below [18].

Automated Multiple-Pass Method

A method for collecting a 24-h recall from in-person interviews or over the telephone is the computerized Automated Multiple-Pass Method (AMPM) [19, 20]. The process of the AMPM incorporates five discussions called "passes" of foods consumed the previous day (Fig. 3.1) [20]. First, the participant is asked for a *quick list* of all foods eaten the previous day; a series of questions are then asked to probe for potential *forgotten foods* (such as snacks, nonalcoholic beverages, sweets). The third pass is a series of questions regarding the *time and occasion* that foods were eaten, and it is used to sort foods into groups by eating occasion. The fourth pass is a *detailed review* of the foods to obtain descriptions and amounts and also to include additions to the foods. The fifth and *final review* is another opportunity to list foods not recalled earlier.

Incorporating the system into a computer model has allowed the interview to be automated, and it standardizes the probing methods. According to Raper et al., the AMPM contains more than 2,400 questions, 21,000 response options, and 500,000 potential pathways [20]. The system allows for prefilled responses, which reduces the interviewer and respondent burden if an item was detailed in the first (*quick list*) pass. For example, identifying the type of juice as orange would not require that information to be asked in the fourth (*detailed* review) pass. Instead, the *detailed* review pass could focus on identifying whether the item was 100 % juice and if it was calcium fortified. The AMPM has been used in the National Health and Nutrition Examination Survey (NHANES) since 2001 and is administered by trained interviewers [21].

The Automated Self-Administered 24-h Recall

Recently, collaborations between the United States Department of Agriculture (USDA), the National Cancer Institute, and Baylor College of Medicine (Houston, TX) have transformed the AMPM methodology into an Internet-based automated self-administered 24-h recall (ASA24™) [18, 22].

Table 3.2 Crude dietary analysis spreadsheet for total kilocalories, carbohydrate, protein and fat using food groups to estimate intake

	A	B	C	D	E	F	G
1	*	Starch	Fruit	Milk†	Nonstarch vegetable	Meat/substitute‡	Fat
2	Breakfast						
3							
4	Lunch						
5							
6	Dinner						
7							
8	Snack						
9							
10	*Total*	=Sum(B2:B9)	=Sum(C2:C9)	=Sum(D2:D9)	=Sum(E2:E9)	=Sum(F2:F9)	=Sum(G2:G9)
11							
12		Carbohydrate	Protein	Fat			
13	Grams	=(15*B10)+(15*C10)+(12*D10)+(5*E10)	=(2*B10)+(8*D10)+(2*E10)+(7*F10)	=(0.5*B10)+(2*F10)+(5*G10)			
14	kcal	=4*B13	=4*C13	=9*D13			
15	Total kcal	=Sum(B14:D14)					
16	kcal%	=(B14/B15)*100	=(C14/B15)*100	=(D14/B15)*100			
17	Keep ratio at:¶	50–55 %	15–20 %	30 % or less			

*To activate this table in a spreadsheet, select cells A1:H16, copy & paste into spreadsheet software; remove the * in cell A1 after pasting. Add the number of servings of each food group at each meal time (e.g., see Table 3.1), then read the results in rows 13–16

†Assumes non-fat milk product is used. If milk product with fat is used, an equivalent number of fat exchanges should be added to column H for that meal

‡Assumes a lean meat exchange is used. If a higher fat content is used, an equivalent number of fat exchanges should be added to column H for that meal

¶Recommended levels to use as reference. Adjust as desired; not linked to any formulae

Table 3.3 Example of crude dietary analysis spreadsheet for total kilocalories, carbohydrate, protein and fat using food groups to estimate intake and showing number of exchanges for each food group listed by meal category

	A	B	C	D	E	F	G
1		Starch	Fruit	Milk	Nonstarch vegetable	Meat/substitute	Fat
2	Breakfast	2	1	1	0	1	2
3							
4	Lunch	3	2	1	2	2	2
5							
6	Dinner	3	2	0	2	3	3
7							
8	Snack	1	1	0.5	0	0	0
9							
10	*Total*	9	6	2.5	4	6	7
11							
12		Carbohydrate	Protein	Fat			
13	Grams	275	88	52			
14	kcal	1,100	352	464			
15	Total kcal	1,916					
16	kcal%	57	18	24			
17	Keep ratio at:	50–55 %	15–20 %	30 % or less			

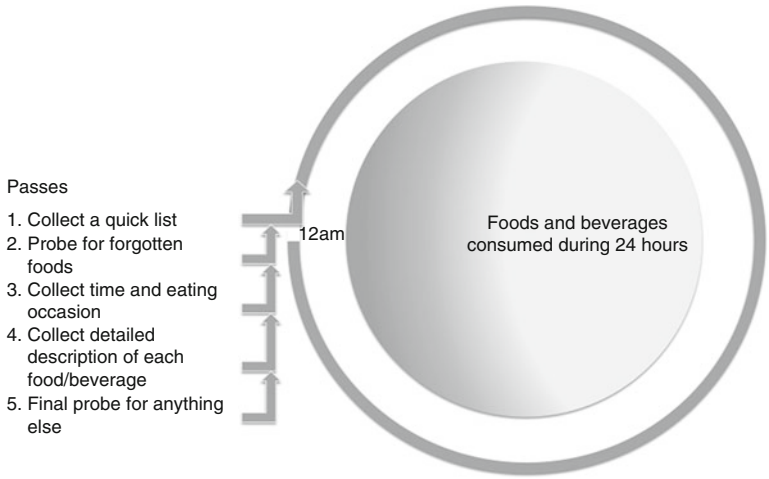

Fig. 3.1 The steps in obtaining a 24-h dietary intake using the Automated Multiple-Pass Method, from midnight to midnight on the previous day

The tool is available on the National Cancer Institute's website [18]. Respondents are guided by the ASA24 through the five passes of the AMPM with over 10,000 food pictures of eight different portion size equivalents. An optional module for collecting dietary supplement information is also available on the portal. The ASA24 consists of two portals: one for respondents where both English and Spanish tools are located and a researcher portal where data analyses are available. The software is freely available to researchers, clinicians, and students [18]. The automation of the ASA24 eases the ability to obtain and analyze a 24-h dietary recall utilizing the proven accuracy of the AMPM.

The dietary intake data captured by the ASA24™ are analyzed based on the Food and Nutrient Database for Dietary Surveys (FNDDS) from the Agricultural Research Service of the USDA [16]. The FNDDS is used to analyze the data from the *What We Eat in America* survey [23], which is the source of dietary intake information used for the NHANES [24]. The FNDDS is a database of nutrient values from foods based on the USDA National Nutrient Database for Standard Reference and is updated approximately every 2 years in association with the NHANES survey. The researcher portal of the ASA24 is designed for professional users (researchers, clinicians, educators) and allows them to set parameters for a study or series and obtain dietary analyses [18]. The professional then reports the results to respondents.

Food Frequency Questionnaire

A FFQ may be considered an adaptation of the diet history. It is typically a general list of structured questions aimed at eliciting food items commonly or uncommonly consumed and settings where foods are consumed in order to obtain a sense of usual food intake. A FFQ may also be aimed at elucidating special or specific foods or food groups, depending on the purpose of the questionnaire. FFQ's are widely used by epidemiologists in large cohort studies due to their ease of use, their ability to reduce variance across individual participants, and because they are relatively inexpensive to implement. Additionally, compared to diet records, the FFQ is noted to be more applicable when evaluating specific food intakes than the diet record, which may be more suitable to evaluating nutrient intakes [25, 26]. Two of the most commonly used FFQ's were developed separately by Block [27, 28] and Willett [29, 30] and have been used in many epidemiologic trials. Many FFQ's are adaptations of the Block or Willett designs.

Block FFQ

The Block FFQ was developed with data obtained from 24-h recalls collected in NHANES II [27, 31]. The food items selected for the FFQ were based on the contribution of foods represented in the 24-h recalls and the energy represented by those foods. Portion sizes from the 24-h recalls were used to represent the portion sizes offered in the FFQ as "small," "medium," or "large." The Block FFQ was used in the Women's Health Trial Feasibility Study. Three 4-day diet records that were collected during a 1-year period prior to administration of the FFQ were compared with the Block FFQ [28]. Correlations ranged from 0.5 to 0.7 between the 24-h recalls and the FFQ [27, 28]. The Block Health Habits and History Questionnaire is another version of the full-length Block FFQ that contains approximately 100 food items [31].

Willett FFQ

The Willett FFQ (or the Harvard Food Frequency Questionnaire) was designed to provide a simple method for ranking the intake of food items representative of dietary intake over the previous year [29] and has been used in the Nurses' Health Study [30, 32] and the Health Professionals Follow-Up Study [33, 34]. The validation of the Willett FFQ has been performed by comparing results of two FFQ reports taken at 1-year intervals to two 7-day diet records completed within approximately 2–3 months of the FFQ [26, 34]. Correlation between the diet record and the Willett FFQ ranged from 0.5 to 0.7 [26, 30, 34].

Diet History Questionnaire

The Diet History Questionnaire (DHQ), which was developed by the National Cancer Institute, is based on the Block FFQ where some of the questions were redesigned using a cognitive evaluation of the question format and grouping [35]. The DHQ has been compared to both the Block FFQ and Willett FFQ [36], and it appears to perform similarly with regard to assessing diet-disease risk. However, the DHQ and Block FFQ may provide better information on absolute intakes than the Willett FFQ. Yet, in a biomarker study measuring doubly labeled water (a biomarker for energy expenditure) and urinary nitrogen excretion (a biomarker for protein intake), the DHQ was shown to underestimate dietary energy and protein intakes [37, 38]. Currently, the DHQ is a 134-food item questionnaire that may be used to assess dietary intake over the previous year (with or without portion size information) or over the past month (with or without portion size estimates) [39].

FFQ Data Analysis

The portion size of a food consumed is multiplied by the frequency of consumption to obtain the nutrient totals in the FFQs. Totals are generally reported as an amount per period (often standardized to estimate daily consumption equivalents or monthly consumption equivalents). Many FFQ's have also been adapted to provide information on how the foods consumed apply to food guidance such as MyPyramid (reported as MyPyramid equivalents per day), the Healthy Eating Index, the Overall Nutrition Quality Index, a prudent vs. Western dietary pattern, servings of food in food groups, or other guidelines, as applicable [26, 39–43].

Diet Record or Diary

The diet record or diary is a prospective record of food consumed. The participant records food and beverage intake throughout the day as the food is consumed, preferably at the end of each meal or snack. The record is maintained on paper or electronic device/system, and it is usually submitted to a reviewer after an agreed number of days' collection. Multiple-day diet records are used for both dietary intake assessments and as a self-monitoring tool for dietary intervention programs [44, 45]. Attainment of dietary goals has been improved by participant engagement in diet record keeping [45–50].

To confirm the accuracy of the content, a professional with expertise in diets, such as a registered dietitian, dietetic technician, or trained dietary interviewer, usually reviews the diet record. Similar to the methods used in the 24-h recall, the reviewer will typically query the participant on portion size, the content of combination foods (e.g., Was the lasagna vegetable, beef, or turkey?), probe for more detail on foods that might be more than the standard food item (e.g., Was the orange juice fortified with calcium?), or how the food was prepared (e.g., Was the food prepared at home or purchased at a restaurant?). The amount of time spent on the review process will depend on the goal for the record keeping. If the goal is weight loss or gain, then a review that would provide information on macronutrient intake will suffice and could be as simple as that outlined in Tables 3.2 and 3.3 where the evaluation is only of food exchanges and number of servings to calculate macronutrient content. These tables are based on the Academy of Nutrition and Dietetics and American Diabetes Association Exchange Lists for Meal Planning [17]. Table 3.2 depicts the formulaic layout in a type of spreadsheet software for tracking the number of food exchanges and resulting macronutrients of an individual's daily intake. Table 3.3 depicts the appearance of the spreadsheet once the data have been entered. These tables are provided for readers to develop a quick-analysis tool using the formulae and layout shown in Table 3.2.

Alternatively, if the goal is to assess dietary intake of a micronutrient (e.g., vitamin D, sodium, or phosphorus), the review process may be more detailed. Analyses of these data may require proprietary computer software, such as is available from Food Processor (ESHA Research, Salem, OR) [51], FoodWorks (The Nutrition Company, Long Valley, NJ) [52], NutriBase (CyberSoft, Phoenix, AZ) [53], NutritionistPro™ (Axxya Systems, Stafford, TX) [54], and others, or accessing the free Nutrient Data Laboratory service from the US Department of Agriculture's Agricultural Research Library [16]. Another variable in choosing the diet record analysis methodology is the setting or purpose of the diet record. Working with an individual or with groups or on a research project will contribute to the decision on which systems to use for analysis as well as the methodology.

Currently, few of the proprietary nutrient analysis software programs provide comparison to the DRIs. As shown in the "Application of Dietary Intake Assessment to Dietary Guidelines" section, this evaluation requires a computational approach and would be an excellent addition to software programs. As more is learned about the DRIs and how to apply them, demand for these features will likely increase.

Application of Dietary Intake Assessment to Dietary Guidelines

Dietary Intake Assessment of Individuals

As indicated in previous sections of this chapter, assessing usual dietary intake is challenging and varies by the method used and frequency of assessment. Multiple records appear to be more informative than one method or record alone. Assessments of usual intake should include variations on the day of the week to account for day-to-day variability. Likewise, assessments should exclude holidays or special occasions because individuals tend to eat differently on these special days.

In the individual setting, estimating that the probability an individual is consuming a diet that is within his/her target level can be accomplished by comparing the EAR to the individual's mean and standard deviation (SD) of usual intake of the nutrient [14]. This concept is illustrated for dietary protein, phosphorus, and magnesium intake in Table 3.4 [55]. It is not recommended to use the RDA as a measure of nutrient intake adequacy because intakes below the RDA cannot be assumed to be inadequate for an individual [14]. This is partly because the RDA exceeds the actual requirement for all individuals except 2–3 % of the population.

If an individual's mean usual intake of a nutrient is largely different than the median requirement (the EAR) and the difference is positive, then it may be assumed that the individual's intake of that nutrient is adequate (or inadequate if the difference is largely negative). A rule of thumb recommended by the IOM is that, for individuals, intakes below the EAR *need to be increased* and those between the EAR and the RDA *probably should be increased* [14, 56]. A more detailed description of this approach and guidance on the approach for nutrients for which no EAR has been established is available from the IOM's Dietary Guidance website [11, 14] and a recent practice paper of the Academy of Nutrition and Dietetics [56].

Dietary Intake Assessment of Groups

The dietary intake of groups of people is important on many levels. From a public health level, the dietary intake of a population (e.g., a country, city, community, school, household; members of healthcare provider groups; people having a medical diagnosis; people having a particular lifestyle) can provide information relevant to planning for food supply needs, healthcare needs and risks, and programs to improve healthcare outcomes. Nonetheless, retrieving such dietary intake information on

Table 3.4 Examples of dietary protein, phosphorus and magnesium intake for healthy adult (19–70+ years of age) men and women and the probability that the dietary intake is adequate

Protein Intake (g/kg/day)[a]	Phosphorus intake (mg/day)	Magnesium—men (mg/day)[b]	Magnesium—women (mg/day)[b]	*z*-Score[c]	Probability of adequacy (%)[d]
0.50	461	278	210	−2.06	2
0.53	485	293	222	−1.64	5
0.56	506	305	231	−1.28	10
0.58	520	314	237	−1.04	15
0.62	549	331	251	−0.53	30
0.66	580	350	265	0	50[d]
0.74	640	386	293	1.04	70
0.76	654	395	299	1.28	85
0.79	675	407	308	1.64	95
0.82	699	422	320	2.06	98[e]

[a]Without additional amino acid supplements

[b]The age group for magnesium represented in the table is 31–70+ years

[c]*z*-Score represents the standard deviation (SD) units above or below the mean and is calculated for these data using the following equation: *z* = (estimated dietary intake − EAR)/SD, where EAR = estimated average requirement of the nutrient. SD units for these nutrients are provided in the Dietary Reference Intakes: The Essential Guide to Nutrient Requirements [55]

[d]The 50 % probability of adequacy is the EAR for the nutrient and represents the amount required by half of the healthy population in the age and sex group represented in the table. Dietary protein and phosphorus requirements are not different between males and females

[e]Represents two SDs above the EAR and is considered the recommended dietary allowance (RDA) that would meet the needs of almost all (97–98 %) of the age and sex group represented in the table

groups is difficult. In the USA, the NHANES provides extensive information on the dietary intake of the noninstitutionalized US population, and it has served as the reference resource for the DRIs [11]. The survey is also capable of providing information on the dietary intake of groups of people with certain medical conditions, but the analytical methodology is critical to getting the most accurate information.

To estimate the proportion of a group that is below the DRI, dietary intake information from more than 1 day is required because the distribution of intakes will vary between individuals and between days. In NHANES, for example, it is possible to evaluate the mean dietary intake or from a single 24-h recall. The dietary data are collected on multiple days of the week, and the large sample sizes available account for between-subject variability. This information may provide insight into the dietary intake of a group of people (e.g., an age group, a socioeconomic group, a group with a certain medical condition), but it is not possible to evaluate how the group compares to the DRIs without evaluating the usual intake of the group. To estimate the usual intake of a group from the NHANES data, both days of the dietary intake record are required [57, 58]. The recommendation for a minimum of 2 nonconsecutive days to estimate the usual dietary intake is based on the need to account for the within-subject variability that is common for individuals.

In general, whether using the NHANES data or developing new dietary intake data, 2 or 3 consecutive days of dietary intake are recommended for estimating the usual intake of a group [14, 59]. The distribution of intake should be part of the dietary assessment technique. Since the spread or distribution of usual intake of most nutrients is wider than the distribution of the requirement, it is not appropriate to compare the mean of the usual intake to the mean of the requirement. Comparing means would result in an overestimation of the group proportion who are consuming adequate or inadequate (e.g., the tail probabilities) nutrients. Methods used for handling the issues of distribution have been described by the National Research Council [60], the Iowa State University [57], and more recently

a webinar series hosted by the National Cancer Institute [58]. These methods vary slightly from each other, but each indicates that the inter- and intrasubject variability, as well as the range of distribution of the nutrient requirement, must be accounted for when making comparisons to other groups, to the DRIs or other clinical guidelines, or to a health condition. The EAR cut-point method, recommended by the IOM and the National Research Council, is one example that can be applied when the variability of the intake of the nutrient is ≤60 % [55]. This method is illustrated in Table 3.4 for dietary protein, phosphorus, and magnesium intake.

Murphy et al. have outlined precautions important for dietary assessment of groups [61]. These precautions include:

- Avoid comparing group mean intake to the RDA because the prevalence of inadequacy would be missed; it is essential to know about the tail probabilities.
- Avoid comparing the mean intake of a group to the EAR because 50 % would have an inadequate intake. It is better to compare the distribution of intakes to determine the proportion of a group below the EAR—the prevalence of inadequacy.
- Use multiple, nonconsecutive day dietary intake information and adjust for variability [58, 61].
- Use validated dietary intake collection methods to avoid systematic errors [56, 58, 61].

Evidence

Whether dietary intake assessment tools can provide accurate results has been tested by several methods, some of which are listed here and discussed below:

- Direct observation—performed with subjects housed in a research or similar setting, receiving prepared and tare-weighed meals compared to self-reported records of what was consumed
- Comparison of one dietary assessment tool to another
- Evaluation of subgroups to determine if characteristics identify those more or less likely to accurately record or recall their intake
- Comparison of the dietary intake assessment tool to a biomarker or series of biomarkers

Assessment of the 24-h Recall, the AMPM

The AMPM was validated in men and women, in different ethnicities, and for macronutrients as well as many micronutrients [62–66]. Conway et al. [62] measured macronutrient intake from a single 24-h dietary recall using the AMPM and compared reported intake to direct observation of intake in 45 men between the ages of 21 and 65 years with a mean BMI of 27.6 kg/m^2 (range, 20.8–39.2 kg/m^2). No relationship was demonstrated between BMI and precision of the dietary recall ($r^2 = 0.01$, $p = 0.44$). Observed EI from protein was 14.4 ± 0.4 % compared to recall at 14.3 ± 0.4 %. Mean total EI observed was 3,294 ± 111 kcal/day compared to recall at 3,541 ± 124 kcal/day.

A similar study design was used by Conway et al. [63] to evaluate the accuracy of a single 24-h dietary recall of women. A group of 49 women, ages 21–63 years, with mean BMI of 29.7 kg/m^2 (range, 20.0–44.6 kg/m^2) were included in the analysis. The observed EI from protein was 15.9 ± 0.6 % compared to recall at 15.6 ± 0.6 % ($p < 0.02$). Mean total observed EI was 2,214 ± 91 kcal compared to recall 2,376 ± 91 kcal ($p < 0.05$). These investigators found that the actual intake of women was within 10 % of the recalled intake 95 % of the time. They concluded that the AMPM was an accurate method for 24-h recall of dietary intake.

Rumpler et al. [67] utilized the AMPM in 12 healthy volunteers to evaluate the degree of reporting error (under- or overreporting) in two 24-h recalls. They assumed the difference between the reported

(AMPM) and measured food intake as bias and were interested in determining both the average and variance in bias. The group mean difference in AMPM and measured food intake was found to be similar, but individual differences were observed. For example, the absolute within-person difference in reporting error averaged 18 % for protein, 23 % for carbohydrate, and 15 % for fat. They concluded that group estimates of macronutrients contained small average bias using the AMPM, but estimates for individuals may contain significant bias and be less accurate. These investigators proposed that some of the bias may be related to how foods are grouped in the AMPM analysis and that foods producing the greatest reporting error might be adjusted in the analysis.

Assessment of the FFQ

Studies performed to test the comparability of FFQ's have shown that the FFQ's correlate modestly with each other but vary on their correlations with the 24-h recall or the diet record. Wirfalt et al. [68] determined that the energy-adjusted correlation coefficient between a reduced Block FFQ and the mean of three 24-h recalls was 0.47 for dietary fat and carbohydrate intake, but not for the Willett FFQ. Likewise, neither FFQ appeared to be associated with the 24-h dietary recall for protein intake. Subar et al. [36] compared the DHQ, Block FFQ, and Willet FFQ to each other and to four 24-h recalls. In this study, the DHQ and the Block FFQ correlated moderately with the 24-h recalls ($r = 0.5$), but the Willett FFQ correlation to the 24-h recall was about 0.3–0.4. After adjusting to EI, all three of the FFQ's had correlations of 0.5–0.6 with the 24-h recall [36].

Comparison of the Willet FFQ to a 7-day diary indicated a correlation of approximately 0.3 for energy and protein between the two dietary intake assessment tools, which did not change significantly when the data were energy adjusted (Spearman's $\rho \approx 0.34$) [69]. However, when the low-energy reporters were excluded, the correlation between the two tools decreased significantly (Spearman's $\rho = 0.22$).

Use of Biomarkers in Assessing Dietary Intake

A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [70]. Biomarkers are recognized as useful in clinical trials for measuring efficacy and, as such, play an important role in research as well as in clinical management. Dietary biomarkers serve as indicators of response to dietary intake and have been used to measure the accuracy of dietary intake assessment [71, 72]. Similar to the issues relating biomarkers to drug metabolism, the correlation of biological levels (e.g., from tissue, blood, urine) of a dietary biomarker is dependent on individual variations in dietary intake, in the nutrient's kinetic action, nutrient–nutrient interactions, biomarker selection, biomarker sample collection, analytic methods, accuracy of the dietary intake assessment tools and of dietary composition tables, and statistical handling of the data [38, 72–74].

A biomarker is often considered a "gold standard"—however, the application of particular biomarkers to dietary intake assessment must be well quantified and understood. For example, the use of urine urea nitrogen (UUN) excretion is considered the biomarker for dietary protein intake (DPI). However, the use of UUN should also account for kidney function because the clearance of urea in people with kidney disease (not just kidney failure) is altered. Adjusting for this variation, however, is possible [75, 76] and increases the applicability for comparing UUN excretion to DPI in the population.

Doubly Labeled Water and Urine Urea Nitrogen for Dietary Energy and Protein Intake Assessment

The AMPM and DHQ were used to assess dietary measurement error in the Observing Protein and Energy Nutrition (OPEN) study [37, 38]. Subjects ($n = 484$), aged 40–69, had three in-person visits over a period of 3 months where they completed the DHQ twice, provided two 24-h recalls (one at visit 1 and again at visit 3), were dosed with doubly labeled water at visit 1, and completed two 24-h urine collections between visits 1 and 2 (9 days apart). Doubly labeled water is used to determine total energy expenditure (TEE), and UUN excretion is used to determine protein catabolism. In this study, approximately 21 % of men and women were under-reporters of EI using the 24-h recall (the AMPM), and 49 % were under-reporters using the DHQ. Similarly, about 12 % were under-reporters of DPI using the AMPM and 35 % were under-reporters using the DHQ. Under-reporting of EI increased as BMI increased in both men and women but was less in the AMPM vs. the DHQ and was not apparent for DPI in the AMPM. These data suggest a greater accuracy of the AMPM than the DHQ for assessing dietary intake, that under-reporting is present in about 21 % of subjects, and that under-reporting increases at higher BMIs.

To further evaluate the ability of the AMPM to be used in large, diverse samples, Moshfegh et al. [77] studied 525 people between the ages of 30 and 69 years, with a BMI range of 18–44, over a 7-week period. They compared the reported EI to TEE by using a doubly labeled water technique. The protocol consisted of three 24-h dietary recalls (one in-person interview and two telephone follow-up interviews interspersed across a 2-week period), one in-person visit where doubly labeled water was consumed, two more in-person visits where urine samples were collected, and a final in-person visit where resting energy expenditure (REE) was measured. The EI/TEE was 100 % in normal weight men and 94 % in normal weight women. However, as weight increased (overweight to obese), this ratio decreased: 86 % and 80 %, respectively, in men and 85 % and 79 %, respectively, in women. More overweight and obese participants were found to be low EI reporters (19.4 and 34.0 % of men, 24.7 and 35.3 % of women). The EI:REE was a mean of 1.43 for the sample with an average physical activity level of 1.61 (95 % CI: 1.15, 2.25). The investigators concluded that the AMPM is valid for evaluation of EI in group samples and extrapolation to the population level. They postulated that the reported EI by overweight and obese individuals could be accurate but not reflective of TEE due to eating less on the days of 24-h recall since the subjects knew the schedule of the interview visits. Further studies need to be performed in overweight and obese subjects to improve the reporting or interpretation of reported dietary intake in these subgroups.

Plasma Ascorbic Acid, Carotenoids, and Vitamin A Levels for Assessing Dietary Intake

Evaluation of antioxidant status has used blood levels of vitamins C, E, and A to reflect dietary and/or supplement use [78]. However, the correlation of these nutrients to dietary intake is only modest. Correlation coefficients of 0.12–0.53 for blood levels of vitamin C and 0.1–0.5 for blood levels of carotenoids to dietary intake are typical [72, 78, 79].

Association of Serum Uric Acid Levels and Urinary Isoflavones with Dietary Intake

NHANES III (1988–1994) was used by Choi et al. [80] to evaluate the association of serum uric acid levels with dietary intake. They noted a positive association of serum uric acid level with increasing intake of meats and seafood and a negative association with increased intake of dairy foods.

Similarly, the NHANES (1999–2002) was used to demonstrate that urinary isoflavone levels could be used as a biomarker of isoflavone intake [81]. Adults reporting an average consumption of 3.1 mg/day of dietary isoflavone had a geometric mean urinary isoflavone concentration of 5.0 ng/mL.

Applications to Kidney Disease Settings

Dietitians working in kidney disease in the late 1970s and 1980s had a unique opportunity to learn about the usefulness of dietary intake assessment. A first-of-its-kind national study was taking place in the relatively newly funded end-stage renal disease program. The National Cooperative Dialysis Study (NCDS) was funded to determine the effect of dialysis prescription on patient morbidity [82]. The NCDS is most renowned for the measurement and monitoring of the dialysis prescription (evolved to what is currently referred to as *Kt*/*V*) and its adequacy. But dietitians involved in the NCDS learned something in addition to monitoring the dialysis prescription—they learned how to monitor the dietary protein prescription. Dietitians working in the NCDS and hemodialysis units at this time were uniquely afforded an in-depth understanding of the intake and metabolism of dietary protein in people receiving chronic hemodialysis [75, 83]. These dietitians also learned that assessing DPI of dialysis patients is similar to pharmacokinetics. How so? Pharmacokinetics is basically a measurement of the time required for a drug to appear in the blood and its rate of disappearance. The NCDS was monitoring how urea nitrogen was removed from the blood by dialysis and re-accumulated between dialysis sessions [82]. In stable patients, the accumulation of urea nitrogen between dialysis sessions was the result of dietary nitrogen intake. So even in people with no kidney function (and, therefore, no measureable urinary nitrogen excretion), it was possible to determine the DPI. This process became known as urea kinetics and protein catabolic rate (PCR) [82–84]. Researchers had the gold standard for DPI assessment in people with kidney disease—a biomarker.

As will be described in the sections below, the DPI of patients with kidney disease has been assessed in multiple reports and related to the PCR. However, no statistical adjustments for the distribution of the DPI or PCR have been described to date in the CKD population, and these variables are known to have inter- and intrasubject variability. Only group means comparisons were available in the reports shown. Additionally, the EI comparison to basal metabolic rate (BMR) or to REE has rarely been described in this population.

The recommended dietary intake of people with kidney disease differs for some nutrients from that of healthy individuals [1, 4, 55]. Guidelines for kidney disease are based on the level of kidney function and the type of treatment for kidney replacement therapy [1, 4, 85]. Dietary assessment approaches as well as some recommendations follow in the sections below.

Acute Kidney Injury

Patients with acute kidney injury (AKI) are at risk for being in a hypercatabolic state, usually due to the underlying disease [86–89]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) AKI work group, AKI is defined as an increase in serum creatinine ≥0.3 mg/dL within 48 h or increase in serum creatinine ≥1.5 times the baseline that is known to have occurred within the previous 7 days or a decrease in urine volume <0.5 mL/kg/h over 6 h [85]. AKI can be present well before acute kidney failure (AKF) occurs where renal replacement therapy (RRT) will be required. This is important because the dietary intake of people with early or milder AKI (e.g., not requiring RRT) may have a critical impact on their outcome. Additionally, a report on 309 cases of AKF indicated that approximately 58 % of the cases demonstrated moderate to severe malnutrition at the time of the AKF diagnosis, that 57 % of the cases were housed in the medical ward of the hospital (compared to 43 % in intensive care units), and that compromised nutritional status was associated with increased mortality in these cases [90]. Once the patient requires nutrition support, while important to provide adequate protein, energy, vitamins, and minerals to attenuate the hypercatabolism, the dietary intake assessment per se becomes an evaluation of the nutrition support provided and not the oral dietary intake. At this juncture, adjustments for kidney function and/or kidney replacement therapy should be applied. This

Table 3.5 Reported dietary protein and energy intake in nondialysis kidney disease assessed using diet records, prior to dietary intervention

Author	*N*	Dietary assessment method	Kidney function (mL/min)	Dietary protein intake (g/kg/day)	Dietary energy intake (kcal/kg/day)
Rotily et al. [95]	31	Willett FFQ	NR	1.22	28
Rotily et al. [95]	34	Willett FFQ	NR	1.22	22.9
Rotily et al. [95]	31	Willett FFQ	NR	1.40	30.7
Hansen et al. [96]	14	3-Day diary	94[a]	1.2	29.6
Hansen et al. [96]	15	3-Day diary	92[a]	1.1	30.8
Dussol et al. [97]	25	Willett FFQ	89[a]	1.09	22.8[b]
Dussol et al. [97]	22	Willett FFQ	82[a]	1.00	21.3[b]
Meloni et al. [98]	37	3-Day diary	44[a]	1.52	37.8[b]
Meloni et al. [98]	32	3-Day diary	48[a]	1.6	38.0[b]
Fassett et al. [99]	113	4-Day diary	41[c]	0.9	21.4
Soroka et al. [100]	9	2-Day diary	31[c]	0.93	27.7
Bernhard et al. [101]	26	3-Day diary	26[d]	1.13	31.7
Mircescu et al. [102][e]	53	3-Day diary	16[d]	0.62[e]	32.3[e]

NR not reported
[a]GFR measured as clearance of diethylene triamine penta-acetic acid
[b]Estimated from total dietary energy intake normalized to reported baseline body weight
[c]Calculated as clearance of creatinine
[d]Calculated as eGFR
[e]Patient selection was from a group already restricting dietary protein intake

situation warrants evaluating the biomarkers of protein and energy metabolism to determine if adequate support is being provided [88, 89, 91]. Recent practice guidelines for AKI make four recommendations related to nutrition, but no recommendation was made regarding assessment of the adequacy of nutrition support [85].

Chronic Kidney Disease

CKD encompasses the reduced or mild kidney dysfunction described by the NKF [92] as stages 1 and 2 (or where solute filtration may be adequate but kidney damage is present from nephrocalcinosis or microalbuminuria, for example), moderate CKD (stages 3a and 3b [93], where kidney function is ~30–60 % of normal), and severe CKD (stages 4 and 5, where kidney function is <30 % of normal or where dialysis is required to sustain life). These descriptions of the levels or stages of kidney function provide insight into the changes that might be necessary for altering dietary intake. The stages also identify that the assessment techniques will vary and become more complex as CKD advances.

Nondialysis CKD

A review of dietary assessment methods in nondialysis CKD identified a mixture of methodologies for collecting, evaluating, and reporting dietary intake in CKD [43, 94–105].

Small Studies

When dietitians examined the intake of people enrolling in trials to use diet as a method for preventing kidney disease progression, baseline data on DPI and DEI indicated variability in intakes (Table 3.5).

Rotily et al. [95] performed dietary intake assessment in a group ($n=96$) of idiopathic calcium stone formers using the Willett FFQ. The FFQ was used to assess baseline dietary intake. Urinary data were available from 24-h urine collections. Urinary GI alkali (the sum of gastrointestinal absorption of sodium, potassium, calcium, magnesium, and chloride with the product of phosphorus and a constant of 1.8) and urinary creatinine excretion had a significant, positive correlation to animal protein intake from the FFQ ($r=0.54$ and 0.50, respectively). Urinary potassium, oxalate, and calcium oxalate saturation also correlated with animal protein intake ($r=0.44$, 0.45 and 0.44, respectively). A significant, negative correlation was seen between urinary oxalate excretion and DEI ($r=-0.43$). Whereas this was a small study, it depicted a relationship between dietary intake and urinary biomarkers of nephrolithiasis, which would be considered a group having stage 1 or stage 2 CKD.

Evaluation of the dietary intake of 29 patients with insulin-dependent diabetic nephropathy used 3-day diet records at baseline and at two 4-week intervals [96]. In this study, a relative difference in DPI correlated to relative change in albuminuria (Spearman's $\rho=0.51$, $p<0.01$).

Dussol et al. [97] used the Willett FFQ to evaluate the dietary energy intake (DEI) and DPI of 47 patients with type 1 or type 2 diabetes with nephropathy. Both DPI and PCR were measured, but no correlation was shown. The DPI vs. PCR at baseline in the usual protein intake group was 1.13 vs. 1.09 g/kg/day (a 3.7 % error); at month 12, 1.18 vs. 1.1 (a 7.3 % error); and at month 24, 1.03 vs. 1.02 (<1 % error). The DPI vs. PCR at baseline in the low protein group was 1.08 vs. 1.0 g/kg/day (8 % error); at month 12, 1.02 vs. 0.84 (21 % error); and at month 24 was 1.10 vs. 0.87 (21 % error).

Fassett et al. [99] evaluated dietary intake using a 4-day diet record (including 1 weekend day) in 113 patients with CKD entering the Lipid lowering and Onset of Renal Disease (LORD) trial. The diary instructions included pictorial references to portion sizes of commonly consumed foods to aid in accuracy. The diary was to be recorded prospectively but "as close to their next pathology visit as possible"—3 months from the time that diary instructions were provided [99]. Valid reporting was assessed as a ratio of the EI to estimated REE of 1.27. This study determined that 70.8 % of subjects underreported their EI. No mention of adjustment for intrasubject variability was indicated in this report, and no PCRs were available for assessing the accuracy of the DPI recording.

Bernhard et al. evaluated a 3-day diary and compared DPI to protein nitrogen appearance (PNA; 1.13 vs. 1.11 g/kg/day; a <2 % error) at baseline [101].

Mircescu et al. utilized a 3-day food diary every 2 weeks during a 12-week baseline phase prior to randomizing subjects to a low protein vs. very low protein diet with ketoacid analogs [102]. The baseline phase was used to assess compliance (±10 % of recommended DPI and DEI) prior to randomization. The authors only report on those subjects who qualified (57/167 evaluated) to be randomized.

Large Cohort and Cross-Sectional Studies

The Block FFQ was used to estimate usual dietary intake at baseline over the previous year in the Multiethnic Study of Atherosclerosis [43]. Foods were grouped to estimate the effect of animal vs. plant foods on microalbuminuria in people with eGFR <60 mL/min compared to ≥60 mL/min. Participants were excluded if they had known cardiovascular disease or diabetes. People consuming a diet high in low-fat dairy foods or a pattern of high intake of whole grains and fruits had independently lower odds for microalbuminuria and a lower urinary albumin-to-creatinine ratio. These baseline data also indicated that people consuming a diet high in nondairy animal products had a higher mean albumin-to-creatinine ratio.

Data from NHANES 2001–2008 have recently been evaluated to determine the mean dietary intake of people with CKD [103–105]. NHANES used the AMPM for dietary intake assessment [19], and the authors applied the MDRD equation for estimating kidney function and staged the kidney function according to the NKF criteria [92, 106]. Mean DEI and DPI were lower in those with CKD compared to those without CKD, even after adjusting for age. Evaluations of the difference from recommended intakes require additional analyses of the intra- and intersubject distributions and have not been completed as yet.

Dialysis

The FFQ in Dialysis

The Willett FFQ was used to evaluate the dietary intake in a group of hemodialysis patients who were awaiting kidney transplantation [26, 107]. No statistical comparisons of the FFQ results were made with biomarkers measured (body composition, serum lipids, PCR). The investigators indicated that since the FFQ was an estimate of long-term dietary intake and the PCR was a near-term assessment, it would be inappropriate to compare the two. Instead, they used the FFQ and biomarkers to demonstrate, separately, the differences in dietary intake and body composition between normal weight, overweight, and obese individuals on chronic hemodialysis waiting for kidney transplantation.

Recently, a dialysis-specific FFQ has been developed using the Block FFQ methodology [94, 108, 109]. Researchers accessed information from a subset of hemodialysis patients participating in the Nutrition and Inflammation in Dialysis Patients (NIED) cohort study in Southern California to develop the Dialysis-FFQ. Participants maintained a 3-day diet record that included the last dialysis day of the week and two subsequent days. Paper records were reviewed with the participants by a trained dietitian and converted to electronic data where food items were ranked according to types of foods and nutrients provided. The Dialysis-FFQ is a 100-item questionnaire, estimated to take 30–40 min to complete and intended to represent the food intake during the previous 3-month period. It can be accessed through NutritionQuest.com (Berkley, CA) [110] and is available as either a scannable, paper, or electronic form. This hemodialysis-specific FFQ was developed in a target population consisting of mostly ethnic minorities (43 % were African American and 38 % were Hispanic) and should be tested in broader hemodialysis populations for wider validity. However, the process represents an important step in gathering representative usual intake of hemodialysis patients.

Diet Records in Dialysis

Diet records or diaries have been utilized in several dialysis studies. The NCDS used a dietary intake record to compare the DPI to the calculated PCR and to compare phosphorus and potassium intake to DPI [82, 111]. At that time (ca. 1978), a mixed diet from 683 diet records indicated a strong correlation of dietary phosphorus to DPI ($r=0.847$) and of dietary potassium to DPI ($r=0.754$). Whether these correlations would hold in today's mixed diet (given that an increased number of foods may have added phosphorus [112, 113]) would need to be determined. However, this was useful information at the time in that it supported the decision to use urea as the surrogate biomarker for dialysis adequacy; urea is a reliable marker of protein catabolism, and protein intake is correlated to phosphorus and potassium intake. Subjects in the NCDS maintained 5-day food records (including a weekend) at five different time points during the 1-year study [111]. The correlation of DPI to PCR in the NCDS study was 0.443, $p<0.01$.

More recently, the HEMO study utilized annual 2-day diet diary-assisted recalls that included 1 dialysis day and 1 nondialysis day over the 7-year study period in 1,397 maintenance hemodialysis patients [114, 115]. The diet was recorded by the patient, reviewed with the dietitian, and then analyzed for energy and protein. In this study, the DPI correlated with the PCR ($r=0.17$, $p<0.0001$) but not to serum albumin, creatinine, or cholesterol. However, no statistical relationship was evident between DPI and PCR for the group of people age 50–64 years.

Chauveau et al. [116] compared dietary recall of DPI to PCR in 99 maintenance hemodialysis patients using a 7-day record. Subjects maintained the food record and reviewed them with a dietitian during dialysis sessions. The correlation of DPI to PCR increased during the week ($r^2=0.26$, 0.49, 0.57 for the first, second, and third dialysis sessions, respectively).

Transplantation

The FFQ in Kidney Transplantation

Guida et al. [117] have reported use of the Willett FFQ in kidney transplant recipients during the first year posttransplant. The FFQ was completed at baseline (time of transplant surgery) and at 1-year posttransplant. Adherence was assessed as having 90 % compatibility between the FFQ and the diet recommendations during the first 90 days posttransplant. For analytical purposes, those considered nonadherent were compared to the group having success with the dietary protocol. Biomarkers of urinary excretion of sodium and urea from 24-h urine collections were used to confirm findings (data not shown). DEI, DPI, and dietary sodium were decreased or maintained in the compliant group compared to increases in the noncompliant group. These results were confirmed by decreased body weight in the compliant group vs. increased body weight in the noncompliant group.

Diet Records in Kidney Transplantation

A 3-day food record was used to determine baseline dietary intake in a prospective study of the effect of dietary changes on serum lipid profile in a group of 23 male and female stable kidney transplant recipients [118]. Decreasing the dietary fat intake from 41 to 33 % of total energy consumed was associated with a significant reduction (13 %, $p<0.01$) in serum total cholesterol levels in men over a 6-month period, but not in women.

Evaluation of 44 stable kidney transplant recipients, using 3-day food record (including 1 weekend day) maintained at four time points during the first year posttransplant, identified that women increased their DPI and DEI significantly compared to no change over the year in men [119]. This dietary change was accompanied by a mean increase in BMI by 1.9 kg/m^2 in women (a mean weight gain of 5.4 kg or 10.6 %). Whole body bone densitometry indicated a 12 % mean increase in body fat mass, a 7 % increase in lean body mass, and a 1.4 % increase in bone mass in these women over the year, while men had a significant reduction in mean body fat mass (8 %) and bone mass (2.3 %) and a 1 % increase in lean body mass (not significant).

A 7-day diet record was maintained by 106 stable kidney transplant recipients (with abnormal glucose tolerance) at the time of transplantation and at 1 and 2 years posttransplantation [120]. Three random days from each food record (including 1 weekend day) were used for the dietary intake assessments. Subjects were randomized to receive either aggressive risk factor modification for coronary vascular disease or standard posttransplant care. No correlations to biomarkers were reported.

Recommendations for Kidney Disease

The concepts relating dietary intake assessment methodologies and correlation to biomarkers or outcomes in the general population are useful for evaluating these tools in kidney disease. The presentation of information provided in this chapter from the kidney disease literature outlines areas where improvement or alternate methodologies may be considered, such as:

- Apply the statistical methodologies suggested for accounting for dietary intake distribution and determine the characteristics of patients with kidney disease who are at risk for inadequate intake using these methods.
- Evaluate the level of DPI, DEI, or other nutrients that is associated with malnutrition or other outcomes in this population using current dietary assessment tools and methodologies.

- Assess the efficacy of multiple days and multiple methods of intake assessment when evaluating dietary intake in individuals and/or groups of people with CKD (by stage of CKD).
- Determine the utility of available data sets for answering some of the questions regarding dietary intake assessment in CKD using new statistical approaches or queries that were not assessed in the original evaluation of the data sets to provide further insight for future trials.

As new research agendas are considered, it is important to express appreciation for all of the effort and expense provided by individual investigators, kidney disease programs and centers, and the patients who offer themselves to this work. Their efforts have helped to define and design the research that has and will answer many questions in kidney disease.

References

1. K/DOQI, National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35(8):S1–140.
2. Fouque D, Vennegoor M, Ter Wee P, Wanner C, Basci A, Canaud B, et al. EBPG guideline on nutrition. Nephrol Dial Transplant. 2007;22 Suppl 2:ii45–87.
3. KDOQI Work Group. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53 Suppl 2:S11–104.
4. Academy of Nutrition and Dietetics. Chronic kidney disease evidence-based nutrition practice guideline. 2010. http://www.adaevidencelibrary.com/topic.cfm?cat=3927. Accessed 16 Jul 2012.
5. The Management of CKD Working Group. Management of chronic kidney disease (CKD) in primary care (2008). US Department of Veterans Affairs. 2008. http://www.healthquality.va.gov/Chronic_Kidney_Disease_Clinical_Practice_Guideline.asp. Accessed 16 Jul 2012.
6. Chronic kidney disease—identification, evaluation and management of patients. Ministry of Health British Columbia. 2008. http://www.bcguidelines.ca/guideline_ckd.html. Accessed 16 Jul 2012.
7. KDOQI Work Group. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49(2):S12–154.
8. Early identification and management of chronic kidney disease in adults in primary and secondary care. National Institute for Health and Clinical Excellence. 2008. http://www.nice.org.uk/CG073. Accessed 16 Jul 2012.
9. Baron JH. Sailors' scurvy before and after James Lind—a reassessment. Nutr Rev. 2009;67(6):315–32.
10. Magiorkinis E, Beloukas A, Diamantis A. Scurvy: past, present and future. Eur J Intern Med. 2011;22(2):147–52.
11. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes. National Academies Press. http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes. Accessed 16 Jul 2012.
12. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. DRI report—calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academies Press; 1997. "http://fnic.nal.usda.gov/dietary-guidance/dri-reports/calcium-phosphorus-magnesium-vitamin-d-and-fluoride. Accessed 16 Jul 2012.
13. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes: applications in dietary planning. Washington, DC: National Academies Press; 2003. http://fnic.nal.usda.gov/dietary-guidance/dri-reports/applications-dietary-planning. Accessed 16 Jul 2012.
14. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes: applications in dietary assessment. Washington, DC: National Academies Press; 2000. http://fnic.nal.usda.gov/dietary-guidance/dri-reports/applications-dietary-assessment. Accessed 16 Jul 2012.
15. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press; 2005. http://fnic.nal.usda.gov/dietary-guidance/dri-reports/energy-carbohydrate-fiber-fat-fatty-acids-cholesterol-protein-and-amino. Accessed 16 Jul 2012.
16. USDA Food and Nutrient Database for Dietary Studies, 4.1. Beltsville, MD: Agricultural Research Service, Food Surveys Research Group; 2011. http://ndb.nal.usda.gov/. Accessed 1 Jul 2012.
17. Exchange Lists for Meal Planning. Chicago: Academy of Nutrition and Dietetics and American Diabetes Association; 2008.
18. ASA24 automated self-administered 24-hour recall. National Cancer Institute. 2012. http://riskfactor.cancer.gov/tools/instruments/asa24/. Accessed 16 Jul 2012.
19. USDA Automated Multiple-Pass Method. USDA Agricultural Research Service. http://www.ars.usda.gov/Services/docs.htm?docid=7710. Accessed 16 Jul 2012.

20. Raper N, Perloff B, Ingwersen L, Steinfeldt L, Anand J. An overview of USDA's dietary intake data system. J Food Compost Anal. 2004;17(3–4):545–55.
21. Dwyer J, Ellwood K, Moshfegh AJ, Johnson CL. Integration of the continuing survey of food intakes by individuals and the National Health and Nutrition Examination Survey. J Am Diet Assoc. 2001;101(10):1142–3.
22. Zimmerman TP, Hull SG, McNutt S, Mittl B, Islam N, Guenther PM, et al. Challenges in converting an interviewer-administered food probe database to self-administration in the National Cancer Institute automated self-administered 24-hour recall (ASA24). J Food Compost Anal. 2009;22S:548–51.
23. What We Eat in America. Washington, DC: United States Department of Agriculture. http://www.ars.usda.gov/Services/docs.htm?docid=13793. Accessed 16 Jul 2012.
24. About the National Health and Nutrition Examination Survey. Atlanta: Centers for Disease Control and Prevention; 2010. http://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed 16 Jul 2012.
25. Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Variability in portion sizes of commonly consumed foods among a population of women in the United States. Am J Epidemiol. 1988;127(6):1240–9.
26. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr. 1999;69(2):243–9.
27. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 1986;124(3):453–69.
28. Block G, Woods SM, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol. 1990;43:1327–35.
29. Willett WC, Stampfer MJ, Underwood BA, Speizer FE, Rosner B, Hennekens CH. Validation of a dietary questionnaire with plasma carotenoid and alpha-tocopherol levels. Am J Clin Nutr. 1983;38(4):631–9.
30. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122(1):51–65.
31. Block Questionnaires. NutritionQuest. 2011. http://www.nutritionquest.com. Accessed 16 Jul 2012.
32. The Nurses' Health Study. Nurses Health Study. http://www.channing.harvard.edu/nhs/. Accessed 16 Jul 2012.
33. Harvard School of Public Health: Health Professionals Follow-up Study. 2011. http://www.hsph.harvard.edu/hpfs/. Accessed 5 Jul 2012.
34. Rimm EB, Giovannucci EL, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992;135(10):1114–26.
35. Subar A, Thompson F, Smith A, Jobe J, Ziegler R, Potischman N, et al. Improving food frequency questionnaires: a qualitative approach using cognitive interviewing. J Am Diet Assoc. 1995;95:781–8.
36. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires. Am J Epidemiol. 2001;154(12):1089–99.
37. Subar A, Kipnis V, Troiano R, Midthune D, Schoeller D, Bingham S, et al. Using biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN study. Am J Epidemiol. 2003;158(1):1–13.
38. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, et al. Structure of dietary measurement error: results of the OPEN biomarker study. Am J Epidemiol. 2003;158(1):14–21.
39. Diet History Questionnaire II. Bethesda: National Cancer Institute, Cancer Control and Population Science Branch, Risk Factor Monitoring Branch. http://riskfactor.cancer.gov/dhq2/. Accessed 16 Jul 2012.
40. Chiuve SE, Sampson L, Willett WC. Adherence to the Overall Nutrition Quality Index and risk of total chronic disease. Am J Prev Med. 2011;40(5):505–13.
41. Millen AE, Midthune D, Thompson FE, Kipnis V, Subar AF. The National Cancer Institute diet history questionnaire: validation of pyramid food servings. Am J Epidemiol. 2006;163(3):279–88.
42. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, Hemphill S, Tsaroucha G, Rushing J, et al. Validity and reproducibility of a food frequency interview in a multi-cultural epidemiologic study. Ann Epidemiol. 1999;9(5):314–24.
43. Nettleton JA, Steffen LM, Palmas W, Burke GL, Jacobs Jr DR. Associations between microalbuminuria and animal foods, plant foods, and dietary patterns in the Multiethnic Study of Atherosclerosis. Am J Clin Nutr. 2008;87:1825–36.
44. Burke LE, Warziski M, Starrett T, Choo J, Music E, Sereika S, et al. Self-monitoring dietary intake: current and future practices. J Ren Nutr. 2005;15(3):281–90.
45. Burke LE, Conroy MB, Sereika SM, Elci OU, Styn MA, Acharya SD, et al. The effect of electronic self-monitoring on weight loss and dietary intake: a randomized behavioral weight loss trial. Obesity. 2011;19(2):338–44.
46. Hollis JF, Gullion CM, Stevens VJ, Brantley PJ, Appel LJ, Ard JD, et al. Weight loss during the intensive intervention phase of the weight-loss maintenance trial. Am J Prev Med. 2008;35(2):118–26.
47. Acharya SD, Elci OU, Sereika SM, Styn MA, Burke LE. Using a personal digital assistant for self-monitoring influences diet quality in comparison to a standard paper record among overweight/obese adults. J Am Diet Assoc. 2011;111:583–8.

48. Helsel DL, Jakicic JM, Otto AD. Comparison of techniques for self-monitoring eating and exercise behaviors on weight loss in a correspondence-based intervention. J Am Diet Assoc. 2007;107(10):1807–10.
49. Johnson F, Wardle J. The association between weight loss and engagement with a web-based food and exercise diary in a commercial weight loss programme: a retrospective analysis. Int J Behav Nutr Phys Act. 2011;8:83.
50. Beasley JM, Riley WT, Davis A, Singh J. Evaluation of a PDA-based dietary assessment and intervention program: a randomized controlled trial. J Am Coll Nutr. 2008;27(2):280–6.
51. ESHA Research. Food processor. http://www.esha.com/. Accessed 16 Jul 2012.
52. FoodWorks. The Nutrition Company. http://www.nutritionco.com/index.htm. Accessed 16 Jul 2012.
53. NutriBase. CyberSoft, Inc. http://www.nutribase.com/. Accessed 8 Jul 2012.
54. Nutritionist Pro. Axxya Systems. 2009. http://www.nutritionistpro.com/index.php. Accessed 16 Jul 2012.
55. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes: the essential guide to nutrient requirements. In: Otten JJ, Hellwig JP, Meyers LD, editors. Washington, DC: The National Academies Press; 2006.
56. Murphy SP, Barr SI. Practice paper of the American Dietetic Association: using the Dietary Reference Intakes. J Am Diet Assoc. 2011;111:762–70.
57. Nusser SM, Carriquiry AL, Dodd KW, Fuller WA. A semiparametric transformation approach to estimating usual daily intake distributions. J Am Stat Assoc. 1996;91:1440–9.
58. Kirkpatrick SI, Dodd KW, Tooze J, Bailey RL, Freedman L, Midthune D, et al. Measurement error webinar series. Risk Factor Monitoring and Methods, National Cancer Institute, National Institutes of Health. 2012. http://riskfactor.cancer.gov/measurementerror/. Accessed 16 Jul 2012.
59. Moshfegh AJ, Goldman J, Cleveland L. What We Eat in America, NHANES 2001–2002: usual nutrient intakes from food compared to Dietary Reference Intakes. U.S. Department of Agriculture, Agricultural Research Service. 2005. http://www.ars.usda.gov/research/publications/publications.htm?seq_no_115=184176. Accessed 16 Jul 2012.
60. National Research Council. Nutrient adequacy: assessment using food consumption surveys. Washington, DC: National Academy Press; 1986.
61. Murphy SP, Guenther PM, Kretsch MJ. Using the dietary reference intakes to assess intakes of groups: pitfalls to avoid. J Am Diet Assoc. 2006;106(10):1550–3.
62. Conway J, Ingwersen L, Moshfegh A. Accuracy of dietary recall using the USDA five-step multiple-pass method in men: an observational validation study. J Am Diet Assoc. 2004;104(4):595–603.
63. Conway J, Ingwersen L, Vinyard B, Moshfegh A. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr. 2003;77(5):1171–8.
64. Blanton CA, Moshfegh AJ, Baer DJ, Kretsch MJ. The USDA Automated Multiple-Pass Method accurately estimates group total energy and nutrient intake. J Nutr. 2006;136(10):2594–9.
65. Ard JD, Desmond RA, Allison DB, Conway JM. Dietary restraint and disinhibition do not affect accuracy of 24-hour recall in a multiethnic population. J Am Diet Assoc. 2006;106(3):434–7. doi:10.1016/j.jada.2005.12.006.
66. Bailey RL, Dodd KW, Gahche JJ, Dwyer JT, McDowell MA, Yetley EA, et al. Total folate and folic acid intake from foods and dietary supplements in the United States: 2003–2006. Am J Clin Nutr. 2010;91(1):231–7.
67. Rumpler WV, Kramer M, Rhodes DG, Moshfegh AJ, Paul DR. Identifying sources of reporting error using measured food intake. Eur J Clin Nutr. 2007;62(4):544–52.
68. Wirfalt AKE, Jeffery RW, Elmer PJ. Comparison of food frequency questionnaires: the reduced Block and Willett questionnaires differ in ranking on nutrient intakes. Am J Epidemiol. 1998;148(12):1148–56.
69. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. Br J Nutr. 2001;86(3):405–14.
70. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
71. Bingham SA. Biomarkers in nutritional epidemiology. Public Health Nutr. 2002;5(Suppl 6a):821–7.
72. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham S. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet. 2009;125(5):507–25.
73. Day N, McKeown N, Wong M, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. Int J Epidemiol. 2001;30(2):309–17.
74. Kipnis V, Midthune D, Freedman L, Bingham S, Day NE, Riboli E, et al. Bias in dietary-report instruments and its implications for nutritional epidemiology. Public Health Nutr. 2002;5(Suppl 6a):915–23.
75. Sargent JA, Gotch FA. Mass balance: a quantitative guide to clinical nutritional therapy. I. The predialysis patient with renal disease. J Am Diet Assoc. 1979;75(5):547–51.
76. Maroni BJ, Steinman T, Mitch W. A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int. 1985;27:58–61.

77. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, et al. The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am J Clin Nutr. 2008;88(2):324–32.
78. Dragsted L. Biomarkers of exposure to vitamins A, C, and E and their relation to lipid and protein oxidation markers. Eur J Nutr. 2008;47:3–18.
79. Holmes MD, Powell IJ, Campos H, Stampfer MJ, Giovannucci EL, Willett WC. Validation of a food frequency questionnaire measurement of selected nutrients using biological markers in African-American men. Eur J Clin Nutr. 2007;61(11):1328–36.
80. Choi H, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum. 2005;52(1):283–9.
81. Chun O, Chung S, Song W. Urinary isoflavones and their metabolites validate the dietary isoflavone intakes in US adults. J Am Diet Assoc. 2009;109(2):245–54.
82. Sargent JA, Lowrie EG. Which mathematical model to study uremic toxicity? National Cooperative Dialysis Study. Clin Nephrol. 1982;17(6):303–14.
83. Sargent JA, Gotch FA, Henry RR, Bennett N. Mass balance: a quantitative guide to clinical nutritional therapy. II. The dialyzed patient. J Am Diet Assoc. 1979;75(5):551–5.
84. Wineman RJ, Sargent JA, Piercy L. Nutritional implications of renal disease. II. The dietitian's key role in studies of dialysis therapy. J Am Diet Assoc. 1977;70(5):483–7.
85. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;2(Suppl):1–138.
86. Saadeh E, Ikizler TA, Shyr Y, Hakim RM, Himmelfarb J. Recombinant human growth hormone in patients with acute renal failure. J Ren Nutr. 2001;11(4):212–9.
87. Chima CS, Meyer L, Hummell AC, Bosworth C, Heyka R, Paganini EP, et al. Protein catabolic rate in patients with acute renal failure on continuous arteriovenous hemofiltration and total parenteral nutrition. J Am Soc Nephrol. 1993;3(8):1516–21.
88. Moore LW, Acchiardo S, Smith SO, Gaber AO. Nutrition in the critical care settings of renal diseases. Adv Ren Replace Ther. 1996;3(3):250–60.
89. Brown RO, Compher C; American Society for Parenteral and Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines. J Parenter Enteral Nutr. 2010;34(4):366–77.
90. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortorella G, Borghetti A. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol. 1999;10:581–93.
91. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Ochoa JB, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enteral Nutr. 2009;33(3):277–316.
92. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1–266.
93. Levin A, Stevens P, Work Group. KDIGO guideline for CKD classification and management—proposed. New York: KDIGO; 2011. http://www.kdigo.org/clinical_practice_guidelines/CKD.php. Accessed 31 Oct 2012.
94. Bross R, Noori N, Kovesdy CP, Murali SB, Benner D, Block G, et al. Dietary assessment of individuals with chronic kidney disease. Semin Dial. 2010;23(4):359–64.
95. Rotily M, Leonetti F, Iovanna C, Berthezene P, Dupuy P, Vazi A, et al. Effects of low animal protein or high-fiber diets on urine composition in calcium nephrolithiasis. Kidney Int. 2000;57(3):1115–23.
96. Hansen HP, Christensen PK, Tauber-Lassen E, Klausen A, Jensen BR, Parving H-H. Low-protein diet and kidney function in insulin-dependent diabetic patients with diabetic nephropathy. Kidney Int. 1999;55:621–8.
97. Dussol B, Iovanna C, Raccah D, Darmon P, Morange S, Vague P, et al. A randomized trial of low-protein diet in type 1 and in type 2 diabetes mellitus patients with incipient and overt nephropathy. J Ren Nutr. 2005;15(4):398–406.
98. Meloni C, Morosetti M, Suraci C, Pennafina MG, Tozzo C, Taccone-Gallucci M, et al. Severe dietary protein restriction in overt diabetic nephropathy: benefits or risks? J Ren Nutr. 2002;12(2):96–101.
99. Fassett RG, Robertson IK, Geraghty DP, Ball MJ, Coombes JS. Dietary intake of patients with chronic kidney disease entering the LORD trial: adjusting for underreporting. J Ren Nutr. 2008;17(4):235–42.
100. Soroka N, Silverberg DS, Greemland M, Birk Y, Blum M, Peer G, et al. Comparison of a vegetable-based (soya) and an animal-based low-protein diet in predialysis chronic renal failure patients. Nephron. 1998;79(2):173–80.
101. Bernhard J, Beaufrere B, Laville M, Fouque D. Adaptive response to a low-protein diet in predialysis chronic renal failure patients. J Am Soc Nephrol. 2001;12(6):1249–54.
102. Mircescu G, Gârneaţă L, Stancu SH, Capusa C. Effects of a supplemented hypoproteic diet in chronic kidney disease. J Ren Nutr. 2007;17(3):179–88. doi:10.1053/j.jrn.2006.12.012.

103. Moore LW, Parrott JS, Rigassio-Radler D, Byham-Gray L, Gaber AO. The effect of menses on the measurement of proteinuria and estimation of dietary intake in US females. J Am Diet Assoc. 2011;111:A15.
104. Moore LW, Byham-Gray L, Parrott JS, Radler D, Jones SL, Mandayam SA, et al. Dietary protein intake in chronic kidney disease from the National Health and Nutrition Examination Survey. J Am Soc Nephrol. 2011;22:175A.
105. Moore LW, Byham-Gray L, Parrott JS, Rigassio-Radler D, Jones SL, Mandayam S, et al. The mean dietary protein intake at different stages of chronic kidney disease is higher than current guidelines. Kidney Int. 2013;83(4):724–732. doi:10.1038/ki.2012.420.
106. Coresh J, Selvin E, Stevens L, Manzi J, Kusek J, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038–47.
107. Guida B, Trio R, Nastasi A, Laccetti R, Pesola D, Torraca S, et al. Body composition and cardiovascular risk factors in pretransplant hemodialysis patients. Clin Nutr. 2004;23:363–72.
108. Kalantar-Zadeh K, Kovesdy CP, Bross R, Benner D, Noori N, Murali SB, et al. Design and development of a dialysis food frequency questionnaire. J Ren Nutr. 2011;21(3):257–62.
109. Kalantar-Zadeh K, Kopple JD, Deepak S, Block D, Block G. Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. J Ren Nutr. 2002;12(1):17–31.
110. Dialysis FFQ. NutritionQuest. 2012. http://www.nutritionquest.com/dialysisFFQ. Accessed 16 Jul 2012.
111. Schoenfeld PY, Henry RR, Laird NM, Roxe DM. Assessment of nutritional status of the National Cooperative Dialysis Study population. Kidney Int. 1983;23 Suppl 13:S80–8.
112. Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. Semin Dial. 2007;20(4):295–301.
113. Murphy-Gutekunst L. Hidden phosphorus: where do we go from here? J Ren Nutr. 2007;17(4):e31–6.
114. Greene T, Beck GJ, Gassman JJ, Gotch FA, Kusek JW, Levey AS, et al. Design and statistical issues of the hemodialysis (HEMO) study. Control Clin Trials. 2000;21(5):502–25.
115. Burrowes JD, Cockram DB, Dwyer JT, Larive B, Paranandi L, Bergen C, et al. Cross-sectional relationship between dietary protein and energy intake, nutritional status, functional status, and comorbidity in older versus younger hemodialysis patients. J Ren Nutr. 2002;12(2):87–95.
116. Chauveau P, Grigaut E, Kolko A, Wolff P, Combe C, Aparicio M. Evaluation of nutritional status in patients with kidney disease: usefulness of dietary recall. J Ren Nutr. 2007;17(1):88–92.
117. Guida B, Trio R, Laccetti R, Nastasi A, Salvi E, Perrino NR, et al. Role of dietary intervention on metabolic abnormalities and nutritional status after renal transplantation. Nephrol Dial Transplant. 2007;22(11):3304–10.
118. Lopes IM, Martin M, Errasti P, Martinez JA. Benefits of a dietary intervention on weight loss, body composition, and lipid profile after renal transplantation. Nutrition. 1999;15(1):7–10.
119. El Haggan W, Vendrely B, Chauveau P, Barthe N, Castaing F, Berger F, et al. Early evolution of nutritional status and body composition after kidney transplantation. Am J Kidney Dis. 2002;40(3):629–37.
120. Orazio LK, Isbel NM, Armstrong KA, Tamarskyj J, Johnson DW, Hale RE, et al. Evaluation of dietetic advice for modification of cardiovascular disease risk factors in renal transplant recipients. J Ren Nutr. 2011;21(6):462–71.

Chapter 4
Anthropometric Assessment in Kidney Disease

Francis Dumler

Key Points

- Understand the importance of anthropometry as a practical and simple tool for quantification of body composition.
- Become familiar with body measurements at the core of the evaluation of clinical nutritional status using anthropometry.
- Develop a better understanding of body mass index, its limitations, and available alternatives for better discrimination between muscle and fat components of body mass.
- Use of anthropometric parameters for evaluating the risk of cardiovascular disease and progression of renal insufficiency in chronic kidney disease patients.
- Provide selective tables from the Anthropometric Reference Data for Children and Adults published by the National Health Statistics Reports as an Appendix.
- Inclusion of a reference textbook on body composition assessment using anthropometric techniques in the reference list for those needing in-depth information.

Keywords Height • Weight • Body mass index • Circumference measurements and ratios • Skinfold thickness • Bone breaths • Somatogram • Frame size • Somatotyping • NHANES III

An adequate nutritional status is inherent to an optimal level of health. In continuing illness states, such as chronic kidney disease (CKD), there is a significant interdependence between both. Nutritional status influences the disease process and its comorbidities. Renal failure and its management may have a negative impact on nutritional status thereby creating a vicious cycle. Thus, monitoring nutritional status and body composition is imperative to the appropriate management of CKD [1].

Anthropometry is the science that defines the size, form, and proportion of the human body and its regional components. A fundamental concept in its application is the intimate relationship between morphology and functional capacity. Anthropometry is an integral element of forensics, biomechanics, and ergonomics. Currently, anthropometry is used in the assessment of nutritional status, body composition, and classification of disease risk. It is also employed to assess the impact of genetics, the environment, and stress on the human physique.

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Table 4.1 Standardized sites for skinfold measurements

Site	Fold direction	Anatomical reference	Measurement
Chest	Diagonal	Axilla and nipple	Fold taken between axilla and nipple as high as possible
Subcapsular	Diagonal	Inferior angle of scapula	Fold taken along natural cleavage line of skin below inferior angle of scapula
Midaxillary	Horizontal	Xiphisternal junction	Fold taken on midaxillary line at level of xiphisternal junction
Suprailiac	Oblique	Iliac crest	Fold taken posteriorly to midaxillary line and superiorly to iliac crest along natural cleavage of skin
Abdominal	Horizontal	Umbilicus	Fold taken 3 cm lateral and 1 cm inferior to center of umbilicus
Triceps	Vertical (midline)	Acromial process of scapula and olecranon process of ulna	Distance between lateral projection of acromial process and inferior margin of olecranon process measured on lateral aspect of arm with elbow flexed 90°. Midpoint is marked on lateral side of arm. Fold is lifted 1 cm above marked line
Biceps	Vertical (midline)	Biceps brachii	Fold is lifted over belly of the biceps brachii at the level marked for the triceps and on line with anterior border of the acromial process and the antecubital fossa
Thigh	Vertical (midline)	Inguinal crease and patella	Fold is lifted on anterior aspect of thigh midway between inguinal crease and proximal border of patella. Body weight is shifted to left foot
Calf	Vertical (midline)	Maximal calf circumference	Fold is lifted at level of maximal calf circumference on medical aspect of calf with knee and hip flexed 90°

Adapted from Heyward VH, Wagner DR. Applied Body Composition Assessment. Chapter 4: Skinfold Method p. 58, Champaign, IL: Human Kinetics, 2004

There is a relationship between body dimensions and its composition, particularly fat, and to a lesser extent, muscle mass. Body fat and muscle content can be measured by more accurate methods including underwater weighing, total body potassium counting, dual-energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging (MRI) [2].

A comprehensive description of anthropometric techniques is beyond the scope of this chapter. There are two excellent sources describing these techniques in great detail: the National Health and Nutrition Examination Survey (NHANES) Anthropometry Manual [3] and the second edition of Applied Body Composition Assessment [4]. The dimensional components of classic anthropometry include weight, height, skinfold thickness, circumferences, and bone breadths. Standardized sites for these measurements are shown in Tables 4.1, 4.2, 4.3, and 4.4. A variety of computed measurements may be derived from the primary data using population specific (linear) or generic (quadratic) equations [5, 6]. By convention, all measurements are made on the right side of the body. Limb amputation, disease, malformation, or a functioning arteriovenous access will require taking measurements on the opposite side. All measures should be done posttreatment in dialysis patients.

Anthropometric methods have been used in large-scale studies, such as the NHANES III [7]. The availability of these data provides the clinician with a reference frame when evaluating individual patients. More relevant to CKD, anthropometry was a significant component of both the Modification of Diet in Renal Disease (MDRD) and the Hemodialysis (HEMO) clinical trials [8, 9]. Based on these studies, it is suggested that weight, height, subcapsular and triceps skinfolds, arm, and calf circumference be part of the nutrition evaluation in CKD patients.

Table 4.2 Standardized sites for circumference measurements (trunk)

Site	Anatomical reference	Position	Measurement
Neck	Laryngeal prominence	Perpendicular	Measure just inferior to laryngeal prominence (Adam's apple)
Shoulder	Deltoid muscles and acromion processes of scapula	Horizontal	Apply tape snugly over maximum bulges of the deltoid muscles, inferior to acromion processes. Record measurement at end of normal expiration
Chest	Fourth costosternal joints	Horizontal	Apply tape snugly around the torso at level of fourth costosternal joints. Record at end of normal expiration
Waist	Narrowest part of torso, level of the "natural" waist between ribs and iliac crest	Horizontal	Apply tape snugly around the waist at level of narrowest part of torso. An assistant is needed to position tape behind the client. Take measurement at end of normal expiration
Abdominal	Maximum anterior protuberance of abdomen, usually at umbilicus	Horizontal	Apply tape snugly around the abdomen at level of greatest anterior protuberance. An assistant is needed to position tape behind the client. Take measurement at end of normal expiration.
Hip (buttocks)	Maximum posterior extension of buttocks	Horizontal	Apply tape snugly around the buttocks. An assistant is needed to position tape on opposite side of body

Adapted from Heyward VH, Wagner DR. Applied Body Composition Assessment. Chapter 4: Additional Anthropometric Methods p. 69, Champaign, IL, Human Kinetics, 2004

Table 4.3 Standardized sites for circumference measurements (limbs)

Site	Anatomical reference	Position	Measurement
Arm (biceps)	Acromion process of scapula and olecranon process of ulna	Perpendicular to long axis of arm	With arms hanging freely at sides and palms facing thighs, apply tape snugly around the arm at level marked for triceps and biceps skinfolds
Forearm	Maximum girth of forearm	Perpendicular to long axis of forearm	With arms hanging down and away from trunk and forearm supinated, measure the maximum girth of the proximal part of the forearm
Wrist	Styloid processes of radium and ulna	Perpendicular to long axis of forearm	With elbow flexed and forearm supinated, measure just distal to the styloid processes of the radius and ulna
Thigh (proximal)	Gluteal fold	Horizontal	Measure around thigh just distal to gluteal fold
Thigh (mid)	Inguinal crease and proximal border of patella	Horizontal	With knee flexed 90° (right foot on bench), measure at level between inguinal crease and proximal border of patella
Thigh (distal)	Femoral epicondyles	Horizontal	Measure proximal to the femoral epicondyles
Knee	Patella	Horizontal	Measure around the knee at mid-patellar level with knee relaxed in slight flexion
Calf	Maximum girth of calf muscle	Perpendicular to long axis of leg	Measure maximum girth of calf while sitting on end of table with legs hanging freely
Ankle	Malleoli of tibia and fibula	Perpendicular to long axis of leg	Measure minimum circumference of leg, just proximal to the malleoli

Adapted from Heyward VH, Wagner DR. Applied Body Composition Assessment. Chapter 4: Additional Anthropometric Methods p. 70. Champaign, IL: Human Kinetics, 2004

Table 4.4 Standardized sites for bony breadth measurements

Site	Anatomical reference	Position	Measurement
Biacromial (shoulder)	Lateral borders of acromion (scapula)	Horizontal	Position: standing, arms hanging vertically, shoulders relaxed, downward, and slightly forward. Apply blade tips to lateral borders of acromion processes. Measure from the rear
Chest	Sixth ribs on midaxillary line	Horizontal	Position: standing with arms slightly abducted. Apply blade tips on the sixth ribs at the midaxillary line. Measure at end of normal expiration
Bi-iliac	Iliac crests	45° downward angle	Position: standing, arms folded across the chest, apply blade tips at a 45° downward angle, at maximum breadth of iliac crest. Measure from the rear
Bitrochanteric	Greater trochanter of femur	Horizontal	Position: standing, arms folded across the chest. Apply blade tips with considerable pressure to compress soft tissues. Measure maximum distance between trochanters from the rear
Knee	Femoral epicondyles	Diagonal or horizontal	Position: sitting and knee flexed to 90°. Apply blade tips firmly on lateral and medial femoral epicondyles
Ankle (bi-malleolar)	Malleoli of tibia and fibula	Oblique	Position: standing and weight evenly distributed. Apply blade tips to the most lateral part of lateral malleolus and most medial part of medial malleolus. Measure from the rear at an oblique plane
Elbow	Epicondyles of humerus	Oblique	Position: elbow flexed 90°, arm raised to the horizontal, forearm supinated. Apply blade tips firmly to the medial and lateral humeral epicondyles at an angle that bisects the right angle at the elbow
Wrist	Styloid process of radius and ulna (snuff box)	Oblique	Position: elbow flexed 90°, upper arm vertical and close to torso, forearm pronated. Apply blade tips firmly at an oblique angle to the styloid processes of the radius (at proximal part of anatomical snuff box) and ulna

Adapted from Heyward VH, Wagner DR. Applied Body Composition Assessment. Chapter 4: Additional Anthropometric Methods p 71. Champaign, IL, Human Kinetics, 2004

Weight and Height Measurements

Body weight usually varies less than 0.5–1 % within a period of 6–10 weeks [10]. A change of 5 % or more suggests a gain/loss of water or tissue mass. A 10 % or greater loss of body weight over a 6-month period is considered clinically significant and warrants full evaluation. Body weight is measured with a physician's scale calibrated to 0.1 kg.

Body height is best measured standing up with a straight back and neck using a height meter or stadiometer. A bar attached to the scale may be used if none is available. For patients having difficulties standing straight, those with spine curvatures, and those unable to stand, alternative measures are taken to derive an estimate of body height. These include knee height or arm span. Knee height is measured sitting down with the knee at 90° using a caliper under the sole and the blade moved up to 2 in. posterior to the knee cap. Arm span is measured from the tip of the longest finger on each hand while standing erect against a wall with arms fully stretched horizontally [11]. Of note, knee height and arm span change very little with age and should be used in the elderly when appropriate [12].

The relationship between weight and stature most commonly used is the body mass index (BMI) expressed as kg/m^2. It is related to overall body fat content (thinness or thickness) but is not a measure of percent body fat. Furthermore, it does not take into account body shape. For the same weight and height, an individual may have relatively more muscle and less fat mass than another with more fat and less muscle mass. Yet, in both circumstances BMI will be the same. Body fat in different parts of the body may have different biology. This has led to consider other measures that may better relate to body shape (hence distribution of fat and muscle mass). These include waist circumference, waist-to-hip ratio, and conicity index [13–15].

Waist circumference is a surrogate for abdominal obesity and visceral adipose tissue. Waist circumference is strongly associated with visceral fat in patients with CKD [16]. However, others have found waist circumference to be poorly correlated with visceral adipose tissue as measured by computed tomography in non-dialysis CKD patients [17]. There is a direct correlation between waist circumference and C-reactive protein [18–20]. Studies suggest that increased visceral but not subcutaneous fat is independently associated with risk of progression of CKD, cardiovascular events, and all-cause mortality [21–25]. The predictive value of triglycerides and cholesterol for survival and atherosclerotic complications in hemodialysis patients is dependent on waist circumference [26].

In a study of overweight patients with hypertension, abdominal obesity persisted as a risk factor even after adjustment for dyslipidemia, elevated blood glucose levels, and other variables associated with renal insufficiency. Even after adjustment for multiple covariates including BMI, higher mortality rates were noted for all waist circumference categories compared with the reference population [27]. These findings suggest that waist circumference may be a simple and inexpensive tool to be used in epidemiological studies. Because waist circumference is a function of both height and abdominal fat, some recommend factoring by height or height square for a tighter correlation to cardiovascular risk factors [28–30].

The predictive value of waist-to-hip ratio has also been evaluated in several studies. Waist-to-hip ratio, but not BMI, is related to cardiac events in patients with CKD. In the general population there is an association between waist-to-hip ratio, but not BMI, and incident CKD and mortality [21, 31]. Abdominal adiposity measured as waist circumference or waist-to-hip to ratio, irrespective of general adiposity, is a more important determinant of CKD risk in adults than BMI [21, 32–34]. Relying exclusively on BMI may underestimate the importance of obesity as a risk factor for developing kidney disease and as a cardiovascular disease risk factor in patients with established CKD.

The conicity index is a measure of visceral fat that evaluates the deviation from a cylindrical shape to a double cone shape with a common base at the waist [14]. The conicity index is an independent predictor of systemic inflammation, cardiovascular risk, and glomerular filtration rate in pre-dialysis patients [35]. However, this may not hold in the general population. In the Framingham study, obesity measured by BMI, but not the conicity index, was an important risk factor for coronary heart disease in men and women and for mortality in women.

Skinfold and Circumference Measurements

Skinfold thickness has been extensively used for estimation of fat mass. The thickness at a given location is assumed to be the sum of the two layers of skin and the subcutaneous mass contained in between (Table 4.1). Single or multiple sites may be selected depending on need and circumstances [3]. The summation of skinfold thickness values provides an assessment of subcutaneous fat content. The internal adipose component is derived from the abdominal circumference. Results are comparable to those obtained by CT and MRI at selected sites. Discrepancies in other areas are attributed to irregular fat tissue deposition or distortion from the supine position during CT or MRI data acquisition [36].

The distribution of subcutaneous and visceral fat is similar within each gender. About 30–50 % of body fat is located in the subcutaneous compartment. Visceral body fat distribution varies considerably between body compartments. Age is an independent predictor of body density in both genders. Older individuals with similar body density have proportionally less subcutaneous fat than younger ones. As individuals gets heavier, subcutaneous fat increases while visceral fat decreases. This highlights the importance of using appropriate reference standards [37].

Mid-arm, mid-thigh, and mid-calf circumferences, when combined with skinfold thickness, allow estimation of skeletal muscle mass. This measurement can be further refined by making adjustments for bone thickness. Muscle mass measured by anthropometry may be expressed as muscle area or circumference. Fat-free mass decreases with aging due to loss of skeletal muscle and visceral organs tissues. Geriatric-based equations are therefore recommended when evaluating an older population [4].

Somatogram

This method compares the circumferences from muscular (shoulders, chest, arm, forearm, thigh, and calf) and nonmuscular sites (abdomen, hip, knee, wrist, and ankle) to the corresponding reference values. The relative deviation (%) is graphed to visually display proportionality. This is particularly useful when assessing an individual over time. A simple Excel spreadsheet may be used for the full calculation and graphic presentation [38].

Frame Size

There is a direct relationship between skeletal breaths and the bone and muscle components of the free mass. Estimation of frame size using skeletal breaths can help differentiate a higher weight due to a larger musculoskeletal mass from that a larger fat mass. Previous studies have shown that wrist, ankle, and elbow breaths are a good predictor of frame size [39]. Frame size may be helpful in determining if a higher body weight is related to greater bone and muscle mass rather than increased fat content.

Somatotyping

This method uses anthropometric measurements to score endomorphy (fat), mesomorphy (muscle), and ectomorphy to establish a proportionality between weight and height. Measured parameters include body height and weight, skinfold thickness (triceps, subcapsular, suprailiac, and calf), muscle circumference (mid-arm and mid-calf), and bony width (humerus and femur). A rating for each component is calculated from a score card or using a computer program. Scores are then plotted into an *X*–*Y* plot (somatochart) that allows allocation to one of seven categories [40].

Reference Data

As described earlier, availability of adequate reference standards is critical to the correct application and interpretation of anthropometry in evaluation nutritional status and body composition. The NHANES III provides the most comprehensive dataset [7, 37]. Anthropometric measurements were

obtained from 19,593 survey participants and included weight, height, recumbent length, circumferences, limb lengths, and skinfold thickness measurements. The Anthropometric Reference Data for Children and Adults published by the National Health Statistics Reports includes weighted population means, standard error of the means, and selected percentiles of body measurement values. As measurements vary by sex, age, and ethnicity or race, results are reported by subgroups [37].

Many anthropometry techniques and methodologies have been described in this chapter. However, from a clinical perspective the most significant components are weight, height, skinfold thickness, and limb circumferences. These measurements are easy to obtain and have been used in the MDRD and HEMO studies, and the reference population is well defined by the NHANES III dataset. Individual patient percentiles can be easily assigned from the reference tables [37].

Summary

Anthropometry is one of the oldest approaches for quantifying body composition. It is the most practical tool for use in the field and clinical settings. It provides an index of nutritional status and risk for malnutrition. In addition, it is a useful instrument for evaluating the risk potential for developing kidney and cardiovascular disease, progression of kidney failure, morbidity, and mortality. Finally, anthropometry is a serial simple, inexpensive, and noninvasive way of monitoring nutritional status, risk assessment, and response to treatment strategies.

References

1. Dumler F. Body composition modifications in patients under low protein diets. J Ren Nutr. 2011;21:76–81.
2. Dumler F. Use of bioelectric impedance analysis and dual-energy X-ray absorptiometry for monitoring the nutritional status of dialysis patients. ASAIO J. 1997;43:256–60.
3. NHANES. Anthropometry manual. http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf
4. Heyward VH, Wagner DR. Applied body composition assessment. Champaign, IL: Human Kinetics; 2004.
5. Jackson AS, Pollock ML, Ward A. Generalized equations for predicting body density of women. Med Sci Sports Exerc. 1980;12:175–82.
6. Jackson AS, Pollock ML. Generalized equations for predicting body density of men. Br J Nutr. 1978;40:497–504.
7. NHANES website. http://www.cdc.gov/nchs/nhanes.htm
8. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang S, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57:1688–703.
9. Chumlea WC, Dwyer J, Bergen C, Burkart J, Paranandi L, Frydrych A, Cockram D, Kusek J, McLeroy S; HEMO Study Group. Nutritional status assessed from anthropometric measures in the HEMO study. J Ren Nutr. 2003; 13:31–8.
10. Khosla T, Billewicz WZ. Measurements of change in body-height. Br J Nutr. 1964;18:227–39.
11. http://www.rxkinetics.com/height_estimate.html
12. Haboubi NY, Hudson PR, Pathy MS. Measurement of height in the elderly. J Am Geriatr Soc. 1990;38:1008–10.
13. Taylor RW, Keil D, Gold EJ, Williams SM, Goulding A. Body mass index, waist girth, and waist-to-hip ratio as indexes of total and regional adiposity in women: evaluation using receiver operating characteristic curves. Am J Clin Nutr. 1998;67:44–9.
14. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3–19 years. Am J Clin Nutr. 2000;72:490–5.
15. Valdez R, Seidell JC, Ahn YI, Weiss KM. A new index of abdominal adiposity as an indicator of risk for cardiovascular disease. A cross population study. Int J Obes Relat Metab Disord. 1993;17:77–82.
16. Sanches FMR, Avesani CM, Kamimura MA, Lemos MM, Axelsson J, Vasselai P, Draibe SA, Cuppari L. Waist circumference and visceral fat in CKD: a cross-sectional study. Am J Kidney Dis. 2008;52:66–73.

17. Velludo CM, Kamimura MA, Sanches FM, Lemos MM, Canziani ME, Pupim LB, Draibe SA, Cuppari L. Prospective evaluation of waist circumference and visceral adipose tissue in patients with chronic kidney disease. Am J Nephrol. 2010;31(12):104–9.
18. Farouche NG, Sitar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. Int J Obes Relat Metab Disord. 2001;25:1327–31.
19. Saijo Y, Kiyota N, Kawasaki Y, Miyazaki Y, Kashimura J, Fukuda M, Kishi R. Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. Diabetes Obes Metab. 2004;6:249–58.
20. Brinkley TE, Hsu FC, Beavers KM, Church TS, Goodpaster BH, Stafford RS, Pahor M, Kritchevsky SB, Nicklas BJ. Total and abdominal adiposity are associated with inflammation in older adults using a factor analysis approach. J Gerontol A Biol Sci Med Sci. 2012;67(10):1099–106. doi:10.1093/gerona/gls077.
21. Elsayed EF, Sarnak MJ, Tighiouart H, Griffith JL, Kurth T, Salem DN, Levey AS, Weiner DE. Waist-to-hip ratio, body mass index, and subsequent kidney disease and death. Am J Kidney Dis. 2008;52:29–38.
22. Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, Kalantar-Zadeh K, Molnar MZ, Mucsi I. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant. 2010;10: 2644–51.
23. Kramer H, Shoham D, McClure LA, Durazo-Arvizu R, Howard G, Judd S, Muntner P, Safford M, Warnock DG, McClellan W. Association of waist circumference and body mass index with all-cause mortality in CKD: the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. Am J Kidney Dis. 2011;58:177–85.
24. Jacobs EJ, Newton CC, Wang Y, Patel AV, McCullough ML, Campbell PT, Thun MJ, Gapstur SM. Waist circumference and all-cause mortality in a large US cohort. Arch Intern Med. 2010;170:1293–301.
25. Zoccali C, Postorino M, Marino C, Pizzini P, Cutrupi S, Tripepi G; CREDIT Working Group. Waist circumference modifies the relationship between the adipose tissue cytokines leptin and adiponectin and all-cause and cardiovascular mortality in hemodialysis patients. J Intern Med. 2011;269:172–81.
26. Postorino M, Marino C, Tripepi G, Zoccali C; CREDIT Working Group. Abdominal obesity modifies the risk of hypertriglyceridemia for all-cause and cardiovascular mortality in hemodialysis patients. Kidney Int. 2011;79:765–72.
27. Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377: 1085–95.
28. Hsieh SD, Muto T. The superiority of waist-to-height ratio as an anthropometric index to evaluate clustering of coronary risk factor among non-obese men and women. Prev Med. 2005;40:216–20.
29. Chehrei A, Sadrnia S, Keshteli AH, Daneshmand MA, Rezael J. Correlation of dyslipidemia with waist to height ratio, waist circumference, and body mass index in Iranian adults. Asia Pac J Clin Nutr. 2007;16:248–53.
30. Costa de Oliveira CM, Rios Melo S, Moreira do vale Mota A, Kubrusly M. Adductor pollicis muscle thickness: a promising anthropometric parameter for patients with chronic renal failure. J Ren Nutr. 2012;22:251–7.
31. Elsayed EF, Tighiouart MS, Weiner DE, Griffith J, Salem D, Levey AS, Sarnak MJ. Waist-to-hip ratio and body index as risk factors for cardiovascular events in CKD. Am J Kidney Dis. 2008;52:49–57.
32. Hanai K, Babazono T, Nyumura I, Toya K, Ohta M, Bouchi R, Suzuki K, Inoue A, Iwamoto Y. Involvement of visceral fat in the pathogenesis of albuminuria in patients with type 2 diabetes with early stage of nephropathy. Clin Exp Nephrol. 2010;14:132–6.
33. Noori N, Hosseinpanah F, Nasiri AA, Azizi F. Comparison of overall obesity and abdominal adiposity in predicting chronic kidney disease incidence among adults. J Ren Nutr. 2009;19:228–37.
34. Burton JO, Gray LJ, Webb DR, Davies MJ, Khunti K, Crasto W, Carr SJ, Brunskill NJ. Association of anthropometric obesity measures with chronic kidney disease risk in a non-diabetic patient population. Nephrol Dial Transplant. 2012;27(5):1860–6. doi:10.1093/ndt/gfr574.
35. Sezer S, Karakan S, Acar NO. Association of conicity index and renal progression in pre-dialysis chronic kidney disease. Ren Fail. 2012;34:165–70.
36. Hayes PA, Sowood PJ, Belyavin A, Cohen JB, Smith FW. Subcutaneous fat thickness measured by magnetic resonance imaging, ultrasound, and calipers. Med Sci Sports Exerc. 1988;20:303–9.
37. Fryar CD, Gu Q, Ogden CL. Anthropometric reference data for children and adults: United States, 2007–2010. http://www.cdc.gov/nchs/nhanes/new_nhanes.htm
38. Heyward VH, Wagner DR. Applied body composition assessment. Chapter 5. Champaign, IL: Human Kinetics; 2004. p. 78–82.
39. Frisancho R. New standard of weight and body composition by frame size and height for assessment of nutritional status of adults and the elderly. Am J Clin Nutr. 1984;40:808–19.
40. Carter JEL. The Heath-Carter anthropometric somatotype. http://www.somatotype.org/Heath-CarterManual.pdf

Chapter 5
Biochemical Nutritional Assessment in Chronic Kidney Disease

David B. Cockram

Key Points

This chapter will enable the reader to:

- Discuss the role of biochemical parameters as a component of a comprehensive nutritional assessment.
- Identify the biochemical parameters and the recommended frequency of measurement suggested in the KDOQI nutrition guidelines and International Society of Renal Nutrition and Metabolism consensus conference for routine, confirmatory, and screening testing.
- List the strengths and weaknesses of various biochemical tests in the CKD population.

Keywords Nutrition assessment • Biochemical tests • Albumin • C-reactive protein • Prealbumin • Transthyretin • Creatinine • Cholesterol • Creatinine index • Protein nitrogen appearance

Introduction

Suboptimal nutritional status is common in people in the latter stages of chronic kidney disease (CKD) and is associated with increased morbidity and mortality and higher health care costs. Data from the Modification of Diet in Renal Disease (MDRD) study demonstrated that protein–energy nutritional status deteriorates as glomerular filtration rate (GFR) declines [1, 2]. Frank protein–energy malnutrition (PEM) prior to initiation of dialysis was fairly rare, but evidence of deteriorating nutritional intake was common as kidney function declined. Among people receiving dialysis, depending on the nutritional assessment parameters chosen and thresholds used for identifying deficits, the literature reports 18–75 % of people receiving maintenance dialysis have evidence of protein deficits [1]. Measures of nutritional status generally deteriorate with time in patients with Stage 5 kidney disease, even in the presence of excellent dialytic care and close nutritional monitoring and interventions [3]. Nutritional status is an important predictor of increased hospitalization rate, hospital days, and mortality. Therefore, assessing and optimizing nutritional status is important to improve patients' quality of life, optimize clinical outcome, and help control cost of care.

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The role of nutrition assessment is to describe a patient's nutritional status from a variety of perspectives to guide individualization of nutrition therapies. Nutrition assessments are comprised of several evaluations, including anthropometric measurements, biochemical testing, a clinical profile, and an evaluation of dietary adequacy and habits. The clinician integrates these data to determine adequacy of acute and chronic nutritional intake in relation to requirements, to determine the need for nutrition therapy, and to guide and monitor responses to therapeutic nutrition interventions.

Nutrition assessments, and the optimal assessment methodologies, vary depending on the objective of the assessment. For screening purposes, simple evaluations that require minimal patient involvement and limited training for the person making the assessment can be used to prioritize patients for a more in-depth assessment. At the other extreme, research assessment tools typically provide very high precision at the cellular or elemental level but tend to be more invasive, require more patient cooperation and highly trained dietetic support. Clinically useful nutrition assessment techniques balance precision, staff time, and patient effort required to provide appropriate levels of detail. The objective of the nutrition assessment, and the availability of appropriate population-specific reference data, needs to be understood to select appropriate techniques.

In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) published recommendations for terminology describing malnutrition in people with kidney disease [4]. The term "protein-energy wasting" was recommended to describe the combination of low serum proteins, decreasing/low body mass, and decreasing/low muscle mass. This phenomenon is frequently observed in people with CKD but may not necessarily be directly caused by the CKD. In contrast, when these symptoms occur due to kidney disease, the consensus panel recommended use of the term "kidney disease wasting" instead. Malnutrition refers to abnormalities induced by an inadequate diet, specifically excess or insufficient intake relative to nutritional requirements. Unlike malnutrition, which is typically responsive to dietary interventions, wasting is not corrected solely by dietary modification. In addition to potentially inadequate intake, wasting typically develops in the presence of inflammation, acidosis, or both, either of which can impair protein synthesis and anabolism. Both biomarkers associated with inflammation and malnutrition correlate with increased relative risk of mortality. However, the relative contributions of malnutrition and inflammation on mortality are difficult to distinguish because biomarkers for each, as well as causes of death associated with them, are similar.

This chapter includes discussions of biochemical nutritional assessment techniques for use in screening, for routine clinical, and for research purposes. A number of common biochemical nutrition assessment parameters are abnormal in many people with CKD. Biochemical testing has the advantages of being objective, requiring minimal patient cooperation, and many measures are commonly available to clinicians. Currently, biochemical testing is the only clinically practical way to help identify the presence of malnutrition, inflammation, or both in people with CKD.

Biochemical Assessment of Nutritional Status

Biochemical assessment of nutritional status offers the advantages of being readily available in most clinical settings, objectivity, and it requires only minimal patient cooperation. Although it is convenient for clinicians, especially for screening purposes, biochemical assessment by itself can rarely be used as the sole means of determining nutritional status. Integrating anthropometric and dietary data, as well as the patient's clinical profile along with the biochemical data, is needed to fully evaluate an individual's nutritional status. CKD and dialysis procedures each can influence nutritional status, limiting nutrient intake due to anorexia, dietary restrictions, socioeconomic constraints, or impaired gastrointestinal motility. In addition, CKD also exerts an indirect effect on nutritional status by increasing requirements and impairing the body's ability to downregulate resting energy expenditure (REE) and protein

Table 5.1 KDOQI biochemical testing regimen in stages 2–5 CKD

Marker type	Marker	Measurement frequency
Routine	Predialysis serum albumin	Monthly in maintenance dialysis (every 1–3 months in CKD)
	nPNA	Monthly (every 3–4 months for peritoneal dialysis; every 3–4 months in CKD)
Confirmatory	Predialysis serum prealbumin	As needed
Screening	Predialysis serum creatinine	As needed
	Predialysis serum cholesterol	As needed
	Creatinine index	As needed

Adapted from [5]
CKD chronic kidney disease, *nPNA* normalized protein equivalent of nitrogen appearance

Table 5.2 ISRNM diagnostic criteria for protein–energy wasting

Category	Criteria	Suggested threshold
Serum chemistries	Serum albumin	<3.8 g/dL by bromocresol green method
	Serum prealbumin	<30 mg/dL (maintenance dialysis only)
	Serum cholesterol	<100 mg/dL
Body mass	Body mass index	<23 kg/m^2 (edema-free dry weight)
	Unintentional weight loss	5 or 10 % over 3 or 6 months, respectively
	Body fat percentage	<10 %
Muscle mass	Muscle wasting	5 or 10 % over 3 or 6 months, respectively
	Mid-arm muscle area	Decrease by >10 % vs. reference population's 50th percentile
	Creatinine appearance	Decrease over time (no specific threshold recommended)
Dietary intake		Unintentional intake for >2 months:
	Protein intake	<0.80 g/kg/day (maintenance dialysis)
		<0.60 g/kg/day (CKD stages 2–5)
	Energy intake	<25 kcal/kg/day

Adapted from [4]

turnover. Biochemical testing provides important insights into adequacy of protein and energy intake, the presence of inflammatory or oxidative stress, and nutritional adequacy over time.

The National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-KDOQI) nutrition practice guidelines recommended the use of a panel of nutritional parameters because no single index comprehensively summarizes all aspects of nutritional status [5]. The KDOQI nutritional guidelines recommend a battery of anthropometric, clinical, and dietary assessments in addition to the biochemical parameters listed in Table 5.1. The work group divided nutritional markers into tests to be done routinely, confirmatory tests to be done as needed, and screening tests requiring further confirmation. Subsequently, the ISRNM consensus report proposed diagnostic criteria for protein–energy wasting (Table 5.2). In addition to providing data for assessment of protein–energy nutritional status, other biochemical parameters frequently are of importance in the dietary and medical management of patients receiving dialysis, such as glucose, hemoglobin A_{1c}, potassium, phosphorus, and calcium, but are beyond the scope of this chapter.

Protein–Energy Nutritional Status

Assessment of protein–energy nutritional status is one of the most common applications of biochemical assessment. The most commonly used proteins for nutritional assessment are serum albumin, prealbumin (or transthyretin), and transferrin. Other biochemical parameters are useful as screening tools: serum creatinine, cholesterol, and bicarbonate.

Serum proteins can be broadly divided into two categories, negative and positive acute phase proteins. Circulating levels of negative acute phase proteins, such as serum albumin and prealbumin, are at their highest in well-nourished, unstressed individuals and decline in the presence of inadequate protein intake, inflammatory stress, or both. In contrast, positive acute phase proteins, such as serum C-reactive protein (CRP), normally circulate at very low levels and rise dramatically in the presence of inflammatory stress. Because both nutrition and inflammation independently influence each of these biochemical markers, both must be considered when concluding serum protein levels are reflections of either nutritional or inflammatory influences.

The expected frequency of laboratory testing should also be considered in selecting nutritional markers. When nutritional assessments are performed monthly in generally stable individuals as in the case of maintenance dialysis patients, longer half-life nutritional parameters are logical choices. In contrast, for patients undergoing acute changes in nutritional and inflammatory state, addition of short half-life nutritional and inflammatory markers may allow adjustment of nutritional interventions based on acute patient response.

Serum Albumin

Albumin is the most abundant protein circulating in the blood, readily available on most biochemistry panels, and is therefore widely used as a nutritional and inflammatory marker [6]. Because of its routine availability and association with nutritional status, it—rightly or wrongly—has become a clinical performance indicator for quality of care for patients with CKD [6].

Interpretation of serum albumin is challenging in people with CKD. Albumin has a clear inverse association with clinical outcome in numerous studies [7–17]. However, both modifiable and nonmodifiable factors influence serum albumin [5, 12, 18]. Older age, female sex, white race, presence of several chronic diseases (chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, and cancer), and being the first year of dialysis are nonmodifiable factors correlated with hypoalbuminemia [19]. Modifiable factors associated with improved albumin include smoking cessation, use of arteriovenous fistulas, or biocompatible dialysis membranes [19]. Longitudinal analyses of serum albumin show a decline in serum albumin in the months immediately preceding death and an improvement during the first year of dialysis [19].

Albumin is synthesized in the liver and functions both to maintain osmotic pressure and carry numerous compounds. The half-life of serum albumin is approximately 20 days, making it a potentially useful tool for monthly nutritional assessments but relatively unresponsive to acute changes in nutritional or inflammatory status. Serum albumin is extensively distributed in both intra- and extravascular compartments and can be redistributed into the extravascular space, resulting in hypoalbuminemia. Serum albumin levels are also reduced in patients with metabolic acidosis. Nutrient intake, particularly protein intake, is one of several factors determining serum albumin levels [6, 20]. However, serum albumin levels are maintained in otherwise healthy individuals until late in the course of PEM in the absence of underlying inflammatory stress. Serum albumin is also preserved with chronically low protein intake because REE is typically simultaneously downregulated [6]. However, systemic inflammation inhibits this normal adaptation to protein–energy deficits. In addition, inflammation also both inhibits albumin synthesis and increases its fractional catabolic rate [20, 21]. Thus, dietary protein and inflammation have separate and opposing influences on serum albumin. Interpretation of hypoalbuminemia must be made in the context of both nutrient intake and presence of inflammation [6, 21].

Subnormal serum albumin levels (<4.0 g/dL) have long been shown to predict both all-cause and cardiovascular mortality in people receiving maintenance dialysis [14, 20]. Without additional information to help differentiate between nutritional deficits, inflammation, or a combination of the two, hypoalbuminemia should not be presumed to be nutrition-related but rather as a marker for the presence of illness [6]. The view that hypoalbuminemia is not primarily due to nutritional deficits appears to be supported by the limited success of enteral or parenteral intervention trials to effectively correct

hypoalbuminemia [6, 22]. Others, however, have concluded that although both inflammation and malnutrition frequently coexist, subnormal levels of serum albumin and prealbumin are principally reflective of nutritional inadequacy [23]. Friedman and Fadem published [6] a framework for evaluating serum albumin. Patients with subnormal serum albumin are assessed for extremely low protein intake and deficits in muscle and fat mass. If all are present then hypoalbuminemia may be nutritional in etiology, and protein–energy nutritional supplementation is initiated. If the serum albumin and body composition responds to supplementation, then the deficit is presumed to be nutritional. If the deficit fails to respond to nutritional intervention or the deficit exists in the absence of a sustained low protein intake and loss of muscle and fat mass, the deficit is likely non-nutritional in etiology and non-dietary etiologies for hypoalbuminemia explored.

Serum Prealbumin

Serum prealbumin, like albumin, is a negative acute phase protein. Prealbumin has a half-life of about 2 days and is therefore very responsive to recent events, especially calorie and protein deficits as well as inflammatory stress. Thus, for patients with acute illnesses or following initiation of nutritional interventions, prealbumin can be a useful early directional indicator of changes in nutritional and inflammatory status [5, 24].

Serum prealbumin, and a decline in serum prealbumin over time, predicts all-cause mortality independently of inflammation (based on CRP) [23]. Predialysis serum prealbumin is directly correlated with other biochemical nutritional markers (serum albumin, creatinine, and cholesterol) as well as predialysis body weight and bioelectrical impedance (BIA)-derived reactance, body cell mass, body water, and phase angle [24]. Prealbumin was predictive of hospitalization over the next 12 months in a univariate analyses, though when included in a multivariate analysis prealbumin was no longer significant [25]. A prealbumin of <30 mg/dL is associated with an increased risk of mortality [24, 26]. Although albumin and prealbumin are highly correlated, both are independent predictors of mortality [24]. Both also correlate with hospitalization, however, prealbumin but not albumin was correlated with infectious hospitalizations [24].

When the KDOQI nutrition guidelines were drafted, there was insufficient published data to conclude that prealbumin was a more sensitive or specific nutritional marker than serum albumin [5]. However, subsequent publications indicate that predialysis serum prealbumin is a useful addition to nutritional profiles and provides additive information to serum albumin [9, 24, 27–29]. Patients with a predialysis serum prealbumin of less than 30 mg/dL should be evaluated for nutritional adequacy [5, 24, 26]. This threshold is within the normal range (approximately 17–45 mg/dL) for people without kidney disease, reflecting decreased renal clearance of prealbumin in patients with CKD.

Serum Creatinine and Creatinine Index

Serum creatinine is a nutritional screening parameter in people receiving maintenance dialysis [4, 5]. Predialysis serum creatinine concentration reflects the sum of creatinine of dietary origin (creatine and creatinine from meat) and that formed endogenously in skeletal muscle tissue less creatinine removed by residual kidney function and dialysis [4, 5]. Creatinine is formed irreversibly from creatine in skeletal muscle at a fairly constant rate that is directly proportional to skeletal muscle mass. Thus, under steady state conditions for diet and dialysis, predialysis serum creatinine is roughly proportional to lean body mass. A declining predialysis serum creatinine over time in otherwise stable dialyzed patients indicates loss of skeletal muscle mass. Although not commonly used in clinical practice, creatinine index can be calculated to easily estimate fat-free body mass, especially in anuric patients [5].

Serum creatinine, and a decline in serum creatinine over time, predicts all-cause mortality independently of inflammation (as measured by CRP) [23]. Serum creatinine levels are directly

correlated with both serum albumin and serum prealbumin. The relationship between serum creatinine and mortality in maintenance dialysis patients is typically "J" shaped, with the lowest mortality occurring at a predialysis creatinine level of 9–11 mg/dL and rising significantly at lower levels and modestly at higher levels [14]. Lower levels of predialysis serum creatinine reflect low dietary intake of creatinine and creatine as well as low lean body mass. High serum creatinine in an otherwise stable dialysis patient typically is suggestive of inadequate dialysis, while a gradually rising serum creatinine must be evaluated carefully to determine whether the rise is related to increasing lean body mass or inadequate dialysis. Data from the HEMO study indicate that low predialysis creatinine is associated with an increased relative risk of mortality, and increases in creatinine are associated with a reduced relative risk [17]. The KDOQI nutrition guidelines recommend that dietary adequacy be evaluated in patients exhibiting serum creatinine levels of less than approximately 10 mg/dL [5].

Serum Total Cholesterol

Low serum total cholesterol is correlated with markers of protein nutritional status (serum albumin, prealbumin, and creatinine) and with mortality in most, but not all, trials. The relationship between nutrient intake and low serum total cholesterol is indirect. The presence of hypocholesterolemia, below 150–180 mg/dL, or a declining serum cholesterol concentration can be an indicator of chronically inadequate protein and energy intake [5].

Serum cholesterol is primarily useful as a screening tool since its sensitivity to, and specificity for, changes in protein and energy intake is poor. Serum cholesterol also is depressed with chronic inflammation. The relationship between mortality and serum cholesterol is usually "U" shaped, with lowest mortality occurring with serum cholesterol levels of about 200–220 mg/dL in most trials and increasing for higher or lower values. A relationship between CRP and serum cholesterol has been reported, with patients at both high and low extremes of the serum cholesterol distribution having higher CRP levels [30]. Low levels of cholesterol and elevated CRP suggest the presence of inflammatory stress and anorexia while elevated levels of both may be more reflective of cardiovascular disease (CVD). Like most other biochemical markers that may be nutritionally influenced, the HEMO study found that low serum cholesterol was associated with higher relative risk of mortality over the short term (i.e., <6 months), but this effect diminished as with longer follow-up [17].

Serum Transferrin

Serum transferrin is frequently used as a marker of protein–energy nutritional status in people without CKD. Compared to serum albumin, it has the advantage of a shorter half-life (about 8.5 days) and a smaller pool size, making it more responsive to nutritional deficits. However, because transferrin is also influenced by the presence of anemia, a comorbidity prevalent in people with CKD requiring maintenance dialysis, it is not recommended for nutritional assessment in patients with stage 4 or 5 CKD because its specificity for protein–energy nutritional deficits is low in this population [5]. Transferrin is a useful nutritional parameter in patients with higher levels of kidney function. In the MDRD study, transferrin and nutrient intake gradually declined as kidney function deteriorated [1].

Markers of Inflammation

Thirty to fifty percent of patients receiving maintenance dialysis have evidence of an active inflammatory response [31, 32]. A growing body of evidence suggests that to accurately interpret serum

protein status, an understanding of a patient's inflammatory state is critical [13, 23, 33–44]. Nutritional and inflammatory stresses frequently coexist in people with CKD and the predictive power of nutritional parameters for clinical outcome is partially or fully attenuated when nutritional parameters are adjusted for the presence of inflammation. Approximately 75 % of patients with CKD also have evidence of concomitant CVD. Proinflammatory cytokines and oxidative stress elicit an inflammatory response and the presence of inflammation is closely associated with accelerated development of CVD and cardiovascular mortality. In contrast to levels of serum albumin and prealbumin, which generally rise during the first year following initiation of dialysis, circulating levels of inflammatory mediators (e.g., CRP, interleukin-6 (IL-6) and interleukin-10 (IL-10)) do not improve with initiation of dialysis [5].

Inflammation blunts appetite and increases protein catabolism, lipolysis, and REE [45]. The effect of inflammation on REE is subtle increasing it by approximately 10–15 %, but over time, this sustained increase may result in protein–energy deficits, especially when combined with anorexia, which is a common side effect of both CKD and inflammation [32, 46]. Others have reported a lower total energy expenditure in CKD patients in inflammation (CRP >5.0 mg/L) compared to either normal controls or people with CKD but without elevated CRP, an effect that was attributed to much lower energy expenditure for physical activity in patients in inflammation [47]. Chronic inflammation in CKD patients can be caused by infections, interactions between the blood and dialyzer, contaminants in the dialysate, concomitant conditions, or a combination of these factors [31]. In addition, dialysis itself, even when biocompatible dialysis membranes are used, results in transient inflammatory response that persists for several hours following treatment [45]. An understanding of inflammatory status is increasingly accepted as a key part of biochemical nutritional assessment [6, 22].

C-Reactive Protein and Proinflammatory Cytokines

A number of positive acute phase proteins can be used to document the presence of acute or chronic inflammation. One of the most common and consistently used is CRP, a nonspecific marker of inflammation and proinflammatory cytokine activity [13, 23, 32, 38–40, 42, 47–54]. CRP has a half-life of approximately 19 h. Its catabolic rate is not affected by inflammation, while its synthetic rate and release is markedly upregulated during an acute phase response. Thus, levels of CRP in stressed patients can rapidly rise by several orders of magnitude. Clinically CRP may not be routinely available but should be considered when inflammation is suspected or when response to nutritional interventions is slower than expected [6].

Other clinically useful markers are the proinflammatory cytokines—tumor necrosis factor (TNF-α) and IL-6. Upregulation of TNF-α and IL-6 contributes both to wasting and the high incidence of cardiovascular morbidity and mortality in people with CKD [55, 56]. Proinflammatory cytokine activity has numerous deleterious effects including the promotion of insulin resistance, anorexia, and oxidative stress. TNF-α stimulates lipolysis and impairs muscle synthesis while IL-6 inhibits insulin growth factor-1 (IGF-1) and plays a role in the development of sarcopenia [56].

Serum albumin levels are inversely correlated with CRP [21, 54]. However, because of its rapid turnover relative to that of albumin, CRP correlates less well with future albumin levels. In contrast, longer half-life positive acute phase proteins (e.g., ceruloplasmin or α-1 acid glycoprotein) are more predictive of future albumin levels [21]. CRP is predictive of hospitalization and cardiovascular morbidity and mortality; it is a marker for the presence of inflammation and CVD and an independent predictor of all-cause and cardiovascular mortality in patients with stage 3 and 4 CKD. Serum albumin and CRP both were independent predictors of all-cause mortality, suggesting that they either act via different mechanisms (e.g., nutritional vs. inflammatory) or at different points in the inflammatory process [15].

Nutritional Adequacy and Management

Protein Intake

The adequacy of protein intake can be estimated in several ways in people with CKD. Diet records or recalls can provide clinicians detailed information about food choices and can be very useful as educational tools but require a substantial effort from the patient and thus can be incomplete records of protein intake. These dietary assessment tools are discussed in Chap. 4. Protein intake can also be estimated in clinically stable patients by determining the protein equivalent of total nitrogen appearance (PNA), also called protein catabolic rate (PCR) [5]. PNA (PCR) reflects the sum of urea generation from endogenous protein turnover and the metabolism of dietary protein minus urea removed from the body by dialysis or residual renal function and change in body urea pool size over the interdialytic interval. The urea pool accounts for changes in blood urea nitrogen (BUN) levels and changes in total body water (TBW) volume over the measurement period. Fecal and dermal nitrogen losses are disregarded because they are quantitatively fairly minor and impractical to collect and analyze under clinical conditions. Detailed procedures for computing PNA for people on hemodialysis (HD) and peritoneal dialysis (PD) are published in the KDOQI Clinical Practice Guidelines [5].

Clinically, PNA is typically normalized so that protein intake, expressed as normalized protein nitrogen appearance (nPNA) or normalized protein catabolic rate (also referred to as nPCR). nPNA (nPCR) can be compared to estimated protein requirements independently of body mass. Unlike typical practice for diet records, where intake is usually normalized to either actual or adjusted body weight, PNA is normalized by dividing it by $V/0.58$. V is the patient's urea volume which can be determined either during urea kinetics, using BIA, or anthropometric equations and is an estimate of fat-free body mass. The 0.58 factor is the typical proportion of V as a fraction of total body weight [5]. The resulting value, nPNA, can be compared to dietary records obtained over the same interdialytic interval to evaluate adequacy of protein intake.

The body turns over substantially more protein on a daily basis than is reflected in nPNA, on the order of 300 g/day, most of which is resynthesized into new body proteins. Subtle increases in degradation rates or decreases in synthesis rates not offset by increased intake can result in gradual loss of lean body mass over time. Uremia per se does not appear to significantly alter nPNA. In addition, there is some loss of blood and amino acids during dialysis, which increase protein requirements. The ability to increase protein synthesis to offset increased losses is limited [57], which can result in significant catabolism in the presence of hypermetabolic or inflammatory states [56].

Care must be taken not to interpret nPNA data as a gold standard surrogate for protein intake, even though it is objectively derived. Protein intakes determined in this manner only accurately reflect dietary protein intake under steady state conditions, which typically is not the case in CKD patients undergoing renal replacement therapy (RRT). Diet records and nPNA provide independent methods for estimating dietary protein intake. As noted in Table 5.3, both have factors that need to be considered in their interpretation, and ideally both methods should be employed together to derive conclusions about the adequacy of intake.

Metabolic Acidosis

Predialysis serum bicarbonate levels should be considered when performing a nutritional assessment. Serum bicarbonate is not a nutritional marker per se, but metabolic acidosis is frequently correlated with low serum albumin [19, 54, 58], prealbumin, and nPNA [58]. Acidosis reduces albumin synthesis and increases amino acid oxidation by stimulating branched-chain amino acid oxidation, increasing the ATP-dependent ubiquitin-proteosome pathway, and reducing insulin-like growth factor and growth hormone receptor expression [58].

Table 5.3 Interpretation of nPNA

Observation	Interpretation	Consider
nPNA exceeds DPI or is unexpectedly high	No or only tentative conclusions about protein intake possible	Catabolic state • Inadequate energy intake • Presence of inflammation or inflammatory stressors (fever, infection, etc.) • Weight loss • Metabolic acidosis • Bioincompatible dialysis membrane Inaccurate diet record Low lean body mass
nPNA less than DPI or is unexpectedly low	No or only tentative conclusions about protein intake possible	Anabolic state • Corticosteroid use • Recovery from infection, illness • Pregnancy or growth Inaccurate diet record Edema Excess body weight
nPNA = DPI	nPNA reflects protein intake	Conclude patient is in nitrogen balance and nPNA reflects intake if none of the above apply

nPNA normalized protein equivalent of nitrogen appearance, *DPI* (*g/kg/day*) normalized dietary protein intake

The presence of acidosis must be evaluated carefully because sample collection technique and delays in analyzing the sample can cause spuriously low results. Patients with good appetites, and thus higher protein intakes, also tend to be acidotic because protein brings dietary acid along with it. Interventional studies correcting serum bicarbonate without changes in protein intake typically have not resulted in improved serum albumin levels, suggesting the benefit of adequate protein intake in maintaining serum albumin exceeds the potentially deleterious effect of the associated higher acid loads on reducing albumin synthesis.

Summary of Biochemical Assessment

Serum protein deficits arise from many etiologies in people with CKD [4, 6, 18, 24, 55, 59]. Simple malnutrition is caused by insufficient nutrient intake relative to requirements and responds to correction of deficient intake. In contrast, low serum protein levels can also be caused by inflammation and secondary effects of other comorbidities that result in hypermetabolism and inefficient utilization of nutrients. With this form of malnutrition, simple nutritional repletion without measures to correct the underlying comorbidities and inflammation is relatively ineffective [6, 22, 46]. Because there are interactions between inflammation, anorexia, and poor nutrient intake, a multifaceted intervention strategy that optimizes dialysis delivery, energy and protein intake, corrects concomitant conditions (e.g., acidosis, anemia, uremia, medication side effects, economic concerns, dental health), and addresses inflammation and elevated proinflammatory cytokines is needed.

Biochemical assessment is an instrumental part in differentially diagnosing the etiology of protein deficits in people with CKD. A reasonable approach evaluating a patient with low serum protein levels who is suspected of being malnourished would proceed as follows. Patients with subnormal serum albumin or prealbumin should be assessed for extremely low protein intake, deficits in muscle and fat mass or both via suitable dietary and anthropometric techniques. A thorough clinical evaluation should be conducted to ascertain to provide a comprehensive patient profile. If both wasting and low

nutrient intake are present, then hypoproteinemia may be nutritional in etiology and protein–energy nutritional supplementation is initiated. If the serum albumin and body composition responds to supplementation, then the deficit is presumed to be nutritional. If the deficit fails to respond to nutritional intervention or the deficit exists in the absence of a sustained low protein intake and loss of muscle and fat mass, the deficit is likely non-nutritional in etiology and non-dietary etiologies for hypoalbuminemia explored [4, 6]. However, the presence of inflammation should not be considered as a contraindication to nutritional intervention [46].

References

1. Kopple JD, Greene T, Chumlea WC, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57:1688–703.
2. Kopple JD, Berg R, Houser H, Steinman TI, Teschan P. Nutritional status of patients with different levels of chronic renal insufficiency. Modification of Diet in Renal Disease (MDRD) study group. Kidney Int Suppl. 1989;27: S184–94.
3. Rocco MV, Dwyer JT, Larive B, et al. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: results of the HEMO study. Kidney Int. 2004;65:2321–34.
4. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
5. KDOQI, National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35:S1–140.
6. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. J Am Soc Nephrol. 2010;21:223–30.
7. Al SK, Elsayed S, Molhem A, Aldrees A, Alzara H. Nutritional assessment of patients on hemodialysis in a large dialysis center. Saudi J Kidney Dis Transpl. 2011;22:675–81.
8. Aparicio M, Cano N, Chauveau P, et al. Nutritional status of haemodialysis patients: a French national cooperative study. French Study Group for Nutrition in Dialysis. Nephrol Dial Transplant. 1999;14:1679–86.
9. Avram MM, Sreedhara R, Fein P, Oo KK, Chattopadhyay J, Mittman N. Survival on hemodialysis and peritoneal dialysis over 12 years with emphasis on nutritional parameters. Am J Kidney Dis. 2001;37:S77–80.
10. Combe C, Chauveau P, Laville M, et al. Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. Am J Kidney Dis. 2001;37:S81–8.
11. Cooper BA, Penne EL, Bartlett LH, Pollock CA. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. Am J Kidney Dis. 2004;43:61–6.
12. Danielski M, Ikizler TA, McMonagle E, et al. Linkage of hypoalbuminemia, inflammation, and oxidative stress in patients receiving maintenance hemodialysis therapy. Am J Kidney Dis. 2003;42:286–94.
13. de Mutsert R, Grootendorst DC, Indemans F, Boeschoten EW, Krediet RT, Dekker FW. Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition. J Ren Nutr. 2009;19:127–35.
14. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15:458–82.
15. Menon V, Greene T, Wang X, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int. 2005;68:766–72.
16. Phelan PJ, O'Kelly P, Walshe JJ, Conlon PJ. The importance of serum albumin and phosphorous as predictors of mortality in ESRD patients. Ren Fail. 2008;30:423–9.
17. Dwyer JT, Larive B, Leung J, et al. Are nutritional status indicators associated with mortality in the Hemodialysis (HEMO) study? Kidney Int. 2005;68:1766–76.
18. Ahuja TS, Mitch WE. The evidence against malnutrition as a prominent problem for chronic dialysis patients. Semin Dial. 2004;17:427–31.
19. Leavey SF, Strawderman RL, Young EW, et al. Cross-sectional and longitudinal predictors of serum albumin in hemodialysis patients. Kidney Int. 2000;58:2119–28.
20. Kaysen GA, Don BR. Factors that affect albumin concentration in dialysis patients and their relationship to vascular disease. Kidney Int. 2003;63 Suppl 84:S94–7.
21. Kaysen GA, Chertow GM, Adhikarla R, Young B, Ronco C, Levin NW. Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. Kidney Int. 2001;60:333–40.
22. Kaysen GA. Serum albumin concentration in dialysis patients: why does it remain resistant to therapy? Kidney Int. 2003;64 Suppl 87:S92–8.

23. Pupim LB, Caglar K, Hakim RM, Shyr Y, Ikizler TA. Uremic malnutrition is a predictor of death independent of inflammatory status. Kidney Int. 2004;66:2054–60.
24. Chertow GM, Ackert K, Lew NL, Lazarus JM, Lowrie EG. Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. Kidney Int. 2000;58:2512–7.
25. Ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim RM. Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: a prospective study. Kidney Int. 1999;55:1945–51.
26. Fellah H, Omar S, Feki M, et al. Is serum transthyretin a reliable marker of nutritional status in patients with end-stage renal disease? Clin Biochem. 2008;41:493–7.
27. Chrysostomou S, Stathakis C, Petrikkos G, Daikos G, Gompou A, Perrea D. Assessment of prealbumin in hemodialysis and renal-transplant patients. J Ren Nutr. 2010;20:44–51.
28. Kopple JD, Mehrotra R, Suppasyndh O, Kalantar-Zadeh K. Observations with regard to the National Kidney Foundation KDOQI clinical practice guidelines concerning serum transthyretin in chronic renal failure. Clin Chem Lab Med. 2002;40:1308–12.
29. Neyra NR, Hakim RM, Shyr Y, Ikizler TA. Serum transferrin and serum prealbumin are early predictors of serum albumin in chronic hemodialysis patients. J Ren Nutr. 2000;10:184–90.
30. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int. 2002;61:1887–93.
31. Kaysen GA. The microinflammatory state in uremia: causes and potential consequences. J Am Soc Nephrol. 2001;12:1549–57.
32. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr. 2005;82:801–5.
33. Qureshi AR, Alvestrand A, Divino-Filho JC, et al. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol. 2002;13 Suppl 1:S28–36.
34. Spittle MA, Hoenich NA, Handelman GJ, Adhikarla R, Homel P, Levin NW. Oxidative stress and inflammation in hemodialysis patients. Am J Kidney Dis. 2001;38:1408–13.
35. Stenvinkel P, Heimburger O, Paultre F, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55:1899–911.
36. Kaysen GA. Inflammation nutritional state and outcome in end stage renal disease. Miner Electrolyte Metab. 1999;25:242–50.
37. Ho LC, Wang HH, Chiang CK, Hung KY, Wu KD. Malnutrition-inflammation score independently determined cardiovascular and infection risk in peritoneal dialysis patients. Blood Purif. 2010;30:16–24.
38. Vannini FD, Antunes AA, Caramori JC, Martin LC, Barretti P. Associations between nutritional markers and inflammation in hemodialysis patients. Int Urol Nephrol. 2009;41:1003–9.
39. Stenvinkel P. Inflammation in end-stage renal disease—a fire that burns within. Contrib Nephrol. 2005;149: 185–99.
40. Lacson Jr E, Levin NW. C-reactive protein and end-stage renal disease. Semin Dial. 2004;17:438–48.
41. Kaysen GA. Inflammation: cause of vascular disease and malnutrition in dialysis patients. Semin Nephrol. 2004;24:431–6.
42. Pupim LB, Himmelfarb J, McMonagle E, Shyr Y, Ikizler TA. Influence of initiation of maintenance hemodialysis on biomarkers of inflammation and oxidative stress. Kidney Int. 2004;65:2371–9.
43. Kaysen GA, Greene T, Daugirdas JT, et al. Longitudinal and cross-sectional effects of C-reactive protein, equilibrated normalized protein catabolic rate, and serum bicarbonate on creatinine and albumin levels in dialysis patients. Am J Kidney Dis. 2003;42:1200–11.
44. Kaysen GA, Eiserich JP. Characteristics and effects of inflammation in end-stage renal disease. Semin Dial. 2003;16:438–46.
45. Caglar K, Peng Y, Pupim LB, et al. Inflammatory signals associated with hemodialysis. Kidney Int. 2002;62: 1408–16.
46. Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. Kidney Int. 2011;80:348–57.
47. Mafra D, Deleaval P, Teta D, et al. Influence of inflammation on total energy expenditure in hemodialysis patients. J Ren Nutr. 2011;21:387–93.
48. Malgorzewicz S, Debska-Slizien A, Rutkowski B, Lysiak-Szydlowska W. Serum concentration of amino acids versus nutritional status in hemodialysis patients. J Ren Nutr. 2008;18:239–47.
49. Wang AY. Prognostic value of C-reactive protein for heart disease in dialysis patients. Curr Opin Investig Drugs. 2005;6:879–86.
50. Johnson DW. Time-integrated CRP, level strongly predicts PD patient outcomes—nice to know, but what should we do about it? Perit Dial Int. 2005;25:234–7.
51. Tsirpanlis G, Bagos P, Ioannou D, et al. Serum albumin: a late-reacting negative acute-phase protein in clinically evident inflammation in dialysis patients. Nephrol Dial Transplant. 2005;20:658–9.
52. Stenvinkel P, Lindholm B. C-reactive protein in end-stage renal disease: are there reasons to measure it? Blood Purif. 2005;23:72–8.

53. Tsirpanlis G, Chatzipanagiotou S, Nicolaou C. Microinflammation versus inflammation in chronic renal failure patients. Kidney Int. 2004;66:2093–4.
54. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004;65:1031–40.
55. Stenvinkel P, Lindholm B, Heimburger O. Novel approaches in an integrated therapy of inflammatory-associated wasting in end-stage renal disease. Semin Dial. 2004;17:505–15.
56. Kalantar-Zadeh K, Stenvinkel P, Pillon L, Kopple JD. Inflammation and nutrition in renal insufficiency. Adv Ren Replace Ther. 2003;10:155–69.
57. Rao M, Sharma M, Juneja R, Jacob S, Jacob CK. Calculated nitrogen balance in hemodialysis patients: influence of protein intake. Kidney Int. 2000;58:336–45.
58. Chauveau P, Fouque D, Combe C, et al. Acidosis and nutritional status in hemodialyzed patients. French Study Group for Nutrition in Dialysis. Semin Dial. 2000;13:241–6.
59. Kaysen GA, Dubin JA, Muller HG, Rosales L, Levin NW, Mitch WE. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. Kidney Int. 2004;65:1408–15.

Chapter 6
Nutrition Physical Assessment in Chronic Kidney Disease (CKD)

Mary Pat Kelly

Key Points

- Outline regulatory mandates for nutrition-focused physical assessment.
- Identify physiological mechanisms responsible for nutrient-based tissue change and/or functional deficit.
- Integrate classic physical assessment techniques into nutrient assessment.
- Use nutrition-focused physical findings as a tissue-based source of knowledge, which can be used along with the patient's nutrient intake/disposition, biochemical profile, medication intake, medical comorbidities, and therapeutic interventions to develop sound nutritional therapy.

Keywords Nutrient assessment • Niacin deficiency • V-B_6 deficiency • V-B_6 toxicity • Zinc deficiency • Zinc toxicity • Nutrient-based lesions • Nutrition physical examination

Rationale for Performing a Nutrition Physical Examination

Since the first Medicare Conditions for Coverage of End-Stage Renal Disease (ESRD) were published in 1976 [1], registered dietitians (RDs) have been directed to perform nutrition-focused physical assessment. Given the potential for both deficiency and toxicity inherent in renal failure, regulatory language suggested a two-step process that first assessed vitamin/mineral adequacy and then translated nutrient requirements into food choices, appropriate supplementation.

The 1995 Comprehensive Accreditation Manual [2] for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) advanced the use of physical findings, as it defined nutritional assessment as a "comprehensive approach to defining nutrition status which employs medical, nutrition, and medication histories; physical examination; anthropometric measurements; and laboratory data." Physical examination for manifestations of nutrient deficiency or excess in all high risk patients was mandated. The Academy of Nutrition and Dietetics (AND) [formerly the American Dietetic Association (ADA)] responded quickly by including physical assessment as a clinical competency for entry-level dietetics practitioners [3].

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The NKF KDOQI Nutrition Guidelines [4] supported the Subjective Global Assessment (SGA) as a useful measure of protein–energy balance, concentrating on its concurrent evaluation of somatic stores and nutrient intake. The Centers for Medicare and Medicaid Conditions for Coverage for End-Stage Renal Disease Facilities [5] endorsed the goal to "achieve and sustain an effective nutritional status," defined as acceptable levels of "nutrients in the blood" with "clinical signs of nutrient deficiency" recognized as outcome measures.

In the 2005 Standards of Practice and Updated Standards of Professional Performance [6], the AND included physical assessment in its precursor template, used as a prototype for the 2009 ADA/National Kidney Foundation (NKF) standards of professional performance in nephrology care. This document integrates nutrition physical examination into the assessment, diagnostic, and monitoring standards of practice [7]. Thus, renal nutrition specialists have federal, KDOQI, Joint Commission, and AND mandates to perform nutrition-focused physical assessment.

Clinicians knowledgeable in nutrition-focused physical assessment value this "hands on" relationship with patients and the clinical empathy that evolves as a patient shares his/her thinning hair, itchy skin, sore tongue, or malformed fingernails. It is this relationship that transcends the usual focus on patient data alone [8] as the RD and patient work collaboratively to modify nutrient intake and foster healing. This process ultimately places the role of nutrition exactly where it should be—at the very basis of tissue integrity.

Nutrition-Focused Physical Examination

Several approaches to nutrition-focused physical examination have been reported. The SGA initially put forward by Detsky et al. [9] and modified for the CKD (chronic kidney disease) population by McCann [10] concentrates more on altered fluid balance and somatic fat and muscle wasting—macronutrient assessment. Changes in weight, dietary intake, gastrointestinal symptoms, functional capacity, and disease processes are also considered. SGA was found to have fair interrator reliability via Internet training and substantial intrarator reliability in renal dietitians, with validity between serum albumin (ALB) and body mass index (BMI) across five of seven SGA numerical ratings [11]. The ability to score SGA provides a quantitative tool to monitor nutritional response to therapy. Used as a nutritional marker for protein–energy nutritional status, SGA was significantly correlated with both physical and mental component summaries of the Kidney Disease-Specific Health Quality of Life Short Form in hemodialysis (HD) patients [12].

Conscientious inspection of discrete tissues in a nutrition-focused physical examination reveals micronutrient-based lesions seen on the visible surfaces of the body—its surface anatomy [13]. Because nutrients play defined roles in tissue synthesis, deficiency/toxicity is known to modify normal structure in vulnerable individuals. Altered tissue integrity observed in the oral mucosa, skin, hair, eyes, and nails provides clues to nutrient(s) involved, time frame of nutritional injury, and functional deficits that may result. Many nutrition physical examination overviews have been published [14–18], but Kight's Nutrition Physical Exam (NPE) has been used in CKD patients for comprehensive physical examination of both micro- and macronutrient status [19], medical grand rounds [20], and case study work [21]. The NPE begins with an examination of oral structures, skin, and related structures (eyes, hair, and nails) for change generally associated with micronutrient imbalance. It concludes with a cardiovascular, central nervous, endocrine, gastrointestinal, immunologic, musculoskeletal, and renal systems assessment that reflects functional adequacy of both micro- and macronutrient status. The remaining chapter will focus on an in-depth NPE.

Approach to Tissue-Specific Physical Assessment

An understanding of normal tissue integrity is necessary, prior to contrast with changes historically documented in nutrient imbalance. The physiological mechanism at the root of altered tissue formation helps RDs anticipate what "nutrient-based lesion clusters" can manifest in nutrient deficiency/toxicity. Because RDs are more familiar with nutrient knowledge bases than physical assessment, three comprehensive nutrient overviews will summarize nutrient disposition, dietary sources, drug/nutrient interactions, laboratory evaluation, and medical comorbidity data, along with nutrient-based lesions/functional deficits. Niacin, V-B_6, and zinc have been selected for closer review, given their vulnerability for altered nutrient disposition in CKD.

Physical Examination

Classic physical assessment involves inspection, palpation, percussion, and auscultation [22]. Vitamin/mineral imbalance in dialysis patients affects tissue integrity inside the mouth skin, scalp, eyes, hair (shafts, follicles), and nails. Inspection and light palpation techniques are used most frequently. While presentation of vitamin and mineral lesions can be discrete (as in aphthous ulcers), they are generally bilateral in appearance.

Observing Oral Tissues

The lips are normally smooth, a deeper color than the face, with a clear vermillion border. Vertical cracking (cheilosis) or erosion at the corners (angular stomatitis) may be observed in active lesions, while scarring can remain from past deficit [23]. Lesion grading has been published [24]. Impaired collagen maturation/elastin cross-links caused by riboflavin and pyridoxine deficit are thought to be the lesion's molecular basis [25].

Breath odor may suggest saburral tongue [26] if dank with decayed food, oral Candida if yeasty in diabetes/iron deficiency [27], or ammoniacal with elevated blood urea nitrogen (BUN) [28]. Clarification of routine dental hygiene and timing of the patient's last dental visit will help distinguish vitamin C deficit from poor oral care in determining cause of bleeding gums. Cracked, fractured teeth at the gumline can become a nidus for inflammation or subsequent fever of unknown origin. Ill-fitting dentures not only suggest recent weight loss but also compromised chewing and contribute to maceration at the corners of the mouth [29].

The extended tongue reveals color and texture. Usual pigment is deep pink, reflecting an adequate concentration of hemoglobin in the more visible lingual capillary bed. Reddening of the oral mucosa can progress to scarlet or magenta in B-vitamin or iron deficiency [30, 31]. The anterior tongue tip (exposed when "sticking out" the tongue) is covered with finger-like projections, including both thin filiform papillae and more knobbed fungiform papillae that hold taste buds. Fungiform papilla density noted at the tongue tip midline correlates well with the total number of fungiform papilla on the healthy tongue [32]. Because there are fewer taste buds found in the fungiform papillae of chronic renal failure patients [33], erosion of papilla at the tip and lateral aspects of the tongue in early nutrient deficiency may compromise ability to taste. Balding and complete atrophy are evidence of long-term disease [34].

A common discrete oral lesion is the aphthous ulcer (canker sore) characterized by a small round or oval lesion with a circumscribed margin, erythematous halo, and a yellow-grey floor. Etiology of this lesion is unknown but has been variously correlated to iron [35], B_{12} [36], thiamine [37], and gluten sensitivity [38, 39].

Scalp, Hair, and Skin Findings

Easily observed at the natural separation in the hair, healthy scalp is intact with natural oil. The patient is asked to show site-specific areas of soreness and irritation. Frequency of hair washing affects texture of hair and may correlate with itchiness. Hair should be evenly distributed without patchiness on the scalp. Thinning of hair may be associated with iron [40] or zinc deficits [41]. Absence of hair on the lower-extremity anterior tibial surface may suggest vascular compromise [22]. The hair shaft is straight, whether round or flat, emerging easily from a smooth hair follicle. A magnifier helps in identifying a coiled shaft that may be a reflection of vitamin C deficit [42] or a hyperkeratosed follicle found in either vitamin A or vitamin C deficiency [43].

Skin along the hairline, behind the ears, and between the eyebrows is intact with adequate lubrication in nutrient repletion. Seborrheic-like dermatitis from zinc deficiency occurs in these areas rich in sebaceous glands and may be related to inadequate zinc to stabilize cell membranes, inhibit lipid peroxidation, and preserve barrier function [44]. Skin around the neck and shoulders, along the arms, and lower extremities is assessed for skin fold and muscle integrity.

Observing the scalp at the natural part in the hair and skin at the midpoint of the upper arm and above the lateral malleolus (ankle) will provide easy reference points for future comparison. Periorbital and sacral sites may reveal edema; pitting at the ankle or sock line can be graded as it extends upwards toward the knee [22].

Examination of the Eyes

The tissue adjacent to the eyes should be intact without inflammation or swelling. Soft elevated beige-colored plaque noted on or near the eyelids may be xanthelasma that can accompany lipid disorders [28]. The lateral palpebral commissure (corner of the eye) is generally darker in color, without redness or irritation. Eye globes are adequately bathed, without excessive tearing. The sclera is white but may be inflamed with calcium/phosphorus imbalance [45]. Glass-like crystals found at the limbus in the 3:00/9:00 by glancing light off the sclera suggest calcific band keratopathy associated with long-standing calcium/phosphorus products >70 [46]. The lower palpebral conjunctiva is examined by placing the index finger beneath the lower eyelid and gently easing downward, as the patient looks up. Normal conjunctiva shows a rich pink capillary bed beneath a pale anterior rim; pallor is defined as little or no red color beneath the anterior rim [47].

Examination of the Nails

Normal nail plates are clear in color, smooth in texture, and convex in both directions. Longitudinal dyschromic bands or vertical ridging in the nail plate are a normal variants. Rubbing a gloved thumb over the nail plate from side to side and nail bed to tip will reveal abnormalities in shape and texture.

Spooning of the nail plates (koilonychia) suggests iron deficiency or softening of the nail plate from environmental exposure to water [48]. Arcuate, horizontal ridging (Beau's lines) may present following sepsis and can be felt across all nail plates [49]. Because this injury occurs during nail plate development within the matrix, the site-specific damage is irreversible, serving as a temporal marker of illness as the nail plate grows out [50].

Paired, nonpalpable white lines observed in the nail bed that span the nail, parallel to the lunula, are called Muehrcke's lines. Attributed to "chronic nutritional deficiency of albumin" [51] (<2.2 g/dL), they are commonly found in nephrotic syndrome. Others have linked the lesion to trauma [52] or cytotoxic exposure [53] that causes a microscopic separation of the tightly adherent nail plate from its nail bed. Expansion of the white lunula toward the middle of the nail plate, with the appearance of a red, pink, or brown band at the distal nail bed, is known as "Half-and-Half" nail, initially described by Lindsay [54], as pathognomonic for azotemia. Observers found the nail bed discoloration disappeared completely within 2–3 weeks of kidney transplantation [55]. Needle-like longitudinal splinter hemorrhages in the nail bed, seen through the nail plate, may suggest subacute bacterial endocarditis, vitamin C deficiency in scurvy, or trauma [56]. Healthy tissue around the nail is smooth without signs of inflammation or infection; paronychia can be found in zinc deficiency [57].

Physical Findings and Functional Deficits in Niacin, B_6, and Zinc Imbalance

Niacin

Pellagra was prevalent in the United States for many years, with the only understanding that it occurred with poverty and corn intake. Joseph Goldberger of the United States Public Health Service reproduced pellagrous symptoms in dogs, leading to the discovery that yeast could prevent and cure pellagra [58]. Bean [34] graded the symmetrical, bilateral dermatitis of sun-exposed skin and redness, inflammation, and papillary atrophy of the tongue found in niacin deficiency. In 1952, Goldsmith et al. [59] monitored niacin depletion in women eating a corn- or wheat-based diet, supplemented with tryptophan to ensure minimal nitrogen balance [60] and adequate B vitamins, without niacin. Lesions developed within 40–135 days in isolated niacin deficiency, with half the patients experiencing some symptom by day 50. Oral lesions occurred with and without characteristic blistering and necrotic skin associated with pellagra [59]. Goldsmith determined that this condition was described as "pellagra sine pellagra" [61] in historical literature, corroborating her finding of niacin deficiency without characteristic skin lesions.

To this day, pellagrins presenting without skin lesions continue to elude diagnosis. A necroscopy study diagnosed 20 cases of pellagra with neuropathology from 74 chronic alcoholics, who presented only with mental, neurological, and gastrointestinal symptoms at their death [62]. Ten of 36 persons in a carcinoid cancer cohort had biochemical evidence of niacin deficiency with only one case of dermatitis [63], leading authors to conclude that "full symptoms of pellagra develop at a very late stage of the carcinoid disease"—when prognosis is poor. Complete nutritional support was recommended, citing literature confirming that the full triad of pellagra symptoms presented in only 20 % of noncancerous pellagrins [64]. Although pellagra is frequently related to excessive alcohol intake [65] or malabsorption [66, 67], cases of selective food restriction in anorexia [68] or allergy management [69] are also reported. Preformed niacin is derived primarily from fortified breads and cereals [70]. Non-fortified grains used as primary energy sources, combined with low-protein and low-tryptophan diets in the developing world, can also expedite niacin deficiency [71]. Food intake data

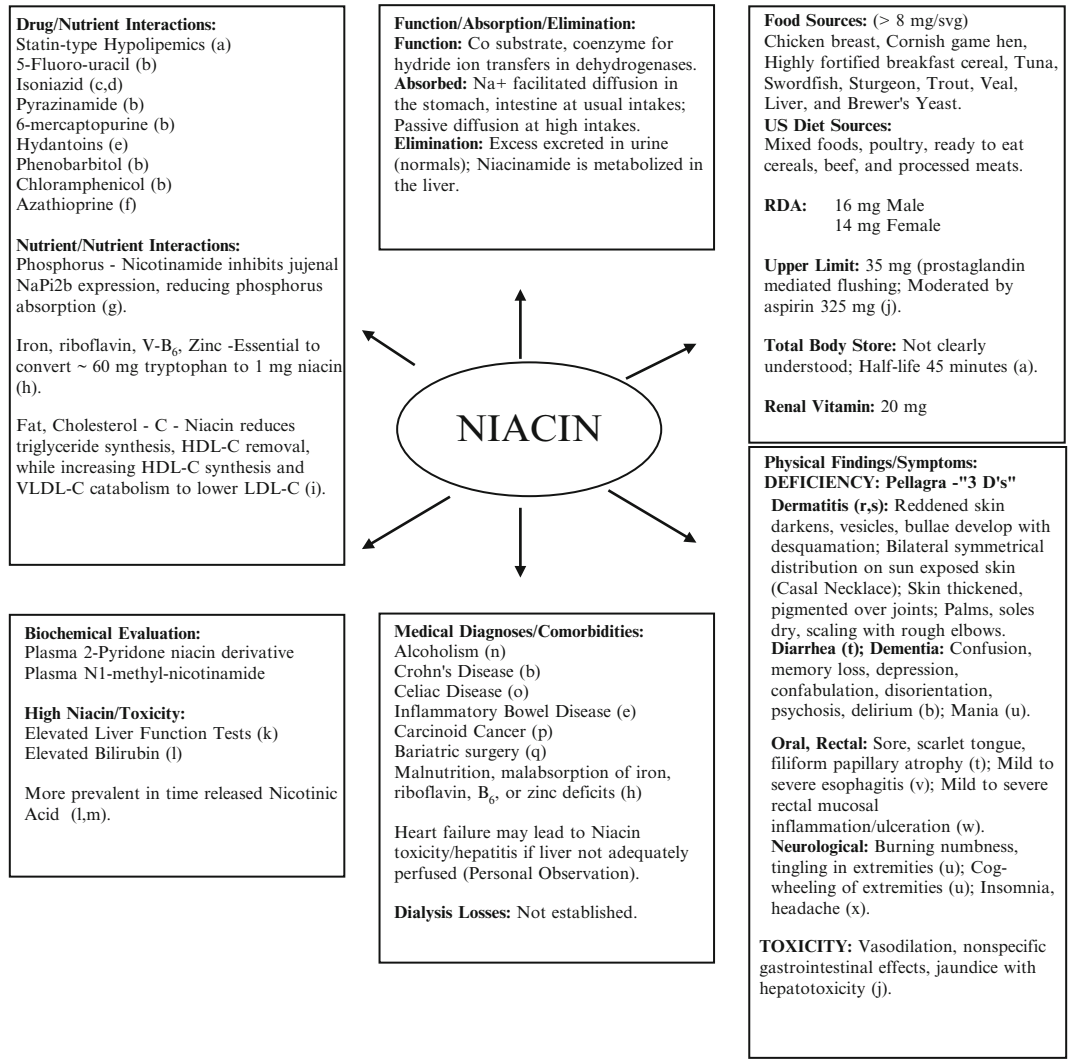

Fig. 6.1 Comprehensive niacin assessment in renal failure. *References for niacin Fig. 6.1*: a. Leikin JB, Paloucek FP, eds. Poisoning and Toxicology Handbook, 2nd edn. Cleveland: Lexi-Comp Inc, 1996–1997:555–556. b. Pitche PT. Pellagra. Sante 2005;15:205–208. c. Dorvay, A, Basareb T, McGregor JM, Russell-Jones R. Isoniazid induced pellagra despite B_6 supplementation. Clin Exp Dermatol 1999;24:167–170. d. Ishii N, Nishihara. Pellagra encephalopathy among tuberculous patients: Its relation to isoniazid therapy. J Neurol Neurosurg Psychiatry 1985:48:628–634. e. Lyon VB, Fairley JA. Anti-convulsant-induced pellagra. J Am Acad Dermatol 2002;46:597–599. f. Jarrett P, Duffill M, Oakley A, Smith A. Pellagra, azathioprine, and inflammatory bowel disease. Clin Exp Dermatol 1997;22:44–45. g. Maccubbin D, Tipping D, Kuznetsova O, Hanlon WA, Bostom AG. Hypophosphatemic effect of niacin in patients without renal failure: A randomized trial. Clin J Am Soc Nephrol 2010;5:582–589. h. Combs GF. The Vitamins, 3rd edn. San Francisco: Elsevier Academic Press. 2008:299–300. i. Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin. Vasc Health Risk Mgt 2009;5:31–43. j. Papadakis MA, McPhee SJ, eds. Current medical diagnosis & treatment, 52nd edn. San Francisco: Lange Medical Books/McGraw-Hill 2013:1265. k. Etchason JA, Miller TD, Squires RW, Allison TG, Gau GT, Marttila JK, Kottke BA. Niacin-induced hepatitis: A potential side effect with low dose, time-release niacin. Mayo Clin Proc 1991;66:23–28. l. Henkin Y, Johnson KC, Segrest JP. Rechallenge with crystalline niacin after drug-induced hepatitis from sustained released niacin. J Am Med Assoc 1990;264:241–243. m. Stern RH, Freeman D, Spence JD. Differences in metabolism of time-release and unmodified nicotinic acid: Explanation of the differences in hypolipidemic action? Metab 1992;41:879–881. n. Dastur DK, Santhadevi N, Quadros EV, Avari FCR. The B-vitamins in malnutrition with alcoholism: A model of intervitamin relationships. Br J Nutr 1976;36:143–159. o. Schattner A. A 70 yo man with isolated weight

from rice-eating, peritoneal dialysis patients [72] tallied thiamin, niacin, and riboflavin intake between 50 and 83 % of the Recommended Dietary Allowances.

Functional niacin deficits include diarrhea (with and without bleeding), dysphagia, nausea, vomiting, and anorexia [73]. Scarlet, exfoliated oral surface, can extend from the esophagus [74] to the rectum [75]. Diffuse inflammation is also found in vaginal mucosal tissues and amenorrhea is common [59, 76–78]. Long-term neuropsychological manifestations including photophobia, asthenia, depression, hallucinations, confusion, memory loss, and psychosis [79] are believed to be mediated by impaired conversion of tryptophan to the neurotransmitter serotonin [78]. Early unresolved cases resulted in dementia and death [77, 80].

A comprehensive niacin assessment is shown in Fig. 6.1. Pellagrous lesions observed in dialysis patients at San Francisco General Hospital (Fig. 6.2) include sore, scarlet, atrophied tongue, angular stomatitis, bullous skin vesicles, necrotic blebs, and exfoliated elbows, palms, and knuckles. "Pellagra sine pellagra" was also observed with severe glossitis but mild tissue-like skin peeling.

Vitamin B_6

Vitamin B_6 Deficiency

Although B_6 deficiency was identified following seizure activity and anemia in infants given purified diets [81], early experimental depletion studies in adults used desoxypyridoxine. Vilter et al. [82] described seborrheic dermatitis of the nasolabial folds, eyebrows, angles of the mouth, retroauricular spaces, and scalp as primary lesions, evolving after 19–21 days of desoxypyridoxine treatment. Dermatitis was followed by glossitis, glossodynia, and red hypertrophied filiform papillae on the lateral aspects of the tongue. Sensory neuritis began as tingling and numbness in the hands and feet and ascended quickly as extremities became hyperesthetic to pinprick.

Microcytic anemia accompanies B_6 deficiency since plasma pyridoxal phosphate (PLP) is necessary to synthesize aminolevulinate synthase, an essential enzyme in the first step of heme synthesis [83]. Without heme to sequester iron, differential blood smears reveal sideroblasts and immature erythroid cells with mitochondrial granules of non-heme iron [84].

Fig. 6.1 (continued) loss and pellagra-like syndrome due to celiac disease. Yale J Biol Med 1999;72:15–18. p. Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RRP. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroerol 2005;100:2307–2314. q. Ashouria N, Mousdicas N. Pellagra-like dermatitis. N Engl J Med 2006:354:15. r. Goldsmith GA. Experimental niacin deficiency. J Am Diet Assoc 1956;32:312–316. s. Darouti M, Abuel Ela M. Necrolytic acral erythema: A cutaneous marker of viral hepatitis C. Int J Dermatol 1996;35:252–256. t. Goldsmith GA, Sarett, HP, Register UD, Gibbens J. Studies of niacin requirements in man. I. Experimental pellagra in subjects on corn diets low in niacin and tryptophan. J Clin Invest 1952;31:533–542. u. Spies TD, Bean WB, Ashe WF. Recent advances in the treatment of pellagra and associated deficiencies. Ann Intern Med 1939;12:1830–1844. v. Segal I, Hale M, Demetriou A, Mohamed AE. Pathological effects of pellagra on the esophagus. Nutr Cancer 1990;14:233–238. w. Segal I, Ou TL, Demetriou A, Paterson A, Hale M, Lerios M. Rectal manifestations of pellagra. Int J Colorectal Dis. 1986;1:238–243. x. Seal AJ, Creeke PI, Debari F, Cheung E, et al. Low and deficient niacin status and pellagra are endemic in post-war Angola. Am J Clin Nutr 2007;85:218–224. *If not annotated otherwise, data cited from: Standing committee on the scientific evaluation of dietary reference intakes Niacin. In: Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington DC: National Academy Press, 1998:123–149

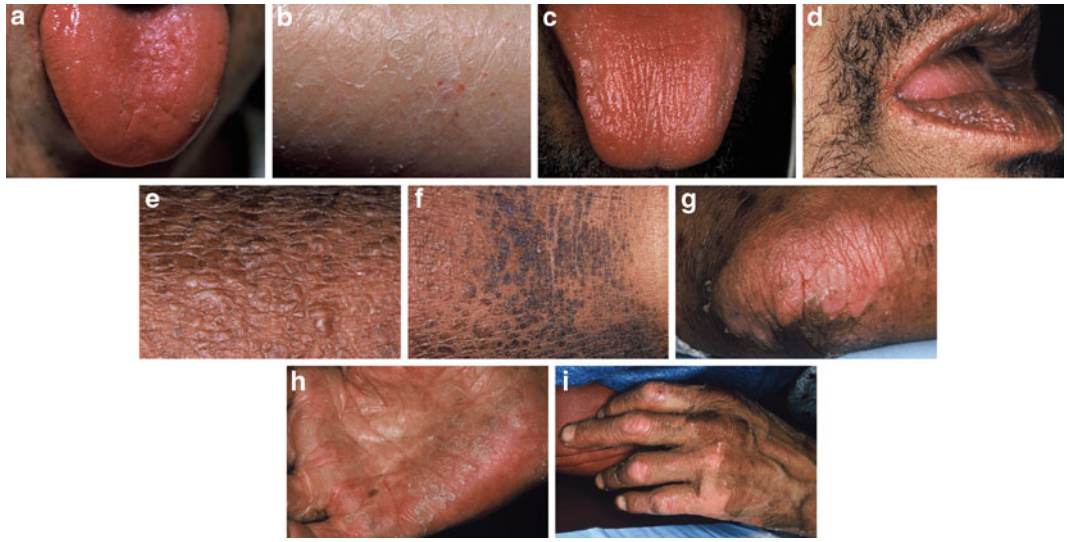

Fig. 6.2 Nutrient-based lesions associated with laboratory-validated niacin deficiency. (**a**) Scarlet, atrophied tongue. "Pellagra sine pellagra." Niacin 3.6 ng/mL (R 3.5–7.0). © Steve Castillo. (**b**) Early skin peeling. "Pellagra sine pellagra." Niacin 3.6 ng/mL (R 3.5–7.0). © Steve Castillo. (**c**) Scarlet, bald tongue. Pellagra. Niacin 1.9 ng/mL (R 3.5–7.0). © Steve Castillo. (**d**) Angular stomatitis. Pellagra. Niacin 1.9 ng/mL (R 3.5–7.0). © Steve Castillo. (**e**) Bullous lesions. Pellagra. Niacin 3.0 ng/mL (R 3.5–7.0). © Steve Castillo. (**f**) Necrotic skin blebs. Pellagra. Niacin 3.0 ng/mL (R 3.5–7.0). © Steve Castillo. (**g**) Exfoliated elbow. Pellagra. Niacin 1.9 ng/mL (R 3.5–0.70). © Steve Castillo. (**h**) Exfoliated palm. Pellagra. Niacin 1.9 ng/mL (R 3.5–7.0). © Steve Castillo. (**i**) Exfoliated knuckles. Pellagra. Niacin 1.9 ng/mL (R 3.5–7.0). © Steve Castillo. Photographs may not be reproduced, copied, projected, televised, digitized, or used in any manner without photographer's express written permission

Functional deficits of deficiency include depression, confusion [85], and hypoactive deep tendon reflexes (DTRs) [82]. Neurological sequelae are not well understood, but are thought to result from altered PLP function in the utilization of synaptic transmitter amines, noradrenalin, adrenaline, tyramine, dopamine, and serotonin [86]. Accumulation of abnormal tryptophan metabolites within the brain is credited in the exacerbation of neuropsychiatric symptoms [87], as B_6 is required in tryptophan conversion to nicotinic acid [83]. PLP is also necessary to form the singular inhibitory neurotransmitter, gamma-aminobutyric acid, whose absence may predispose to seizure activity, recalcitrant to anti-seizure medications in severe B_6 deficiency [88, 89].

Drug therapies can contribute to B_6 deficit. Loop diuretics deplete B_6 in early kidney failure as they decrease tubular resorption of water. B_6, vitamin C, and oxalate losses directly correlate with extent of diuresis [90]. The antihypertensive hydralazine forms hydrazone with PLP, compromising B_6 decarboxylase activity [91]. Antitubercular isoniazid (INH) combines with pyridoxine to form isonicotinyl hydrazine, which can result in PLP-mediated isoniazid neurotoxicity in low B_6 intake, i.e., in alcoholic [92], malnourished [93], or CKD populations [94–97]. Recent work suggests B_6 depletion may also occur in hepatitis C infection when pegylated interferon and ribavirin are used [98].

Dialyzer B_6 loses are significant, doubling with high-efficiency, high-flux (HF) cellulose triacetate membranes, compared to cuprophan [99]. Losses through the peritoneum are lower than HF membranes, but dietary intake alone has not been able to sustain PLP concentrations [100]. Increased awareness of B_6 adequacy is crucial when transitioning from peritoneal to HD modalities, given observations of anemia and seizures related to B_6 deficiency in peritoneal dialysis patients new to HD [101].

A comprehensive B_6 assessment is shown in Fig. 6.3. The primary lesion photographed by Castillo in deficient HD persons was filiform papillary hypertrophy (Fig. 6.4). Mild seborrheic-like dermatitis and increased tearing were also identified in those with PLP concentrations between 1.3 and 6.4 ng/mL (lab range 3.6–18.0). It is important to recognize nutrient-responsive lesions/dysfunction can be found within low normal laboratory ranges, as described with B_6-responsive polyneuropathy [102], reinforcing the need to individualize nutrient requirements. Though no indicator is ideal, PLP is believed to reflect tissue stores of the nutrient and was used by the National Academy of Sciences to estimate the RDA for B_6 [83].

Vitamin B_6 Toxicity

High doses of B_6 present in foods rarely cause toxicity, but B_6 accumulates when supplemented, due to the body's non-saturable passive absorption process. Toxicity generally involves dorsal root ganglia function with its increased blood vessel permeability, while the blood–brain barrier insulates the brain [103]. Clinical symptoms of B_6 toxicity include numbness, paresthesia, ataxia, Lhermitte's sign, and pain. Sensory deficit, ataxia, (+) Romberg's sign, and loss of Achilles reflexes are symptoms noted [104]. Neuropathy associated with B_6 toxicity presents in a bilateral, stocking-glove distribution beginning at the distal digits [105]. Limited clearance of B_6 in hemodialysis has been associated with markedly elevated PLP concentrations with compromised dialysis clearance following supplementation as low as 50 mg daily [21]. With its potential for both deficiency and toxicity, it remains good nutrition practice to document PLP concentrations with uncertain renal vitamin intake (deficiency) or when supplemental B_6 is prescribed with antitubercular drugs or for homocysteine reduction [106].

Zinc

Zinc Deficiency

Prasad et al. [107] first described zinc deficiency as "adolescent nutritional dwarfism," documenting the nutrient's role in growth and sexual maturity. While the early syndrome occurred with iron deficiency, identification of an autosomal recessive defect causing acrodermatitis enteropathica [108] produced a clear phenotypic presentation of zinc deficiency alone. Skin lesions with predictable distribution at body orifices and extremities predominate, with functional deficits of diarrhea, compromised T-cell function, and altered central nervous function. Zinc's pivotal role in gene expression, cellular growth, and differentiation is the underlying cause of generalized catalytic, structural, regulatory impairment in deficiency [109].

Subjects without kidney disease enrolled in well-controlled, induced zinc depletion studies showed classic dermatitis around the mouth and nose, inflammation of the mucosal membranes [110], and structural changes in hair bulb formation [111]—signs that appear as plasma zinc falls. Use of plasma/serum zinc has been criticized, but kinetic research suggests that plasma zinc concentration, free from contamination of the erythrocyte, may be a valid indicator of whole body zinc status in the absence of infection or stress, particularly when the levels are low [110]. The cutoff concentration for normal prebreakfast samples is 70 μg/dL [112].

Zinc studies in kidney failure generally reveal reduced plasma/serum concentrations [113] compared to normal controls. Metabolic research in patients receiving maintenance HD on fixed zinc intakes documents increased fecal loss as a major contributor [114]. Aluminum hydroxide gels and

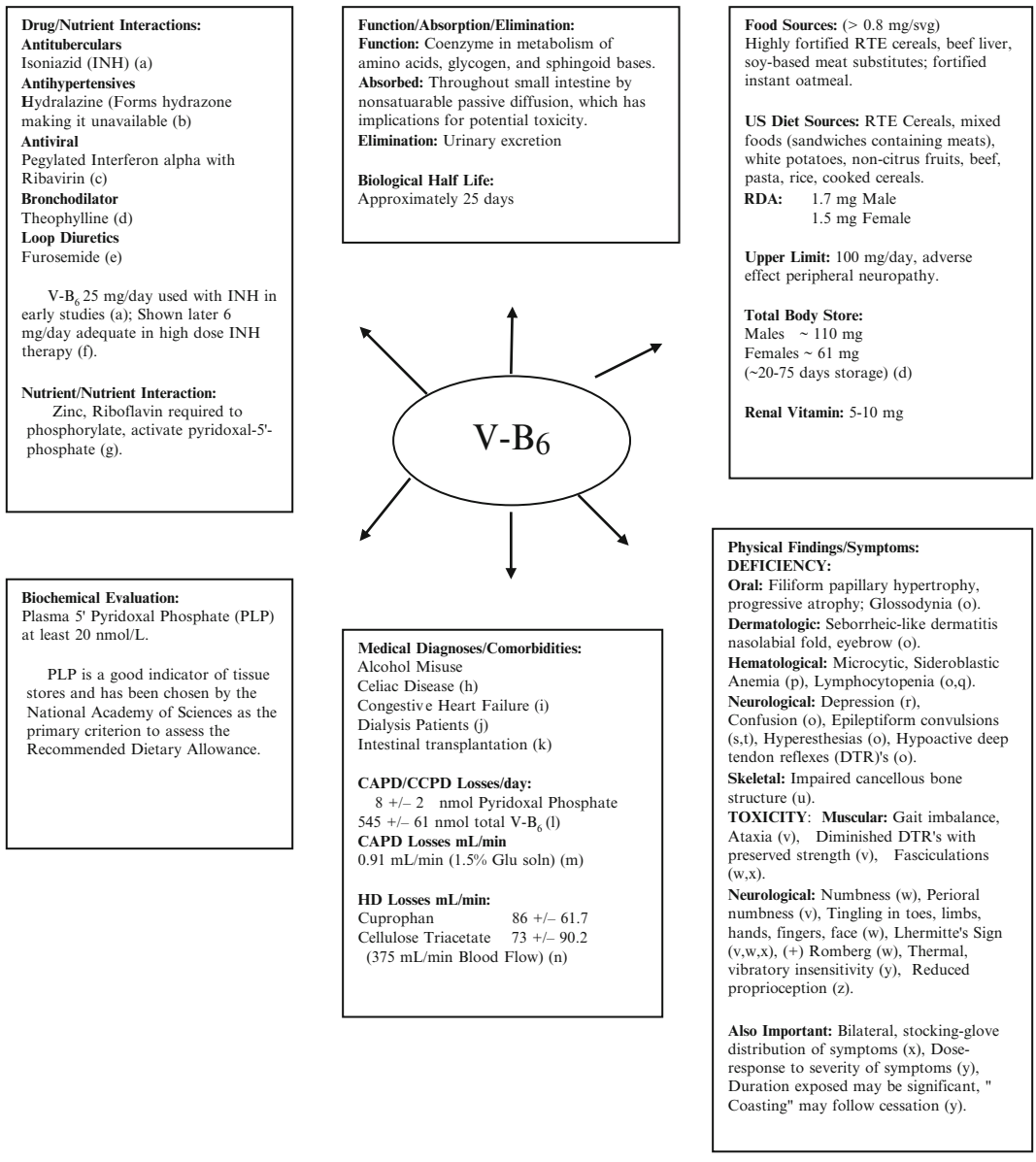

Fig. 6.3 Comprehensive vitamin B_6 assessment in renal failure. **References vitamin B_6 Fig. 6.2*: a. Oestreicher R, Dressler SH, Middlebrook G. Peripheral neuritis in tuberculous patients treated with isoniazid. Am Rev Tuberculosis 1954;70:504–508. b. Vidrio H. Interaction with pyridoxal as a possible mechanism of hydralazine hypotension. J Cardiovasc Pharmacol 1990;15:150–156. c. Lin CC, Yin MC. Vitamins B depletion, lower iron status and decreased antioxidant defense in patients with chronic hepatitis C treated by pegylated interferon alpha and ribavirin. Clin Nutr 2009;28:34–38. d. Coombs GF. The Vitamins, 3rd edn. San Diego: Elsevier Academic Press, 2008:318. e. Mydlik M, Derzsiova K, Zemberova E. Influence of water and sodium diuresis and furosemide on urinary excretion of V-B_6, oxalic acid, and V-C in chronic renal failure. Min Elec Metab 1999;25:352–356. f. Tuberculosis Chemotherapy Centre, Madras. The prevention and treatment of INH toxicity in the therapy of pulmonary TB: An assessment of the prophylactic effect of pyridoxine in low dosage. Bull World Health Org 1963;29:457–481. g. Zinc and the regulation of V-B_6 metabolism. Nutr Rev 1990;48:255–258. h. Dawson AM, Holdsworth CD, Pitcher CS. Sideroblastic anaemia in adult coeliac disease. Gut 1964;5:304. i. Keith ME, Walsh NA, Darling PB, Hanuman SA, Thirugnanam S, Leong-Poi H, Barr A, Sole MJ. B-vitamin deficiency in hospitalized patients with heart failure. J Am Diet Assoc 2009;109:1406–1410. j. Gill H, Yip T, So CC, Lo WK. Anemia in a patient newly transferred from peritoneal dialysis to hemodialysis.

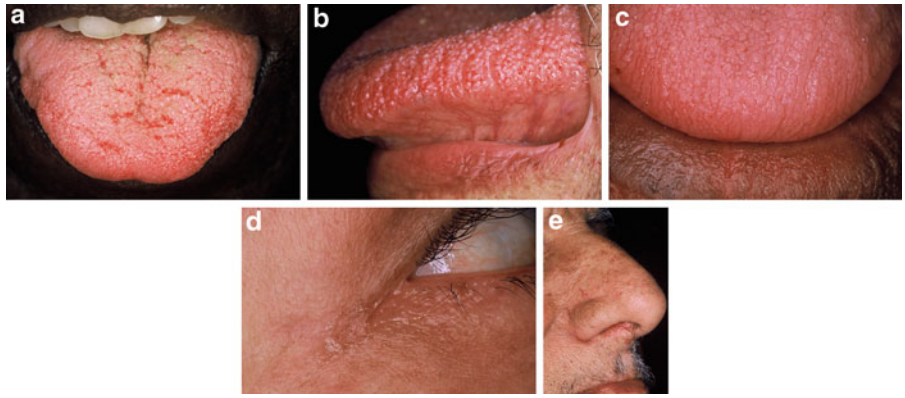

Fig. 6.4 Nutrient-based lesions associated with laboratory-validated vitamin B_6 deficit. (**a**) Filiform papillary hypertrophy with fused papilla. Plasma pyridoxal phosphate (PLP) 1.3 ng/mL (R 3.6–18). © Steve Castillo. (**b**) Filiform papillary hypertrophy. Lateral view. PLP 1.3 ng/mL (R 3.6–18). © Steve Castillo. (**c**) Erosion of papilla with long-standing V-B6 deficit. PLP 3.1 ng/mL (R 3.6–18). © Steve Castillo. (**d**) Tearing of eyes. V-B_6 depletion. PLP 6.4 ng/mL (R 3.6–18). © Steve Castillo. (**e**) Seborrheic-like dermatitis. Nasolabial fold, nares. PLP 1.3 ng/mL (R 3.6–18). © Steve Castillo. Photographs may not be reproduced, copied, projected, televised, digitized, or used in any manner without photographer's express written permission

Fig. 6.3 (continued) Am J Kidney Dis 2010;56:37–39. k. Matarese LLE, Dvorchik I, Costa G, Bond GJ, Koritsky DA, Ferraris R, Touger-Decker R, O'Sullivan-Maillet JK, Abu-Elmagd KM. Pyridoxal-5′-phosphate deficiency after intestinal and multivisceral transplantation. Am J Clin Nutr 2009;89:204–209. l. Ross EA, Shah GM, Reynolds RD, Sabo A, Pichon M. V-B_6 requirements of patients on chronic peritoneal dialysis. Kidney Inter 1989;36:702–706. m. Mydlik M, Derzsiova K, Svac J, Dlhopplcek P, Zemerova E. Peritoneal clearance and peritoneal transfer of oxalic acid, V-C, and V-B_6 during Continuous Ambulatory Peritoneal Dialysis. Artificial Organs 1998;22:784–788. n. Kasama R, Koch T, Canals-Navas C, Pitone JM. V-B_6 and hemodialysis: The impact of high-flux/high efficiency dialysis and review of the literature. Am J Kidney Dis 1996;27:680–686. o. Vilter RW, Mueller JF, Glazer HS, Jarrold T, Abraham J, Thompson C, Hawkins VR. The effect of V-B_6 deficiency induced by desoxypyridoxine in human beings. J Lab Clin Med 1953;42:335–357. p. Hillman RS, Finch CA. Red Cell Manual, 7th edn. Philadelphia: FA Davis Company, 1996:159. q. Cheslock KE, McCully MT. Response of human beings to a low V-B_6 diet. J Nutr 1960;70:507–513. r. Merete C, Falcon LM, Tucker KL. Vitamin B_6 is associated with depressive symptomatology in Massachusetts elders. J Am Coll Nutr 2008;27:421–427. s. Guilarte TR. V-B_6 and cognitive development: Recent research findings from human and animal studies. Nutr Rev 1993 51:193–198. t. Gerlach AT, Thomas S, Stawicki SP, Whitmill ML, Steinberg SM, Cook CH. Vitamin B_6 deficiency: A potential cause of refractory seizures in adults. J Parenter Enteral Nutr 2011;35:272–275. u. Holstein JH, Herrmann M, Splett C, Herrmann W, Garcia P, Histing T, Graeber S, Ong MF, Kurz K, Siebel, Menger MD, Pohlemann T. Low serum folate and V-B_6 are associated with an altered cancellous bone structure in humans. Am J Clin Nutr 2009;90:1440–1445. v. Shaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. Sensory neuropathy from pyridoxine abuse. N Engl J Med 1983;309:445–448. w. Parry GJ. Sensory neuropathy with low-dose pyridoxine. Neurology 1985;35:1466–1468. x. Dalton K, Dalton MJT. Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurol Scand 1987;76:8–11. y. Berger AR, Schaumberg HH, Schroeder C, Apfel S, Reynolds R. Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy: A prospective study of pyridoxine neurotoxicity. Neurology 1992;42:1367–137. z. Ludolph AC, Masur H, Oberwittler C, Koch HG, Ullrich, K. Sensory neuropathy and V-B_6 treatment for homocystinuria. Eur J Pediatr 1993;152:271. *If not annotated otherwise, data cited from: Standing committee on the scientific evaluation of dietary reference intakes Vitamin B_6. In: Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington DC: National Academy Press, 1998:150–195

ferrous sulfate were shown to increase zinc losses [115]. Calcium carbonate also binds zinc but to a lesser degree than calcium acetate [116]. Other factors that may contribute to zinc depletion in predialysis patients include reduced zinc intake with low-protein diets [112, 117, 118] and increased urinary losses with early angiotensin enzyme inhibitors [119] and loop/thiazide diuretics [120–122].

Elevated red blood cell (RBC) zinc documented in renal failure has been attributed to increased levels of zinc protoporphyrin [123] formed when zinc is incorporated into the protoporphyrin ring in iron deficiency [124]. Increased RBC concentrations of the zinc-containing enzyme carbonic anhydrase (CA) are also thought to contribute, as CA rises to maintain acid–base equilibrium and facilitate oxygen transfer to peripheral tissues in anemia [125].

Functional studies in HD patients present conflicting reports on the ability of zinc to improve taste acuity, impotence, and immunity. Supplementation of 120 mg elemental zinc as sulfate post-HD treatment for 6 weeks was shown to improve taste acuity in 95 % of cases [126]; 50 mg zinc as acetate over a 6–12 week period was associated with significant improvement in taste thresholds for salt, sweet, and bitter [127]. But Matson et al. [128] failed to demonstrate improved taste acuity or increased serum zinc in HD patients or controls following 60 mg elemental zinc as sulfate. Poor response may have related to a failure to normalize plasma zinc concentrations in this study. Indeed, research by Henkin et al. [129, 130] in non-renal patients suggests correction of salivary zinc concentration best correlates with reversal of taste dysfunction.

A double-blind study by Mahajan et al. [131] showed increased serum testosterone and improved potency, libido, and frequency of sexual intercourse by HD patient report, following a 6-month oral zinc supplementation, dosed as a 25 mg zinc acetate tablet, twice daily before meals. Vecchio et al. [132] confirmed the role of oral zinc supplementation as a "promising intervention" in a systematic review of randomized controlled studies (RCT) designed to treat sexual dysfunction in CKD, as RCT's supplementing zinc in the dialysate [133–135] either did not report or prove statistical significance.

Ribeira et al. [136] showed improved delayed hypersensitivity skin tests with *Escherichia coli* and phytohemagglutinin (PHA) stimulated lymphocyte blastogenesis after 100 days of 15 mg elemental zinc as acetate twice daily, consistent with improved skin tests by Brodersen et al. [137], Bonomini et al. [138], and Antoniou et al. [139]. Research has continued to implicate zinc in immune compromise as elevated copper/zinc ratios (Cu/Zn) have been linked to reduced percentages of B- and T-lymphocyte cell subsets and increased concentrations of oxidative products including high-sensitivity C-reactive protein, malondialdehyde, and protein carbonyl [140]. Negative correlations were also observed between elevated Cu/Zn and classic malnutrition indicators, BMI, and albumin.

The role zinc deficit may play in reducing oxidative stress continues to be explored as efforts are made to understand its ability to either reduce reactive oxidative species or provide antioxidant defense mechanisms [141]. Hypothetical frameworks have been proposed exploring the relationship between zinc and leptin [142] and atherosclerosis [143]. Further research by Ari et al. [144] found significant negative correlation between serum zinc and carotid artery intima–media thickness ($r = -0.70$, $p < 0.01$) and was supported by linear regression revealing a significant positive correlation between early carotid atherosclerosis and Cu/Zn ratio.

Newer research defining the molecular role of zinc-containing matrix metalloproteinases, previously known to proteolyze all components of renal extracellular matrix, has now revealed their role in regulating nephron formation and mediating fibrotic kidney disorders that include acute kidney injury, diabetic nephropathy, glomerulonephritis, inherited kidney disease, and chronic allograph nephropathy [145]. Positive studies documenting the use of zinc to induce metallothionein in proximal tubular cells in cadaver allografts may point to a therapeutic role of zinc supplementation in improving antioxidant capacity [146].

A comprehensive zinc assessment is found in Fig. 6.5; lesions observed in hypozincemic dialysis patients are shown in Fig. 6.6. Seborrheic-like dermatitis in the scalp, between the eyebrows, behind the ears, and along the nasolabial folds predominates; angular stomatitis, circumorificial dermatitis, alopecia, and leukonychia are also seen. Beau's lines [147] were observed in the nails of an HD patient hospitalized with bacteremia and complete the probable zinc-related lesions identified.

Zinc Toxicity

Given research using zinc supplementation 3–10 times the RDA, concerns about zinc-induced copper deficiency are appropriate. Literature supports increased risk for copper deficiency with modest zinc supplementation, when the zinc/copper ratio is high [148]. Monitored zinc/copper intake at 15:1 has shown limited effects on copper absorption [149] and is frequently used as the industry standard for nutritional supplements. Classic copper deficiency symptoms of anemia (normocytic, hypochromic), leukopenia, and neutropenia have been observed in patients receiving total parenteral nutrition [150] and jejunostomy feedings [151]. Idiopathic myelopathy is recently described as a functional copper deficiency that curiously mimics sensory ataxia and gait disturbances observed in B_{12} deficiency [152]. With consistent evidence that zinc deficiency exists in kidney failure, the best advice may be to "start low and go slow." Copper indicators should be monitored if zinc supplementation continues for more than 90 days.

Placing Physical Findings Within the Clinical Context of the Patient

Lesions and functional deficits must be placed within the clinical context of the patient in hypotheses suggesting nutrient imbalance. Their presence fits within a time frame, consistent with the patient's nutritional history, disease state, and laboratory findings. These data must support the nutrient-focused hypothesis, explaining why a particular nutrient imbalance would occur in a particular patient, at a particular time. Findings are shared with the interdisciplinary team and the RD develops the nutrition care plan with the patient.

Advanced-practice RDs must balance the nutrient store and availability from food/supplements against the nutritional "cost" [153] of dialysis therapy, hospitalization, and medical diagnoses with their prerequisite drug/nutrient profiles. Assiduous physical assessment aimed at early identification of physical findings and functional deficits consistent with nutrient imbalance, with prompt nutrient replacement response, is crucial in end-organ failure. It is the author's belief that nutrient-focused physical examinations will ultimately direct nutritional management required by Medicare guidelines [5] to achieve "effective nutritional status."

Summary of the Nutrition Physical Assessment

RDs in today's interdisciplinary team must master comprehensive nutrient assessments that consider tissue stores, dietary intake, nutrient disposition in health and disease, interaction with pharmaceuticals/nutraceuticals, and laboratory assessment. Professional and regulatory statutes have strengthened the RD's role by mandating a physical assessment component. Physical assessment techniques,

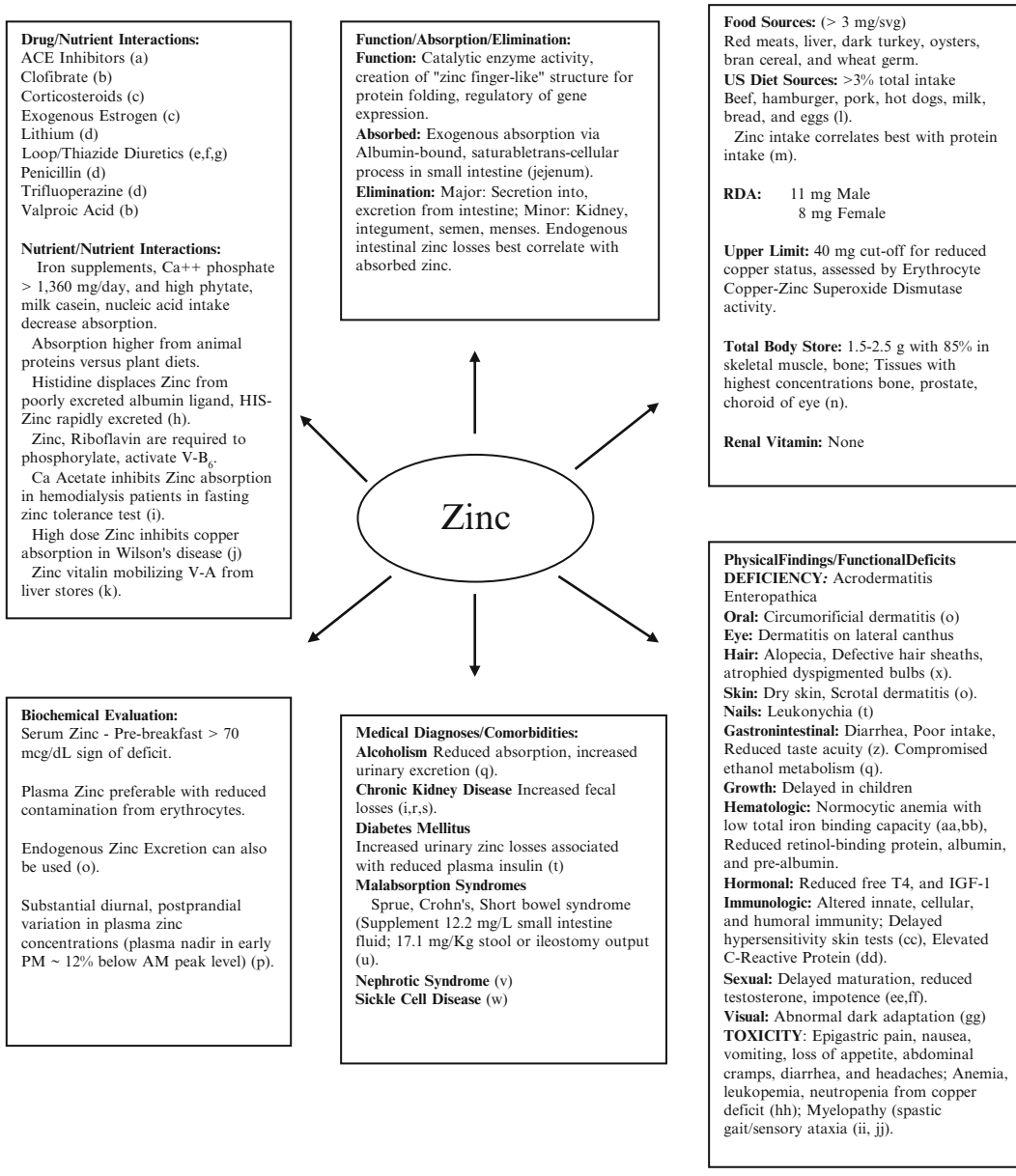

Fig. 6.5 Comprehensive zinc assessment in renal failure. **References for zinc Fig. 6.5*: a. Golik A, Modai D, Averbukh Z, Sheffy M, Shamis A, Cohen N, Shaked U, Dolev E. Zinc metabolism in patients treated with captopril versus enalapril. Metab 1996;39:665–667. b. Boullata JI, Armenti VT, eds, Handbook of Drug-Nutrient Interactions, 2nd edn. New York: Humana Press, 2010. c. Pelton R, LaVelle JB, Hawkins EB, Krinsky DL, eds. Drug-Induced Nutrient Depletion Handbook, 2dn ed. Hudson, OH: Lexi-Comp, Inc., 2001. d. Bicknell JM, Wiggins RV. Taste disorder from zinc deficiency after tonsillectomy. West J Med 1988;149:457–460. e. Cohen N, Golik A, Dishi V, Zaidenstein R, Weissgarten J, Averbukh Z, Modai D. Effect of furosemide oral solution versus furosemide tablets on diuresis and electrolytes in patients with moderate congestive heart failure. Miner Electrolyte Metab 1996;22:248–252. f. Leary WP, Reyes AJ, Wynne RD, Van der Byl K. Renal excretory actions of furosemide, of hydrochlorothiazide and vasodilator flosequinan. J Int Med Res 1990;18:120–141. g. Wester PO. Urinary zinc excretion during treatment with different diuretics.

historical studies describing lesions/functional deficits in selected nutrient imbalance, and physiological mechanisms responsible for altered tissue integrity have been explored. Conscientious nutrition-focused physical examinations are complementary to the renal nutrition specialist's disciplined, hypothetical nutrient-based reasoning. Observable lesions and functional deficits emerge as the ultimate expression of clinically significant nutritional disease.

Fig. 6.5 (continued) Acta Med Scand 1980;208:209–212. h. Henkin RI, Patten BM, Re PK, Bronzert DA. Syndrome of acute zinc loss. Arch Neurol 1975;32:741–751. i. Hwang SJ, Lai YH, Chen HC, Tsai JH. Comparison of the effect of calcium carbonate and calcium acetate on zinc tolerance test in hemodialysis patients. Am J Kidney Dis 1992; 19:57–60. j. Brewer GJ, Yuzbasiyan-Gurkan V, Lee DY. Use of zinc-copper metabolic interactions in the treatment of Wilson's disease. J Am Coll Nutr 1990;9:487–491. k. Solomons NW, Russell RM. The interaction of Vitamin A and zinc: Implications for human nutrition. Am J Clin Nutr 1980;33:2031–2040. l. Mares-Perlman JA, Subar AF, Block G, Greger JL, Luby MH. Zinc intake and sources in the US adult population: 1976–1980. J Am Coll Nutr 1995;14:349–357. m. Haeflein KA, Rasmussen AI. Zinc content of selected foods. J Am Diet Assoc 1977;70:610–616. n. Dibley MJ. Zinc. In: Bowman BA, Russell RM, eds. Present Knowledge in Nutrition, 8th edn. Washington DC: ILSE Press, 2001:329–343. o. Lowe NM, Woodhouse LR, Sutherland B, Shames DM, Burri BJ, Abrams SA, Turnlund JR, Jackson MJ, King JC. Kinetic parameters and plasma zinc concentration correlate well with loss and gain of zinc from man. J Nutr 2004;134:2178–2181. p. King JC, Hambidge M, Westcott, Kern DL, Marshal G. Daily variation in plasma zinc concentrations in women fed meals at six-hour intervals. J Nutr 1994;124:508–516. q. Das I, Hahn HKJ. Effects of zinc deficiency on ethanol metabolism and ethanol aldehyde dehydrogenase activities. J Lab Clin Med 1984;104:610–617. r. Mahajan SK, Bowersox EM, Rye DL, Abu-Hamdan DK, Prasad AS, McDonald FD, Biersack KL. Factors underlying abnormal zinc metabolism in uremia. Kidney Int 1989;36(Supp 27):S-269–S273. s. Abu-Hamdan DK, Mahajan, SK, Migdal SD, Prasad AS, McDonald FD. Zinc tolerance test in uremia. Ann Intern Med 1986:104:50–52. t. Brandao-Neto J, Silva CAB, Shuhama T, Silva JA, Oba L. Renal handling of zinc in insulin-dependent diabetes mellitus patients. BioMetals 2001;14:75–80. u. American Medical Association Department of Foods and Nutrition. Guidelines for essential trace element preparations for parenteral use. J Am Med Assoc 1979;241:2051–2054. v. Lindeman RD, Baxter DJ, Yunice AA, Kraikipanitch S. Serum concentrations and urinary excretions of zinc in cirrhosis, nephrotic syndrome, and renal insufficiency. Am J Med Sci 1978;275:17–31. w. Prasad AS, Beck FWJ, Kaplan J. Effect of zinc supplementation on incidence of infections and hospital admissions in sickle cell disease. Am J Hematol 1999;61:194–202. x. Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. Am J Clin Nutr 1984;39:556–570. y. Pfeiffer CC, Jenney EH. Fingernail white spots: Possible zinc deficiency. J Am Med Assoc 1974;228:157. z. Mahajan SK, Prasad AS, Lambujon J, Abbasi AA, Briggs WA, McDonald FD. Improvement of uremic hypogeusia by zinc. Am J Clin Nutr 1980;33:1517–1521. aa. Nishiyama S, Irisa K, Matsubasa T, Higashi A, Matsuda I. Zinc status relates to hematological deficits in middle-aged women. J Am Coll Nutr 1998;17:291–295. bb. Fukushima T, Horike H, Fujiki S, Sasaki T, Kashihara N. Zinc deficiency anemia and effects of zinc therapy in maintenance hemodialysis patients. Ther Apher Dial 2009;13:231–219. cc. Ribeiro RC, Sales, VSF, Neves FA, Draibe S, Brandao-Neto J. Effects on cell-mediated immunity in chronic hemodialysis patients. Biol Trace Element Res 2004:98:209–218. dd. Rashidi AA, Salehi M, Piroosmand A, Sagheb MM. Effects of zinc supplementation on serum zinc and C-reactive protein concentrations in hemodialysis patients. J Ran Nutr 2009;19:475–478. ee. Mahajan SK, Abbasi AA, Prasad AS, Rabbinic P, Briggs WA, McDonald F. Effect of oral zinc therapy on gonad function in hemodialysis patients. Ann Intern Med 1982;97:357–361. ff. Echo M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Querques M, Saglimbene V, Ruospo M, Bonifati C, Jannini EA, Strippoli GFM. Treatment options for sexual dysfunction in patients with chronic kidney disease: A systematic review of randomized controlled trials. Am Soc Nephrol 2010;5:985–995. gg. Morrison SA, Russell RM, Carney EA, Oaks EV. Zinc deficiency: a cause of abnormal dark adaptation in cirrhotics. Am J Clin Nutr 1978;31:276–281. hh. Irving JA, Mattman A, Lockitch G, Farrell K, Wadsworth LD. Element of caution: A case of reversible cytopenias associated with excessive zinc supplementation. Can Med Assoc J 2003;169:129–131. ii. Fosmire GJ. Zinc toxicity. Am J Clin Nutr 1990;51:225–227. jj. Kumar N. Copper deficiency myelopathy. Mayo Clin Proc 2006;81:1371–1384. *If not annotated otherwise, data cited from: Standing committee on the scientific evaluation of dietary reference intakes Zinc. In: Dietary Reference Intakes for V-A, V-K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington DC: National Academy Press. 2001:442–501

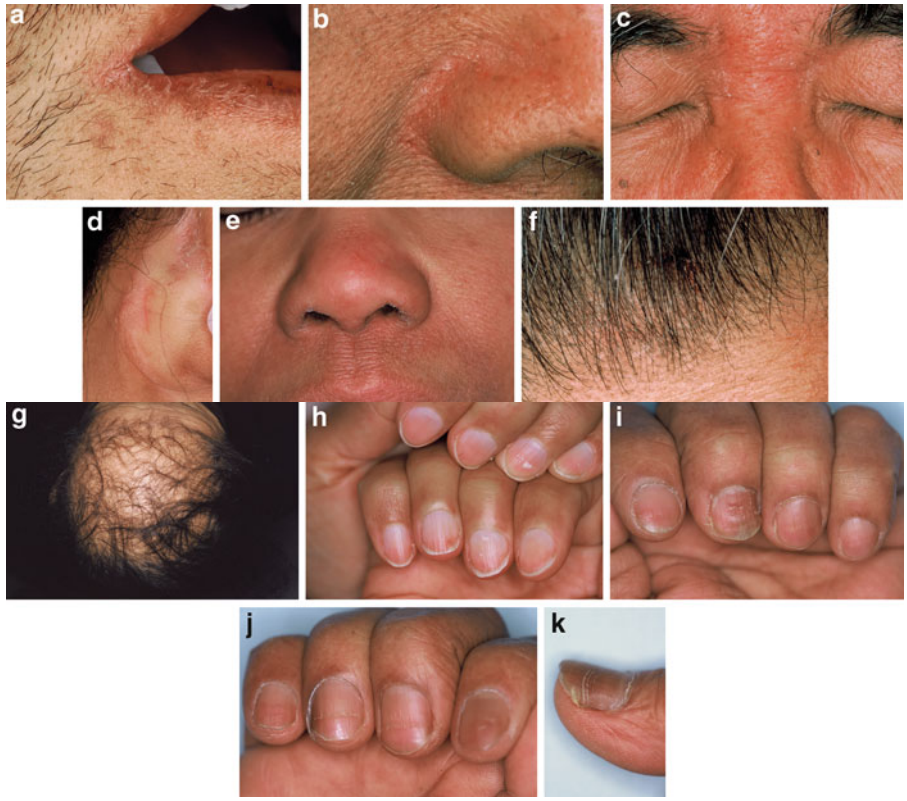

Fig. 6.6 Nutrient-based lesions associated with laboratory-validated zinc deficiency. (**a**) Angular stomatitis. Zinc 50 **µ**g/dL (R 50–150). © Steve Castillo. (**b**) Seborrheic-like dermatitis of the nasolabial fold. Zinc 50 **µ**g/dL (R 50–150). © Steve Castillo. (**c**) Seborrheic-like dermatitis between eyebrows. Zinc 50 **µ**g/dL (R 50–150). © Steve Castillo. (**d**) Retroauricular dermatitis. Zinc 50 **µ**g/dL (R 50–150). © Steve Castillo. (**e**) Circumorificial dermatitis. Zinc 52 **µ**g/dL (R 50–150). © David Giacalone. (**f**) Seborrheic-like dermatitis of the scalp. Zinc 50 **µ**g/dL (R 50–150). © Steve Castillo. (**g**) Alopecia. Zinc 45 **µ**g/dL (R 50–150). © Steve Castillo. (**h**) Leukonychia. Zinc 45 **µ**g/dL (R 50–150). © David Giacalone. (**i**) Beau's Lines R hand. Hospitalization, bacteremia. © David Giacolone. (**j**) Beau's Lines L hand. Hospitalization, bacteremia. © David Giacolone. (**k**) Beau's Lines Thumb. Hospitalization, bacteremia. © David Giacolone. Photographs may not be reproduced, copied, projected, televised, digitized, or used in any manner without photographer's express written permission

References

1. Federal Register. Fed Register (41 FR 22501). 3 June 1976.
2. 1995 Comprehensive accreditation manual for hospitals. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations; 1994. p. 151–2.
3. Gilmore GA, Maillet JO, Mitchell BE. Determining educational preparation based on job competencies of entry-level dietetics practitioners. J Am Diet Assoc. 1997;97:306–16.
4. K/DOQI, National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35 Suppl 2:S1–140.
5. Department of Health and Human Services. Centers for Medicare and Medicaid Services; conditions for coverage for end stage renal disease facilities; proposed rule. Fed Regist. 2005;70(23):6184–232.
6. Kiesselhosrst KJ, Skates J, Pritchett E. American Dietetic Association: standards of practice in nutrition care and updated standards of professional performance. J Am Diet Assoc. 2005;105:641–5.e10.
7. Joint Standards Task Force of the American Dietetic Association Renal Dietitians Dietetic Practice Group; National Kidney Foundation Council on Renal Nutrition, Brommage D, Karalis M, Martin C, McCarthy M,

Benner D, Goeddeke-Merickel CM, Wiesen K, Byham-Gray L, House JL, Pavlinac J, McCann L. American Dietetic Association and the National Kidney Foundation Standards of Practice and Standards of Professional Performance for Registered Dietitians (generalist, specialty, and advanced) in nephrology care. J Am Diet Assoc. 2009;109:1617–25.e33.
8. Verghese A. A touch of sense. Health Aff. 2009;28:1177–82.
9. Detsky AS, McLaughlin JR, Baker JP. What is subjective global assessment. J Parenter Enteral Nutr. 1987;11:8–13.
10. McCann L. Subjective global assessment as it pertains to nutrition status. Dial Transplant. 1996;25:190–225.
11. Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, Sehgal AR, Kalantar-Zadeh K. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. J Ren Nutr. 2007;17:336–42.
12. Mazairac AHA, de Wit A, Penne EL, van der Weerd NC, Grooteman MPC, van den Dorpel MA, et al. Protein-energy nutritional status and kidney disease-specific quality of life in hemodialysis patients. J Ren Nutr. 2011;21:376–86.
13. Marieb EN, Wilhelm PB, Mallatt J. Human anatomy. 6th ed. San Francisco: Addison Wesley Longman; 2012.
14. Morrison SG. Clinical nutrition physical examination. Support Line. 1997;19(2):16–8.
15. Hammond KA. Nutritional dimension of physical assessment. Nutrition. 1999;15:411–9.
16. Hammond KA, Hillhouse J. Nutrition-focused physical assessment skills for dietitians, study guide. 2nd ed. Chicago, IL: Dietitians in Nutrition Support; 2000.
17. Williams FH. Neuromuscular complications of nutritional deficiencies. Phys Med Rehabil Clin N Am. 2008;19:125–48.
18. Pogatshnik C, Hamilton C. Nutrition-focused physical examination: skin nails, hair, eyes, and oral cavity. Support Line. 2011;33(2):7–13.
19. Kight MA. The nutrition physical examination. CRNQ. 1987;11(3):9–12.
20. Kight MA, Kelly MP, Castillo ST, Migliore V. Conducting physical examination rounds for manifestations of nutrient deficiency or excess. Nutr Clin Pract. 1999;14:93–8.
21. Kelly MP, Kight MA, Rodriguez R, Castillo ST. A diagnostically reasoned case study with particular emphasis on B_6 and zinc imbalance directed by clinical history and nutrition physical examination findings. Nutr Clin Pract. 1998;13:32–9.
22. Bickley LS, Szilagyi PG. Bates' guide to physical examination and history taking. 10th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009.
23. Hills OW, Liebert E, Steinberg DL, Horwitt MK. Clinical aspects of dietary depletion of riboflavin. Arch Intern Med. 1951;87:682–93.
24. Blanck HM, Bowman BA, Serdula MK, Khan LK, Kohn W, Woodruff BA; Bhutanese Refugee Investigation Group. Angular stomatitis and riboflavin status among adolescent Bhutanese refugees living in southeastern Nepal. Am J Clin Nutr. 2002;76:430–5.
25. Prasad R, Lakshmi AV, Bamji MS. Impaired collagen maturity in vitamins B2 and B6 deficiency—probable molecular basis of skin lesions. Biochem Med. 1983;30:333–41.
26. Garcia ER, Padilla AM, Romo SA, Ramirez MB. Oral mucosa symptoms, signs and lesions, in end stage renal disease and non-end stage renal disease diabetic patients. Med Oral Patol Oral Cir Bucal. 2006;11:E467–73.
27. Osaki T, Ohshima M, Tomita Y, Matsgi N, Nomura Y. Clinical and physiological investigations in patients with taste abnormality. J Oral Pathol Med. 1996;25:38–43.
28. LeBlond RF, DeGowin RL, Brown DD, editors. DeGowin's diagnostic examination. 9th ed. San Francisco: McGraw-Hill; 2009.
29. Ellenberg M, Pollack H. Pseudo ariboflavinosis. JAMA. 1942;119:790–2.
30. McLaren DS. A colour atlas and text of diet-related disorders. 2nd ed. Aylesbury: Mosby-Year Book Europe Limited; 1992.
31. Dreizen S. Nutritional changes in the oral cavity. J Prosthet Dent. 1966;16:1144–50.
32. Shahbake M, Hutchinson I, Laing DG, Jinks AL. Rapid quantitative assessment of fungiform papillae density in the human tongue. Brain Res. 2005;1052:196–201.
33. Astbäck J, Fernström A, Hylander B, Arvidson K, Johansson O. Taste buds and neuronal markers in patient with chronic renal failure. Perit Dial Int. 1999;19 Suppl 2:S315–23.
34. Bean WB. An analysis of subjectivity in the clinical examination in nutrition. J Appl Physiol. 1948;1:458–68.
35. Challacombe SJ, Scully C, Keevil B, Lehner T. Serum ferritin in recurrent oral ulcerations. J Pathol. 1983;12:290–9.
36. Porter SR, Scully C, Flint S. Hematologic status in recurrent aphthous stomatitis compared with other oral disease. Oral Surg Oral Med Oral Pathol. 1988;66:41–4.
37. Haisraeli-Shalish M, Livneh A, Katz J, Doolman R, Sella BA. Recurrent aphthous stomatitis and thiamine deficiency. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;82:634–6.

38. Shakeri R, Zamani R, Sotoudehehmanesh R, Amiri A, Mohamadnejad M, Davatchi F, Karakani AM, Malekzadeh R, Shahram F. Gluten sensitivity enteropathy in patients with recurrent aphthous stomatitis. BMC Gastroenterol. 2009;9:44.
39. Rashid M, Zarkadas M, Anca A, Limeback H. Oral manifestations of celiac disease: a clinical guide for dentists. J Can Dent Assoc. 2011;77:b39.
40. Deloche C, Bastien P, Chadoutaud S, Galan P, Bertrais S, Hercberg S, DeLacharriere O. Low iron stores: a risk factor for excessive hair loss in non-menopausal women. Eur J Dermatol. 2007;17:507–12.
41. Goldberg LJ, Lenzy Y. Nutrition and hair. Clin Dermatol. 2010;28:412–9.
42. Crandon JH, Lund CC, Dill DB. Experimental human scurvy. N Engl J Med. 1940;223:353–69.
43. Kiel H. The follicular lesions of vitamin A and C deficiencies: critical survey. Am J Dig Dis. 1938;5:40–8.
44. Brenner S, Horwitz C. Possible nutrient mediators in psoriasis and seborrheic-like dermatitis. World Rev Nutr Diet. 1988;55:165–82.
45. Berlyne GM, Shaw AB. Red eyes in renal failure. Lancet. 1967;1:4–7.
46. Walsh FB, Howard JE. Conjunctival and corneal lesions in hypercalcemia. J Clin Endocrinol Metab. 1947;7:644–52.
47. Sheth TN, Choudhry NK, Bowes M, Detsly A. The relation of conjunctival pallor to the presence of anemia. J Gen Intern Med. 1997;12:102–6.
48. Tosti A, Baran R, Dawber P. The nails in systemic disease and drug-induced changes. In: DeBerker DAR, Baran R, Dawber RPR, editors. Handbook of diseases of the nails and their management. Osney Mead, Oxford: Blackwell Science; 1995. p. 91.
49. DeBerker D. What do Beau's lines mean? Int J Dermatol. 1994;33:545–6.
50. Kelly MP, Kight MA, Castillo ST. Trophic implications of altered body composition observed in or near the nails of hemodialysis patients. Adv Ren Replace Ther. 1998;5:241–51.
51. Meuhrcke R. The fingernails in chronic hypoalbuminaemia. Br Med J. 1956;1:1327–8.
52. Feldman SR, Gammon WR. Unilateral Muehrcke's lines following trauma (letter). Arch Dermatol. 1989;125:133–4.
53. Schwartz RA, Vickerman CE. Muehrcke's line of the fingernails. Arch Intern Med. 1979;139:242–3.
54. Lindsay PG. The half-and-half nail. Arch Intern Med. 1967;119:583–7.
55. Lubach D, Strubbe J, Schmidt J. The "half-and-half nail" phenomenon in chronic hemodialysis patients. Dermatologica. 1982;164:350–3.
56. Cashman MW, Sloan SB. Nutrition and nail disease. Clin Dermatol. 2010;28:420–5.
57. Sarno Ryan A, Goldsmith LA. Nutrition and the skin. Clin Dermatol. 1996;14:389–406.
58. Goldberger J, Waring CH, Willets DG. The prevention of pellagra. Public Health Rep. 1915;30:3117.
59. Goldsmith GA, Sarett HP, Register UD, Gibbons J. Studies of niacin requirements in man. I. Experimental pellagra in subjects on corn diets low in niacin and tryptophan. J Clin Invest. 1952;31:533–42.
60. Rose WC. Amino acid requirements of man. Fed Proc. 1949;8:546.
61. Harris HF. Pellagra. New York: McMillan Company; 1919. p. 234.
62. Ishii N, Nishihara Y. Pellagra among chronic alcoholics: clinical and pathological study of 20 necroscopy cases. J Neurol Neurosurg Psychiatry. 1981;44:209–15.
63. Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RR. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroenterol. 2005;100:2307–14.
64. Spivak JL, Jackson DL. Pellagra: an analysis of 18 patients and a review of the literature. Johns Hopkins Med J. 1977;140:295–309.
65. Delgado-Sanchez L, Godkar D, Niranjan S. Pellagra: rekindling of an old flame. Am J Ther. 2008;15:173–5.
66. Schattner A. A 70-yr old man with isolated weight loss and a pellagra-like syndrome due to celiac disease. Yale J Biol Med. 1999;72:15–8.
67. Ashourian N, Mousdicas N. Pellagra-like dermatitis. N Engl J Med. 2006;354:15.
68. Prousky JE. Pellagra may be a rare secondary complication of anorexia nervosa. Altern Med Rev. 2003;8:180–5.
69. MacDonald A, Forsyth A. Nutritional deficiencies and the skin. Clin Exp Dermatol. 2005;30:388–90.
70. Standing committee on the scientific evaluation of dietary reference intakes niacin. In: Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 123–49.
71. Seal AJ, Creeke PI, Dibari F, Cheung E, Kyroussis E, Semedo E, van den Briel T. Low and deficient niacin status and pellagra are endemic in postwar Angola. Am J Clin Nutr. 2007;85:218–24.
72. Wang AY-M, Sea MM-M, Ip T, Law MC, Chow KM, Lui SF, Li PK-T, Woo J. Independent effects of residual renal function and dialysis adequacy on dietary micronutrient intakes in patients receiving continuous ambulatory peritoneal dialysis. Am J Clin Nutr. 2002;76:569–76.
73. Goldsmith GA. Experimental niacin deficiency. J Am Diet Assoc. 1956;32:312–6.
74. Sega I, Hale M, Demetriou A, Mohamed AE. Pathological effects of pellagra on the esophagus. Nutr Cancer. 1990;14:233–8.

75. Sega I, Ou TL, Demetriou A, Paterson A, Hale M, Lerios M. Rectal manifestations of pellagra. Int J Colorectal Dis. 1986;1:238–43.
76. Goldsmith GA, Rosenthal HL, Gibbens J, Unglaub WG. Studies of niacin requirement in man. II. Requirement on wheat and corn diets low in tryptophan. J Nutr. 1955;56:371–86.
77. Saunders EB. The gynecological, obstetrical, and surgical aspects of pellagra. Am J Insanity. 1911;67:541–51.
78. Daya SM. Vitamin A, abnormalities, pellagra, vitamin C deficiency. In: Mannis MJ, Macsai MS, Huntley AC, editors. Eye and skin disease. Philadelphia: Lippincott-Raven; 1996. p. 124–5.
79. Pitche PT. Pellagra. Sante. 2005;15:205–8.
80. Perry ML. A report of two cases of pellagra. Am J Insanity. 1911;67:553–7.
81. Snyderman SE, Carretteto R, Holt LE. Pyridoxine deficiency in the human being. Fed Proc. 1950;9:371–84.
82. Vilter RW, Mueller JF, Glazer HS, Jarrold T, Abraham J, Thompson C, Hawkins VR. The effect of V-B_6 deficiency induced by desoxypyridoxine in human beings. J Lab Clin Med. 1953;42:335–57.
83. Standing committee on the scientific evaluation of dietary reference intakes vitamin B_6. In: Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, and V-B_{12}, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 153.
84. Hoffman LM, Ross J. The role of heme in the maturation of erythroblasts: the effects of inhibition of pyridoxine metabolism. Blood. 1980;55:762–71.
85. Hawkins WW, Barsky J. An experiment on human V-B_6 deprivation. Science. 1948;108:284–6.
86. Snyder D. Pyridoxine supplementation during isoniazid therapy. Tubercle. 1980;61:191–6.
87. Guilatre TR. Vitamin B_6 and cognitive development. Nutr Rev. 1993;51:193–8.
88. Roberts E. Gamma-aminobutyric acid-V-B_6 relationships in the brain. Am J Clin Nutr. 1963;12:291–307.
89. Wood JD, Peesker SJ. The effect on GABA metabolism in brain of isonicotinic acid hydrazine and pyridoxine as a function of time after administration. J Neurochem. 1972;19:1527–37.
90. Mydlik M, Derzsiova K, Zemberova E. Influence of water and sodium diuresis and furosemide on urinary excretion of V-B_6, oxalic acid, and V-C in chronic renal failure. Miner Electrolyte Metab. 1999;25:352–6.
91. Vidrio J. Interaction with pyridoxal as a possible mechanism of hydralazine hypotension. J Cardiovasc Pharmacol. 1990;15:150–6.
92. Friedli A, Saurat JH. Oculo-orogenital syndrome—a deficiency of vitamins B_2 and B_6. N Engl J Med. 2004;350:1130.
93. Caselli MA, Prywes HC, Sharnoff DG. Isoniazid toxicity as a cause of peripheral neuropathy. J Am Podiatry Assoc. 1981;71:691–3.
94. Wood ER. Isoniazid toxicity: pyridoxine controlled seizures in a dialysis patient. J Kans Med Soc. 1981;82:551–2.
95. Blumberg EA, Gil RA. Cerebellar syndrome caused by isoniazid. Ann Pharmacother. 1990;24:829–31.
96. Siskind MS, Thienemann D, Kirlin L. Isoniazid-induced neurotoxicity in chronic dialysis patients: report of three cases and a review of the literature. Nephron. 1993;64:303–6.
97. Asnis DS, Bhat G, Melchert AF. Reversible seizures and mental status changed in a dialysis patient on isoniazid preventive therapy. Ann Pharmacother. 1993;27:444–6.
98. Lin CC, Yin MC. Vitamins B depletion, lower iron status, and decreased antioxidative defense in patients with chronic hepatitis C treated by pegylated interferon alfa and ribavirin. Clin Nutr. 2009;28:34–8.
99. Kasama R, Koch T, Canals-Navas C, Pitone JM. V-B_6 and hemodialysis: impact of high-flux/high efficiency dialysis and review of the literature. Am J Kidney Dis. 1996;27:680–6.
100. Ross EA, Shah GM, Reynolds RD, Sabo A, Picon M. V-B_6 requirements of patients on chronic peritoneal dialysis. Kidney Int. 1989;36:702–6.
101. Gill H, Yip T, So CC, Lo WK. Anemia in a patient newly transferred from peritoneal dialysis to hemodialysis. Am J Kidney Dis. 2010;56:37–9.
102. Okacda H, Moriwaki K, Kanno Y, Sugahara S, Nkamoto H, Yoshizawa M, Suzuki H. Vitamin B_6 supplementation can improve peripheral neuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin. Nephrol Dial Transplant. 2000;15:1410–3.
103. Schaumberg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. Sensory neuropathy from pyridoxine abuse. N Engl J Med. 1983;309:445–8.
104. Parry GJ, Bredsen DE. Sensory neuropathy with low-dose pyridoxine. Neurology. 1985;35:1466–8.
105. Dalton K, Dalton MJT. Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurol Scand. 1987;76:8–11.
106. Lindner A, Bankson DD, Stehman-Breen C, Mahuren JD, Coburn SP. Vitamin B_6 metabolism and homocysteine in end-stage renal disease and chronic renal insufficiency. Am J Kidney Dis. 2002;39:134–45.
107. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia. Am J Med. 1961;31:532–46.
108. Moynahan EJ. Acrodermatitis enteropathica: a lethal inherited human zinc deficiency disorder. Lancet. 1974;2:399–400.

109. Otten JJ, Hellwig JP, Meyers LD, editors. Dietary reference intakes. Washington, DC: The National Academies Press; 2006.
110. Lowe NM, Woodhouse LR, Sutherland B, Shames DM, Furri BJ, Abrams AS, Turnlund JR, Jackson MJ, King JC. Kinetic parameters and plasma zinc concentrations correlate well with loss and gain of zinc from man. J Nutr. 2004;134:2178–81.
111. Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. Am J Clin Nutr. 1984;39:556–70.
112. Standing committee on the scientific evaluation of dietary reference intakes Niacin. In: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2001. p. 442–501.
113. Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B, Thadhani R, Gill J. Trace elements in hemodialysis patients: a systematic review and meta-analysis. BMC Med. 2009;7:25.
114. Mahajan SK, Bowersox EM, Rye DL, Abu-Hadan DK, Prasad AS, McDonald FD, Biersack KL. Factors underlying abnormal zinc metabolism in uremia. Kidney Int. 1989;36 Suppl 27:S269–73.
115. Abu-Hamdan DK, Mahajan SK, Migdal SD, Prasad AS, McDonald FD. Zinc tolerance test in uremia: effect of ferrous sulfate and aluminum hydroxide. Ann Intern Med. 1986;104:50–2.
116. Hwang SJ, Lai YH, Chen HC, Tsai JH. Comparison of the effects of calcium carbonate and calcium acetate on zinc tolerance test in hemodialysis patients. Am J Kidney Dis. 1992;19:57–60.
117. Gili P, Fagioli F, Paoli E, Vitali E, Farinelli A. Is zinc status a problem in dietary treatment of chronic renal failure? (letter). Nephron. 1985;40:382.
118. Blendis LM, Ampil M, Wilson DR, Kiwan J, Labranche J, Johnson M, Williams C. The importance of dietary protein in the zinc deficiency of uremia. Am J Clin Nutr. 1981;34:2658–61.
119. Golik A, Modai D, Averbukh M, Sheffy M, Shamis A, Cohen N, Shaked U, Dolev E. Zinc metabolism in patients treated with captopril vs. enalapril. Metabolism. 1990;39:665–7.
120. Wester PO. Urinary zinc excretion during treatment with different diuretics. Acta Med Scand. 1980;208:209–12.
121. Leary WP, Reyes AJ, Wynne RD, Van der Byl K. Renal excretory actions of furosemide, of hydrochlorothiazide, and vasodilator flosequinan. J Int Med Res. 1990;18:120–41.
122. Cohen N, Golik A, Dishi V, Zaidenstein R, Weissgarten J, Averbuhk Z, Modao D. Effect of furosemide oral solution versus furosemide tablets on diuresis and electrolytes in patients with moderate congestive heart failure. Miner Electrolyte Metab. 1996;22:248–52.
123. Mafra D, Cuppari L, Favero DIT, Cozzolino SMF. Zinc levels after iron supplementation in patients with chronic kidney disease. J Ren Nutr. 2004;14:164–9.
124. Labbe RF, Rettmer RL. Zinc protoporphyrin: a product of iron-deficient erythropoiesis. Semin Hematol. 1989;26:40–6.
125. Mafra D, Cozzolino SMF. Erythrocyte zinc and carbonic anhydrase levels in nondialyzed chronic kidney disease patients. Clin Biochem. 2004;37:67–71.
126. Atkin-Thor E, Goddard BW, O'Nion J, Stephen RL, Kolff WJ. Hypogeusia and zinc depletion in chronic dialysis patients. Am J Clin Nutr. 1978;31:1948–51.
127. Mahajan SK, Prasad AS, Lanbujon J, Abbasi AA, Briggs WA, McDonald FD. Improvement of uremic hypogeusia by zinc: a double blind study. Am J Clin Nutr. 1980;33:1517–21.
128. Matson A, Wright M, Oliver A, Woodrow G, King N, Dye L, Blundell J, Brownjohn A, Truney J. Zinc supplementation at conventional doses does not improve the disturbance of taste perception in HD patients. J Ren Nutr. 2003;13:224–8.
129. Henkin RI, Martin BM, Agarwal RP. Decreased parotid saliva gustin/carbonic anhydrase VI secretion: an enzyme disorder manifested by gustatory and olfactory dysfunction. Am J Med Sci. 1999;318:380–91.
130. Henkin RI, Martin BM, Agarwal RP. Efficacy of exogenous oral zinc in treatment of patients with carbonic anhydrase VI deficiency. Am J Med Sci. 1999;318:392–404.
131. Mahajan SK, Abbasi AA, Prasad AS, Rabbani P, Briggs WA, McDonald FD. Effect of oral zinc therapy on gonadal function in hemodialysis patients. Ann Intern Med. 1982;97:357–61.
132. Vecchio M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Querques M, Saglimbene V, Ruospo M, Bonifati C, Jannini EA, Strippoli GFM. Treatment options for sexual dysfunction in patients with chronic kidney disease: a systematic review of randomized controlled trials. Clin J Am Soc Nephrol. 2010;5:985–95.
133. Antoniou LD, Shalhoub RJ, Sudhakar T, Smith JC. Reversal of uraemic impotence with zinc. Lancet. 1977;2:895–8.
134. Brook AC, Johnson DG, Ward MK, Watson MJ, Cook DB, Kerr DN. Absence of a therapeutic effect of zinc in the sexual dysfunction of haemodialyzed patients. Lancet. 1980;2:618–20.
135. Wabrek AJ. Zinc: a possible role in the reversal of uremic impotence. Sexuality and Disability Winter. 1982;5(4):213–21.

136. Ribeira CJF, Sales VSF, Neves DAR, Draibe S, Brandao-Neto J. Effects of zinc on cell-mediated immunity in chronic hemodialysis patients. Biol Trace Elem Res. 2004;98:209–17.
137. Brodersen HP, Holtkamp W, Larbig D. Zinc supplementation and cellular and humoral immune function in chronic hemodialysis patients (letter). Nephrol Dial Transplant. 1994;9:736–7.
138. Bonomini M, Manfrini V, Cappelli P, Albertazzi A. Zinc and cell-mediated immunity in chronic uremia. Nephron. 1993;65:1–4.
139. Antoniou LD, Shalhoub RJ. Zinc-induced enhancement of lymphocyte function and viability in chronic uremia. Nephron. 1985;40:13–21.
140. Guo C-H, Chen P-C, Yeh MS, Hsiung D-Y, Wang C-L. Cu/Zn ratios are associated with nutritional status, oxidative stress, inflammation, and immune abnormalities in patients on peritoneal dialysis. Clin Biochem. 2011;44:275–80.
141. Koca T, Berber A, Koca HB, Demire TA, Koken T. Effects of hemodialysis period on levels of blood trace elements and oxidative stress. Clin Exp Nephrol. 2010;14:463–8.
142. Lobo JC, Aranha LN, Moraes C, Brito LC, Mafra D. Linking zinc and leptin in chronic kidney disease: future directions. Biol Trace Elem Res. 2012;146:1–5.
143. Lobo JC, Torres JPM, Fouque D, Mafra D. Zinc deficiency in chronic kidney disease: is there a relationship with adipose tissue and atherosclerosis? Biol Trace Elem Res. 2010;135:16–21.
144. Ari E, Kaya Y, Demir H, Asicioglu E, Keskin S. The correlation of serum trace elements and heavy metals with carotid artery atherosclerosis in maintenance hemodialysis patients. Biol Trace Elem Res. 2011;144:351–9.
145. Tan RJ, Liu Y. Matrix metalloproteinases in kidney homeostasis and diseases. Am J Physiol Renal Physiol. 2012;302:F1351–6.
146. Alscher DM, Braun N, Biegger D, Stuelten C, Gawroski K, Murdter TE, Kuhlmann U, Fritz P. Induction of metallothionein in proximal tubular cells by zinc and its potential as an endogenous antioxidant. Kidney Blood Press Res. 2005;28:127–33.
147. Weismann K. Lines of Beau: possible markers of zinc deficiency. Acta Derm Venereol. 1977;57:88–90.
148. Sandstead HH. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. Am J Clin Nutr. 1995;61:621S–4.
149. August D, Jangbhorbani M, Young VR. Determination of zinc and copper absorption at three dietary zinc:copper ratios by using stable isotopic methods in young adult and elderly subjects. Am J Clin Nutr. 1989;50:1457–63.
150. Fujita M, Itakura R, Takagi Y, Okada A. Copper deficiency during TPN: clinical analysis of three cases. J Parenter Enteral Nutr. 1989;13:421–5.
151. Jayakumar S, Micallif-Eynaud PD, Lyon TDB, Cramb R, Jilaihawi AN, Prakash D. Acquired copper deficiency following prolonged jejunostomy feeds. Ann Clin Biochem. 2005;42:227–31.
152. Kumar N, Gross JB, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology. 2004;63:33–9.
153. Kelly MP, Kight MA, Torres M, Migliore V. Nutritional cost of hospitalization for HD patients and time to achieve nutritional resiliency. J Ren Nutr. 1994;4:1–11.

Part II
Chronic Kidney Disease Among Adults

Chapter 7
Hypertension

Kristie J. Lancaster

Key Points

- To identify the nutrients and foods most commonly believed to be associated with blood pressure
- To evaluate the evidence for or against the effect of certain nutrients and food groups on blood pressure
- To discuss the current dietary recommendations for the prevention and treatment of hypertension
- To describe how current dietary recommendations for hypertension apply to people with chronic kidney disease

Keywords Blood pressure • Sodium • Potassium • DASH diet • Calcium • Omega-3 fatty acids • Monounsaturated fatty acids • Vitamin C • Protein • Magnesium

Introduction

According to national data, approximately 29 % of US adults had hypertension in 2007–2008. The prevalence has changed little in the previous 10 years [1]. A significant number of patients with chronic kidney disease (CKD) have hypertension. Hypertension can be treated and sometimes prevented with the proper dietary intake. Some studies suggest that certain nutrients, including sodium, potassium, calcium, magnesium, protein, unsaturated fats, and vitamin C, may have an effect on blood pressure level. Research has also found associations of blood pressure (BP) with food groups such as fruits, vegetables, and dairy products. This chapter will review the evidence for treating hypertension with diet modification.

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Nutrients and Blood Pressure

Sodium

Although the debate over the extent of dietary sodium's influence on BP has raged for decades, Intersalt, the cross-sectional epidemiological study conducted in 32 countries in the mid-1980s, found that higher 24-h urine sodium excretion (a marker for sodium intake) was positively associated with higher BP [2, 3]. The association was stronger for the older participants (40–59 years old). Other cross-sectional studies have also found an association between sodium intake and blood pressure [4].

Randomized controlled trials (RCTs) that reduce sodium intake have also found significantly lower BP in the sodium restricted group [5–7]. A meta-analysis of 167 RCTs that included only studies that confirmed sodium intake through 24-h urine sodium excretion found that normotensive people who had a low sodium intake had lower systolic blood pressure (SBP) than those with a high sodium intake [8]. Hypertensive people with a low sodium intake had lower SBP and diastolic blood pressure (DBP) than those with a high sodium intake. The second trial of Dietary Approaches to Stop Hypertension (DASH) tested both the DASH diet—a diet high in fruits, vegetables, and low-fat dairy foods—and sodium intake [9]. Participants with an SBP of 120–139 mmHg and/or DBP of 80–99 were randomized into the typical US diet (control) or the DASH diet in a parallel group design and spent a month consuming that diet at each of three sodium levels: high, intermediate, and low. In both diet groups, BP was significantly lower for the lower sodium levels, showing an independent effect of sodium on BP.

One 2-year prospective study did not find a significant association between sodium excretion and BP, but found that fewer than 20 % of 296 healthy participants experienced a significant increase in BP at high sodium intakes [10]. Indeed, some people seem to be more sensitive than others to sodium's effect on BP. Despite this fact, most recent studies show that sodium restriction does reduce BP. The effect is more pronounced in African Americans, older people, and persons diagnosed with hypertension.

Limiting sodium intake is especially important in CKD because excess sodium increases extracellular fluid volume, which may not only increase BP but also weight gain, increasing the amount of fluid to be removed in dialysis [11].

The 2004 Dietary Reference Intake (DRI) for sodium recommends consuming no more than 1,500 mg of sodium per day, 1,300 mg for those over age 50 [12]. The 2010 Dietary Guidelines for Americans recommends that most people consume less than 2,300 mg/day, but highlights the 1,500 limit for people with hypertension [13]. The mean intake of sodium among US adults is 3,266 mg/day [14]; in 2005–2006 only 5.5 % of US adults consumed less than 1,500 mg of sodium daily [15]. The food category contributing the most sodium to the US diet was breads and rolls (7.4 %) due to the high rate of consumption of these products [14]. Additionally, 65 % is from store-bought foods, and 24.8 % comes from restaurants. These categories of foods present opportunities for intervention.

Potassium

Both observational and experimental studies have shown that potassium intake is inversely associated with BP. In a meta-analysis of five RCTs of at least 8 weeks in duration, potassium supplementation reduced SBP and DBP in three of the trials, but in the five trials, overall supplementation did not affect BP [16]. In contrast, a meta-analysis of 33 RCTs conducted from 1981 to 1995 found that potassium supplementation (from the diet in six of the studies) significantly reduced SBP by 3.11 mmHg and DBP by 1.97 mmHg [17]. It is of note that this analysis included interventions of short duration.

Another meta-analysis also found that low potassium significantly increased risk of hypertension [18]. In addition to interventions, cross-sectional epidemiological studies suggest the same result [4, 19]. Even a low dose (600 mg) of potassium can significantly reduce BP [20]. Since potassium is readily available in the food supply, it is recommended to achieve the recommended level of potassium through foods instead of supplementation.

Increasing potassium intake can have a greater effect on BP when sodium intake is high [21]. This association may be due to the increase in sodium excretion that results from increasing potassium intake. Data suggest that the sodium–potassium ratio may be more important than potassium intake alone [2, 6, 22]. Intersalt and other studies have also found a significant association of BP with the sodium–potassium ratio, the lower the sodium–potassium ratio, the lower the BP [2, 4, 17]. However, the literature does not mention an ideal ratio.

The DRI adequate intake of 4,700-mg potassium per day [12] was instituted in large part in an effort to prevent and treat hypertension. However, because of the increased risk of hyperkalemia in CKD, KDOQI recommends limiting potassium to no more than 2,000–4,000 mg/day in stages 3 and 4 [23].

Calcium and Dairy Foods

Data from the 1999 to 2004 NHANES found an inverse association between fluid milk and SBP and DBP [24]. A systematic review and meta-analysis of prospective cohort studies by Ralston et al. [25] found that consuming more low-fat dairy foods reduced risk of elevated BP (RR = 0.87). A review of milk products and BP management found that in most cross-sectional and prospective studies, dairy intake was associated with SBP [26]. An association was seen with DBP less often, and fluid milk and low-fat dairy foods were more likely to be associated with reduced BP. Results from some cross-sectional studies and RCTs examining dietary and supplementary calcium and BP have been mixed [4, 27–32]. However, two meta-analyses that examined 13 and 40 RCTs ([33] and [34], respectively) found that supplementation with an average of about 1,200-mg calcium significantly lowered SBP but not DBP. Additionally, a pooled analysis of 42 RCTs found a small BP reduction from calcium supplements and dietary calcium [35]. Dietary calcium had almost twice the reduction in BP compared to supplemental calcium, but the difference was not significant.

Some studies have shown that diets high in calcium, mostly from dairy products, have a BP lowering effect. Of greatest note, the DASH trials found that increasing low-fat dairy intake in a diet high in fruits and vegetables reduced BP even further than high fruit and vegetable intake alone [36]. However, a study that examined BP and milk intake included three treatment groups: (1) skim milk, (2) high-calcium skim milk, and (3) high-calcium skim milk enriched with potassium. Only the group consuming the high-potassium milk significantly reduced BP [37]. Any association between dairy consumption and BP may be due to calcium, but may also involve other nutrients present in milk. More studies are needed to determine the extent of the influence of calcium intake on BP.

Magnesium

Magnesium's role in vascular tone and contractility suggests that it can aid in BP reduction [38], but trials examining the effect of magnesium intake on BP have yielded inconsistent results. This may be due in part to the variety of methods used in the studies. Meta-analyses in 2012 and 2002 of trials administering magnesium supplements suggest small, but clinically significant dose-dependent

reductions in BP [39, 40]. A more recent review of magnesium supplementation in hypertension found mixed results [41]. Most of the trials that have included magnesium to date have had small sample sizes, which limit the conclusions that can be drawn from the data. As with calcium, more carefully controlled studies are needed to further elucidate any association between magnesium and BP.

Protein

A 1996 review of studies examining the association of dietary protein with BP found little or no effect of protein intake on BP among intervention studies [42]. However, some observational studies did find decreased BP with higher protein intake. Since that review, the cross-sectional Intersalt study found that total and urea nitrogen excretion, as markers of protein intake, were associated with lower BP when adjusting for age, sex, alcohol intake, BMI, and urinary sodium, potassium, calcium, and magnesium excretion [43]. The INTERMAP study suggests that the effect of protein on diet may vary depending on the type of protein. The cross-sectional study found an inverse association between vegetable protein intake and BP, but a positive association between animal protein intake and BP [19]. A prospective cohort study and a systematic review had similar findings [44, 45]. In addition, three randomized trials that found an inverse association between protein and BP increased the protein levels in the diet by adding vegetable protein [46–48]. These studies suggest that vegetable protein may be beneficial in controlling BP, but more examination is needed.

Fatty Acids

A population-based study of Japan, the People's Republic of China, the United Kingdom, and the United States found that a high intake of omega-3 fatty acids from food was associated with small but significant reductions in SBP and DBP when considering the fatty acids separately or together and across countries [49]. Three meta-analyses of RCTs administering large doses of omega-3 oils to people with hypertension found an inverse association with BP [50–52]. There was a greater effect on BP for persons 45 years or older [50]. However, there was little effect of omega-3 fatty acids on healthy adults or in trials using small doses of the oil. Although the evidence for this association is relatively strong, the potential side effects associated with consuming large doses of fish oil may be prohibitive.

Some studies suggest that monounsaturated fat can also reduce BP in people with hypertension. The OmniHeart Study examined the effects of a high-carbohydrate diet, a high-protein diet, and a diet rich in mono-unsaturated fatty acids (MUFAs) in the form of olive, canola, and safflower oils and nuts and seeds [41]. The MUFA diet lowered BP more than the high carbohydrate and had a similar effect to the high-protein diet. These and other studies [53, 54] suggest that omega-3 and MUFAs may have a beneficial effect on BP. However, most of these studies had small sample sizes and involved people with hypertension, limiting the generalizability of the results.

Vitamin C

Baseline data from a prospective study showed an inverse association between plasma vitamin C concentration and SBP [55], as have cross-sectional studies examining dietary vitamin C [56, 57]. However, this association may just be a marker for fruit and vegetable intake. Although a 2012

meta-analysis found that vitamin C supplementation significantly reduced both SBP and DBP, the reduction was small and the studies were short term [58]. One cross-sectional study divided survey respondents into four groups: high vitamin C-high fruits and vegetables, high vitamin C-low fruits and vegetables, low vitamin C-high fruits and vegetables, and low vitamin C-low fruits and vegetables (control) [59]. The women in the two high fruits and vegetables groups had lower SBP compared to the control group, but the high vitamin C-low fruits and vegetables group did not have improved BP compared to the control group. This suggests that any differences in BP may largely be due to fruit and vegetable intake, not dietary vitamin C intake. Additionally, two interventions found little difference in BP between vitamin C and placebo groups [60, 61].

The DASH Diet

The key to modifying diet to reduce BP may rest in overall dietary patterns as opposed to consumption of a single nutrient or food. The DASH studies illustrate how a dietary pattern can successfully affect BP level. The original DASH study featured three treatment arms: (1) a usual intake that mirrored the typical US diet; (2) the typical diet modified to include higher amounts of fruits, vegetables, and fiber and lower in snacks and sweets; and (3) a diet high in fruits, vegetables, and low-fat dairy foods and lower in total fat, saturated fat, and cholesterol [36]. Table 7.1 shows the components of the DASH (combination) diet. Participants ate the assigned diet for 8 weeks. At the end of the 8 weeks, participants eating the fruits and vegetables diet had SBP and DBP 2.8 and 1.1 mmHg lower than the mean BP in the control group ($p<0.001$ and $p=0.07$, respectively). The combination fruit, vegetable, and low-fat dairy diet group had SBP 5.5 mmHg and DBP 3.0 mmHg lower than the control group ($p<0.001$ for both). The effect of the diet was greater for African Americans and for those with hypertension.

The second investigation into this diet compared the control and combination (DASH) diets at three different sodium levels as described above and found that BP decreased as sodium intake decreased [7]. Consuming the DASH diet at the lowest sodium level (50 mmol/day) resulted in lowest BP. A behavioral intervention using the DASH diet (Premier) showed that it is possible to successfully incorporate the DASH dietary pattern and reduce BP in a community setting [62]. The results of these carefully controlled studies and the subsequent behavioral study show that an eating pattern can be an effective tool in reducing BP.

Table 7.1 The DASH eating plan (based on 2,000 cal diet)

Food group	Servings per day	Nutrient sources
Grains and grain products	7–8	Major sources of energy and fiber
Vegetables	4–5	Rich sources of potassium, magnesium, and fiber
Fruits	4–5	Important sources of potassium, magnesium, and fiber
Low-fat or fat-free dairy foods	2–3	Major sources of calcium and protein
Meats, poultry, and fish	2 or less	Rich sources of magnesium and protein
Nuts, seeds, and dry beans	4–5 per week	Rich sources of magnesium, potassium, protein, and fiber
Fats and oils	2–3	27 % calories as fat
Sweets	5 per week	

Taken from "Facts about the DASH Eating Plan." National Institutes of Health, Department of Health and Human Services. NIH Publication No. 03-4082. May 2003

Table 7.2 JNC 7 diet-related lifestyle modifications

Modification	Recommendation	Approximate systolic BP reduction, range
Weight reduction	Maintain normal body weight (BMI, 18.5–24.9)	5–20 mmHg/10-kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4-g sodium or 6-g sodium chloride)	2–8 mmHg
Moderation of alcohol consumption	Limit consumption to no more than two drinks per day (1-oz or 30-mL ethanol [e.g., 24-oz beer, 10-oz wine, or 3-oz 80-proof whiskey]) in most men and no more than one drink per day in women and lighter-weight persons	2–4 mmHg

Taken from ref. [63]

Table 7.3 KDOQI nutritional recommendations

	Stage of CKD	
Nutrient	Stages 1–4	
Sodium (mg/day)	<2,400	
Total fat (% of energy)	<30	
Saturated fat (% of energy)	<10	
Cholesterol (mg/day)	<200	
Carbohydrate (% of energy)	50–60	
	Stages 1–2	Stages 3–4
Protein (g/kg/day, % of energy)	1.4 (~18)	0.6–0.8 (~10)
Phosphorus (g/day)	1.7	0.8–1.0
Potassium (g/day)	>4	2–4

Reprinted with permission from ref. [23]

Dietary Recommendations for Hypertension

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) Recommendations

The importance of lifestyle modification, especially dietary change, in prevention and treatment of hypertension is well recognized. JNC 7 was written in 2003 to incorporate results from the latest hypertension studies and trials into useful guidelines for preventing and treating hypertension [63]. JNC 7 sees lifestyle modification as a critical component of hypertension management. Its dietary recommendations (Table 7.2) include losing weight if overweight or obese, reducing sodium intake to less than 100 mEq/L (2.4 g) of sodium, limiting alcohol consumption to no more than two drinks per day, and adopting the eating pattern shown to effectively lower BP in the DASH studies. The report also includes an approximate amount of reduction in systolic BP that can be achieved for each of these dietary changes. It advocates adopting more than one strategy to achieve even greater results.

KDOQI Guidelines

Dietary modification is a critical component of managing CKD. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) has guidelines for diet in hypertension in CKD (Table 7.3) [23]. With the exception of potassium and protein intake, the KDOQI recommendations

for macronutrient intake in CKD largely mirror the recommendations for the general population. The sodium recommendations are in keeping with the sodium recommendations described above. However, because of potassium retention in kidney disease, the recommended intake of 4,700 mg/day is not advisable for CKD patients, especially for those with GFR <60 mL/min/1.73 m^2. Similarly, protein intake should be lower in CKD (about 10 % of energy), especially in stages 3 and 4, to reduce the production of nitrogenous wastes and to try to slow the progression of the disease. Although the DASH diet is beneficial in lowering BP, the higher potassium and phosphorus intakes that result from the diet may lead to hyperkalemia and hyperphosphatemia, respectively, especially in patients with GFR <60 mL/min/1.73 m^2. Recommendations for adopting a DASH dietary pattern should be made with these considerations.

Summary

In summary, current evidence suggests that lowering sodium intake and increasing intake of potassium, vegetable protein, omega-3 and monounsaturated fatty acids, fruits, and vegetables can help lower BP. In CKD, however, increasing some of these nutrients and food groups, especially potassium, dairy, and protein, may be contraindicated.

References

1. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. JAMA. 2010;303:2043–50.
2. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. BMJ. 1988;297:319–28.
3. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. BMJ. 1996;312:1249–53.
4. Hajjar IM, Grim CE, George V, Kotchen TA. Impact of diet on blood pressure and age-related changes in blood pressure in the US population: analysis of NHANES III. Arch Intern Med. 2001;161:589–93.
5. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly [TONE]. Arch Intern Med. 2001;161:685–93.
6. Espeland MA, Kumanyika S, Yunis C, Zheng B, Brown WM, Jackson S, Wilson AC, Bahnson J. Electrolyte intake and nonpharmacologic blood pressure control. Ann Epidemiol. 2002;12:587–95.
7. TOHP Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992;267:1213–20.
8. Graudal NA, Hubeck-Graudal T, Jürgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride [Cochrane Review]. Am J Hypertens. 2012;25:1–15.
9. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER III, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3–10.
10. Ducher M, Fauvel JP, Maurin M, Laville M, Maire P, Paultre CZ, Cerutti C. Sodium intake and blood pressure in healthy individuals. J Hypertens. 2003;21:289–94.
11. Sanders PW. Assessment and treatment of hypertension in dialysis: the case for salt restriction. Semin Dial. 2007;20:408–11.
12. Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academy Press; 2004.
13. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary guidelines for Americans, 2010. 7th ed. Washington, DC: U.S. Government Printing Office; 2010.

14. Centers for Disease Control and Prevention (CDC). Vital signs: food categories contributing the most to sodium consumption—United States, 2007–2008. MMWR Morb Mortal Wkly Rep. 2012;61:92–8.
15. Centers for Disease Control and Prevention (CDC). Sodium intake among adults—United States, 2005–2006. MMWR Morb Mortal Wkly Rep. 2010;59:746–9.
16. Dickinson HO, Nicolson DJ, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev. 2006;(3):CD004641.
17. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997;277:1624–32.
18. Geleijnse JM, Kok FJ, Grobbee DE. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. Eur J Public Health. 2004;14:235–9.
19. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: the INTERMAP study. Arch Intern Med. 2006;166:79–87.
20. Naismith DJ, Braschi A. The effect of low-dose potassium supplementation on blood pressure in apparently healthy volunteers. Br J Nutr. 2003;90:53–60.
21. Gallen IW, Rosa RM, Esparaz DY, Young JB, Robertson GL, Batlle D, Epstein FH, Landsberg L. On the mechanism of the effects of potassium restriction on blood pressure and renal sodium retention. Am J Kidney Dis. 1998;31:19–27.
22. Huggins CE, O'Reilly S, Brinkman M, Hodge A, Giles GG, English DR, Nowson CA. Relationship of urinary sodium and sodium-to-potassium ratio to blood pressure in older adults in Australia. Med J Aust. 2011; 195:128–32.
23. National Kidney Foundation. Guideline 6: dietary and other therapeutic lifestyle changes in adults. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(Suppl 1):S115–9.
24. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr. 2008;87:1914–25.
25. Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens. 2012;26:3–13.
26. Kris-Etherton PM, Grieger JA, Hilpert KF, West SG. Milk products, dietary patterns and blood pressure management. J Am Coll Nutr. 2009;28 Suppl 1:103S–19.
27. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetiere P, Arveiler D, Amouyel P, Bingham A, Ferrieres J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. J Hypertens. 2006;24:671–81.
28. Dwyer JH, Dwyer KM, Scribner RA, Sun P, Li L, Nicholson LM, Davis IJ, Hohn AR. Dietary calcium, calcium supplementation, and blood pressure in African American adolescents. Am J Clin Nutr. 1998;68:648–55.
29. Kawano Y, Yoshimi H, Matsuoka H, Takishita S, Omae T. Calcium supplementation in patients with essential hypertension: assessment by office, home and ambulatory blood pressure. J Hypertens. 1998;16:1693–9.
30. Reid IR, Horne A, Mason B, Ames R, Bava U, Gamble GD. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. J Clin Endocrinol Metab. 2005;90: 3824–9.
31. Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. Hypertension. 1995;26(6 Pt 1):950–6.
32. Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. Hypertension. 1998;31:131–8.
33. Dickinson HO, Nicolson DJ, Cook JV, Campbell F, Beyer FR, Ford GA, Mason J. Calcium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev. 2006;(2):CD004639.
34. van Mierlo LA, Arends LR, Streppel MT, Zeegers MP, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. J Hum Hypertens. 2006;20:571–80.
35. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. Am J Hypertens. 1999;12(1 Pt 1):84–92.
36. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial on the effects of dietary patterns on blood pressure. N Engl J Med. 1997;336:1117–24.
37. Green JH, Richards JK, Bunning RL. Blood pressure responses to high-calcium skim milk and potassium-enriched high-calcium skim milk. J Hypertens. 2000;18:1331–9.
38. Cunha AR, Umbelino B, Correia ML, Neves MF. Magnesium and vascular changes in hypertension. Int J Hypertens. 2012;2012:754250. doi:10.1155/2012/754250.

39. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur J Clin Nutr. 2012;66:411–8.
40. Jee SH, Miller III ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. Am J Hypertens. 2002;15:691–6.
41. Houston M. The role of magnesium in hypertension and cardiovascular disease. J Clin Hypertens. 2011;13:843–7.
42. Obarzanek E, Velletri PA, Cutler JA. Dietary protein and blood pressure. JAMA. 1996;275:1598–603.
43. Stamler J, Elliott P, Kesteloot H, Nichols R, Claeys G, Dyer AR, Stamler R. Inverse relation of dietary protein markers with blood pressure. Findings for 10,020 men and women in the INTERSALT study. INTERSALT Cooperative Research Group. INTERnational study of SALT and blood pressure. Circulation. 1996;94:1629–34.
44. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension. 2002;39:1000–6.
45. Altorf-van der Kuil W, Engberink MF, Brink EJ, van Baak MA, Bakker SJ, Navis G, van 't Veer P, Geleijnse JM. Dietary protein and blood pressure: a systematic review. PLoS One. 2010;5:e12102.
46. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER III, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005;294:2455–64.
47. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: a randomized, controlled trial. Ann Intern Med. 2005;143:1–9.
48. Burke V, Hodgson JM, Beilin LJ, Giangiulioi N, Rogers P, Puddey IB. Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. Hypertension. 2001;38:821–6.
49. Ueshima H, Stamler J, Elliott P, Chan Q, Brown IJ, Carnethon MR, Daviglus ML, He K, Moag-Stahlberg A, Rodriguez BL, Steffen LM, Van Horn L, Yarnell J, Zhou B; INTERMAP Research Group. Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure: INTERMAP study. Hypertension. 2007;50:313–9.
50. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002;20:1493–9.
51. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation. 1993;88:523–33.
52. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, Williams B, Ford GA. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006;24:215–33.
53. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello Russo A, Marotta T. Olive oil and reduced need for antihypertensive medications. Arch Intern Med. 2000;160:837–42.
54. Lahoz C, Alonso R, Ordovas JM, Lopez-Farre A, de Oya M, Mata P. Effects of dietary fat saturation on eicosanoid production, platelet aggregation and blood pressure. Eur J Clin Invest. 1997;27:780–7.
55. Myint PK, Luben RN, Wareham NJ, Khaw KT. Association between plasma vitamin C concentrations and blood pressure in the European prospective investigation into cancer-Norfolk population-based study. Hypertension. 2011;58:372–9.
56. Bates CJ, Walmsley CM, Prentice A, Finch S. Does vitamin C reduce blood pressure? Results of a large study of people aged 65 or older. J Hypertens. 1998;16:925–32.
57. Ness AR, Khaw KT, Bingham S, Day NE. Vitamin C status and blood pressure. J Hypertens. 1996;14:503–8.
58. Juraschek SP, Guallar E, Appel LJ, Miller III ER. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012;95:1079–88.
59. Beitz R, Mensink GB, Fischer B. Blood pressure and vitamin C and fruit and vegetable intake. Ann Nutr Metab. 2003;47:214–20.
60. Fotherby MD, Williams JC, Forster LA, Craner P, Ferns GA. Effect of vitamin C on ambulatory blood pressure and plasma lipids in older persons. J Hypertens. 2000;18:411–5.
61. Block G, Mangels AR, Norkus EP, Patterson BH, Levander OA, Taylor PR. Ascorbic acid status and subsequent diastolic and systolic blood pressure. Hypertension. 2001;37:261–7.
62. Elmer PJ, Obarzanek E, Vollmer WM, Simons-Morton D, Stevens VJ, Young DR, Lin PH, Champagne C, Harsha DW, Svetkey LP, Ard J, Brantley PJ, Proschan MA, Erlinger TP, Appel LJ; PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med. 2006;144:485–95.
63. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289:2560–72.

Chapter 8
Diabetes Mellitus and Chronic Kidney Disease (Stages 1–5)

Dana Whitham and Arti Sharma Parpia

Key Points

- To describe screening procedures and identification of diabetic nephropathy.
- To integrate the goals of diabetes therapy with the progressive dietary restrictions necessary with declining kidney function.
- To clearly identify the nutrition recommendations for patients with concurrent comorbidities [diabetes mellitus (DM), chronic kidney disease (CKD), hypertension (HTN), cardiovascular disease (CVD), and to dispel any myths that remain related to the above].

Keywords Nephropathy • Diabetes • Hypoglycemia • Dialysis • Insulin • Hyperglycemia • Blood glucose

Introduction

Diabetes mellitus is a disease marked by high levels of blood glucose resulting from defects in insulin production (type 1 diabetes) or insulin sensitivity (type 2 diabetes). Symptoms of diabetes include weight loss, polyuria, polydipsia, and polyphagia. Type 2 diabetes (T2DM) represents approximately 90 % of all patients with diabetes. Risk factors for T2DM include age, genetics, ethnicity, and obesity. T2DM is a progressive condition, which generally begins with insulin resistance and an initial compensatory increase in the production of insulin by the pancreas. Over time, unless there is removal of the precipitating condition (i.e., insulin resistance), the pancreas eventually begins to lose its ability to produce the quantity of insulin required to maintain normoglycemia. The rate of pancreatic decline varies based on many factors but generally takes approximately 5–10 years to develop into diabetes.

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Table 8.1 Glycemic targets and diagnostic criteria

	ADA	AACE	IDF	CDA
Glycemic target				
A1C (%)	<7.0[a]	≤6.5	<6.5	≤7.0[b]
Fasting glucose (mg/dL)	90–130	<110	<100	72–126
Postprandial glucose (mg/dL)	<180	<145	<145	90–180 (90–144 if A1C targets not met)
Diagnostic tests				
Fasting glucose (mg/dL)	≥126	≥126	≥125	≥126
Casual plasma glucose	≥200	≥200	≥200	≥200
2-h plasma glucose	≥200	≥200	≥200	≥200
A1C (%)	≥6.5	n/a	≥6.5	≥6.5

Adapted from ADA: American Diabetes Association; AACE: American Association of Clinical Endocrinologists; IDF: International Diabetes Federation; CDA: Canadian Diabetes Association

[a]May be individualized to target 6.5–8.0 %

[b]May be individualized to target 6.5 %–8.5 %

In the case of T2DM, symptoms of diabetes are usually rare or mild and can often be overlooked. As such, many individuals with T2DM have already developed complications by the time they are diagnosed with the disease. From that point onwards, the production of insulin from the pancreatic beta cells continues to decline over the course of the disease. Although T2DM is a chronic, progressive disease, steps can be taken to control the disease and to lower the risk of associated complications. Today, almost 26 million people (8 % of the population) in the United States have diabetes, and due to the chronic nature and frequently overlooked symptoms listed above, nearly one-third are unaware that they have the disease [1]. An estimated 79 million people have prediabetes [1]; a condition characterized by insulin resistance that results in an above normal blood glucose reading without meeting the cutoffs for the diagnosis of diabetes (Table 8.1).

Type 1 diabetes (T1DM) is an autoimmune disease in which the destruction of the pancreatic beta cells results in an absolute insulin deficiency [2]. Type 1 represents approximately 10 % of the patient population and its onset is usually acute and at a younger age.

It is estimated that 174 billion dollars is spent in the United States on diabetes and its complications [1]. Diabetes is the leading cause of kidney failure, accounting for 44 % of new cases of end-stage renal disease (ESRD). Diabetes is also the leading cause of blindness, nontraumatic lower limb amputation, and a large component of vascular disease. In people with T2DM, the presence of hypertension (HTN) generally comes before kidney disease and is in large part a factor in its development. In T1DM, the presence of HTN is usually a result of chronic kidney disease (CKD). Early intervention to promote optimization of glycemic control and blood pressure is important to slow the progression of CKD [2–4].

Pathophysiology of Diabetic Nephropathy

Persistent hyperglycemia leads to the development of nephropathy via several mechanisms, including glomerular hypertrophy, increased glomerular permeability to proteins, and increased matrix protein synthesis. Hyperglycemia causes an increase in vasodilatory prostaglandins, which promote an increase in renal perfusion and intra-glomerular pressure, resulting in initial hyperfiltration [5]. There is a direct correlation between elevated blood pressure and the degree of decline in the glomerular filtration rate

(GFR). Alterations of hemodynamic factors produce increases in mesangial matrix formation and basement membrane thickening. Higher systolic blood pressure (SBP) specifically leads to extracellular matrix accumulation, increased glomerular permeability, proteinuria, and glomerulosclerosis [5]. Risk factors for the incidence and progression of diabetic nephropathy include hyperglycemia, HTN, elevated total and low-density lipoprotein (LDL) cholesterol and cigarette smoking [2]. Observational studies have demonstrated an association between elevated levels of serum phosphorus and the progression of CKD but no clinical trials have been completed to confirm a causal link [6].

In addition to the above factors, there appears to be a genetic susceptibility in both T1DM and T2DM to both the incidence and severity of diabetic nephropathy [7–9]. The increase in risk may be associated with an abnormal sodium handling by the kidney and the presence of HTN. The incidence and severity of diabetic nephropathy is increased in Mexican Americans and Pima Indians and is three- to sixfold higher in African Americans compared to Caucasians [10–12], further suggesting a role for genetics in addition to diet, lifestyle, obesity, and other socioeconomic factors on the incidence and progression of nephropathy. A high BMI has been associated with increased incidence of diabetic nephropathy and weight loss has been shown to reduce proteinuria in patients with CKD [13]. Nonetheless, weight loss would also positively impact HTN and hyperglycemia therefore making any direct links between weight status and CKD difficult to determine.

The earliest clinical evidence of nephropathy is often the appearance of urinary albumin (>30 mg/day). Persistent albuminuria in the range of 30–300 mg/day is frequently the earliest stage of nephropathy and a marker for the development of ESRD in diabetes. At this point, without specific interventions, approximately 20–30 % of people with T1DM will develop albuminuria (>300 mg/day) within 15 years of diagnosis, but with tighter glycemic control and intensive blood pressure management, less than half will progress to overt nephropathy [14, 15]. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial, which compared intensive blood glucose to conventional control, less than 2 % of the intensively treated patients developed renal insufficiency (defined as serum creatinine >2.0 mg/dL or renal replacement therapy [RRT]) over an average 30 years of diabetes duration [16]. Evidence is available to support that the renal risk is equivalent in the two types of diabetes and that the lower prevalence of ESRD seen in T2DM is due to a later disease onset and thereby shorter duration of exposure. High rates of comorbidities and other diseases in people with T2DM may also shorten the lifespan and thus impact prevalence [17, 18]. In people with T2DM, 20–40 % will progress to overt nephropathy (defined as albuminuria >300 mg/day) but by 20 years duration only 20 % will have progressed to ESRD [7].

The gold standard for determining albuminuria remains the 24-h collection; however, due to frequent collection errors, not to mention the burden to the patient, it is not a test frequently completed. In years past, a urine dipstick for albumin was conducted, however, because urinary albumin excretion can vary mildly with exercise and volume dilution, and largely with infection, fever, marked hyperglycemia, and HTN [2], an alternate method called the albumin creatinine ratio (ACR) was accepted. The ACR is now the most common test used for screening. Creatinine is freely filtered by the kidney while albumin varies according to urine concentration, therefore, by using a ratio, a consistently reproducible test that corrects for urine concentration can easily be done with a spot urine sample. Individuals with diabetes should be screened for nephropathy using the ACR annually (after at least 5 years of disease for those with T1DM) [2]. Monitoring albuminuria annually can also help assess response to drug therapy and to lifestyle modification steps taken towards achieving blood pressure and glycemic targets.

According to the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines [19], staging of CKD is done according to six categories of GFR (G stages), and three categories of albuminuria (A stages). See Table 8.2 for classification of the stages. GFR is expressed as mL/min per 1.73 m^2 and albuminuria expressed as the ACR. As GFR decreases and ACR increases, there is a continuous

Table 8.2 Classification of stage of CKD

GFR stages	GFR (mL/min per 1.73 m^2)	Relative kidney function
G1	>90	High or optimal
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure (G5d if on dialysis)
Albuminuria stages	*ACR (mg/mmol)*	*Terms*
A1 <30 mg/day	<3.0	Normal to mildly increased
A2 30–300 mg/day	3–30	Moderately increased
A3 >300 mg/day	>30	Severely increased

Adapted from KDIGO Composite Ranking for Relative risks by GFR and Albuminuria; 2012, KDOQI 2002, and CDA 2008

association with risk for mortality and adverse kidney outcomes. The staging system for CKD is designed to help identify patients who are at greatest risk for progression and complications of kidney disease.

Decreased GFR can occur in the absence of albuminuria in a substantial number of adults with diabetes; therefore, serum creatinine should be measured at least annually to estimate GFR and the stage of CKD in all adults with diabetes, regardless of the degree of albuminuria [2]. GFR is most frequently estimated using the Modification of Diet in Renal Disease (MDRD) study equation; however, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been shown to be more accurate, especially at higher levels of GFR, and is slowly replacing the MDRD study equation [20, 21]. Both equations contain factors such as age, sex, race, and serum creatinine. Estimated GFR can be calculated by using the MDRD and CKD-EPI equations at the following website: www.kidney.org/professionals/kdoqi/gfr.cfm

Albuminuria is also used as a marker for increased cardiovascular morbidity and mortality as the presence of albuminuria doubles the risk in those with T2DM and highlights the need for screening and aggressive interventions aimed at reducing cardiovascular disease (CVD) risk [2, 22, 23].

Advanced glycation end-products (AGEs) are heterogeneous compounds considered to promote inflammation and oxidation, and have been correlated with risk factors for vascular damage seen in diabetes and CVD [24]. Accumulation of AGEs has been seen in conditions of oxidative stress, such as hyperglycemia and uremia. In fact, AGE compounds exist in patients who are uremic at up to ten times normal levels. In patients with diabetic nephropathy, AGEs have been associated with diabetic vascular complications, atherosclerosis, and a higher prevalence of cardiovascular and cerebrovascular problems. AGEs have also been associated with structural renal changes, which may lead to the progression of renal disease. Further studies are needed to confirm a causal relationship between AGEs and adverse outcomes. Cooking methods that require very high temperatures, such as frying, broiling, and grilling, lead to the formation of dietary AGEs [25]. Studies have shown that altering food preparation methods can decrease serum levels of AGEs, as well as biomarkers of oxidative stress and inflammation. Furthermore, a randomized study showed that restricting dietary AGEs improved insulin resistance in diabetic patients [199]. Examples of how to decrease dietary sources of AGEs include using water during cooking (i.e., stewing), using acidic marinades for foods (i.e., lemon juice and vinegar), and increasing consumption of raw, unprocessed foods that are naturally low in AGEs (i.e., fruits and vegetables). Further studies are needed to determine whether a reduction in dietary and serum AGEs leads to improvements in renal and cardiac outcomes.

Goals of Therapy

The goals of therapy can be divided into three main categories: (1) The prevention of microvascular complications including retinopathy, nephropathy, and neuropathy; (2) the prevention of macrovascular complications of diabetes including CVD, stroke, and peripheral vascular disease; and (3) the management and prevention of acute complications of poor glycemic control including hypoglycemia and the hyperglycemic conditions of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Conventional management strategies include treatment to target blood glucose, blood pressure, and lipids. Many studies both large and small have attempted to determine the effects of intensive BG, blood pressure (BP), and lipid lowering on both micro- and macrovascular complications in either those with T1DM or T2DM (newly diagnosed or those at high risk of complications).

Microvascular Complication Prevention

Two main trials guide practice related to microvascular disease, namely, the Diabetes Control and Complications Trial (DCCT) in people with T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) in those with T2DM. When examining the data related to nephropathy, the DCCT showed that intensive glycemic control (achieved A1C = 7.0 % compared to 9 %) resulted in fewer incidences of diabetic nephropathy [26]. The development of albuminuria was reduced by one-third, and in those with preexisting albuminuria, the risk of progressing to overt proteinuria was reduced by 54 % [2, 3, 26]. Intensive therapy was defined as three or more insulin injections per day or insulin pump, frequent self-monitoring of blood glucose (SMBG) and using principles of pattern management to adjust insulin doses. Participants also used carbohydrate counting to determine the insulin dose with meals.

The UKPDS had a similar design, evaluating the impact of intensive vs. conventional control in the management of T2DM. There were two arms to the trial, one an intensive glucose arm (achieving an A1C of 7.0 % vs. 7.9 % in the control) and the second being an intensive blood pressure arm. With respect to blood glucose, the UKPDS found that patients with T2DM had a 25 % reduction in nephropathy with intensive diabetes therapy and for every percentage point decrease in A1C, there was a 35 % reduction in the risk of complications [2, 4, 27]. The UKPDS also highlighted the importance of tight blood pressure control (<144/82 mmHg) on the prevention of nephropathy [28]. In general, for every 10 mmHg reduction in SBP, there was a 12 % drop in the risk for any diabetes-related complication [29].

Macrovascular Complication Prevention

The initial 10-year UKPDS trial demonstrated a nonsignificant trend towards reduction in macrovascular disease with intensive glucose control; however, a statistically significant 15 % reduction was only found when study subjects were followed over an additional 10-year period [30]. The 15 % reduction for every 1 % improvement in A1C was also demonstrated in a meta-analysis examining the effect of blood glucose control on nonfatal myocardial infarction (MI) [31]. Unlike the UKPDS, no significant benefits were seen for stroke or all cause mortality. Based on the suggestion that progression of macrovascular disease occurs even at prediabetes glucose levels [31], and that tight glucose control might be even more critical in those at higher risk, a series of trials were completed to determine the impact of further intensified glucose control on CVD risk. The Action to Control

Cardiovascular Risk in Diabetes (ACCORD), trial attempted to determine the impact of essentially normalizing glycemic control (target A1C of 6.0 or 6.5 %) on cardiovascular end points in older patients with established T2DM. In 2008, the ACCORD trial failed to demonstrate a positive impact of a target A1C of 6 % on cardiovascular end points and instead the trial was brought to an early end due to a 22 % increase in mortality for those in the intensive interventional arm [32]. Other trials also failed to demonstrate a benefit in the lower A1C target of 6–6.5 % on cardiovascular end points in older individuals with established T2DM [33, 34]. These data suggest that patients without overt CVD or risk, shorter duration of diabetes, and lower initial A1C levels are those that may benefit the most from intensive glucose control.

BP targets remain a point of continued discussion as there are little to no data to support aiming for SBP of less than 140 mmHg. The UKPDS found a significant reduction in macrovascular disease in patients with T2DM randomized to tight blood pressure control (target SBP <150 mmHg; achieved SBP <144 mmHg). The ACCORD trial again tried to determine the impact of further reductions in blood pressure and randomized 4,733 patients to intensive (target BP less than 120 mmHg) or standard treatment (target BP to less than 140 mmHg) on cardiovascular events in high-risk individuals with T2DM. Over a 5-year duration, there were no significant differences on CV outcomes or death from any cause between the intensive and standard groups. Total and nonfatal stroke was the only secondary outcome that was significantly impacted with a more intensive approach to BP management [35].

Studies have demonstrated that it is important not only to reduce the systemic blood pressure but also to specifically reduce in intra-glomerular pressure. Treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) are effective at reducing intraglomerular pressure as well as other local renin-angiotensin-aldosterone system (RAS)-mediated effects and subsequently the decline in kidney function, independent of any additional systemic blood pressure lowering effect [23]. There is no evidence to suggest that dual blockade of the RAS has additional benefit over one agent alone and this approach is not recommended in most cases [36].

The UKPDS trial also demonstrated what is now known as the legacy effect, in that those who achieved tight glycemic control early on in their disease course maintained improvements over a longer time period. The theory is that early intervention allows the beta cells of the pancreas to rest and slows the decline of insulin production. Because of these data, it is now recommended that intensive diabetes management with the goal of achieving near normal glycemia, blood pressure, and lipid targets be implemented as early as possible using a physician-coordinated collaborative and integrated health-care team approach [37]. Careful attention to the relationship between diet, medication, and physical activity is necessary to achieve A1C goals without the undesired hypoglycemia and weight gain seen impediments of tight glycemic control. Variations in intake and activity levels, often explain erratic blood glucose results and episodes of hypo- and hyperglycemia [38].

The above trials were key in the development of the evidenced-based recommendations related to glycemic control [39]. The KDIGO guidelines recommend a target A1C of less than 7 % to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. In addition, individuals in CKD stages 1-4 with co-morbidities, limited life expectancy or at high risk for hypoglycemia can target an A1C that exceeds 7 % [200]. Current American Diabetes Association (ADA) recommended targets include an A1C of less than 7 % [2] with individualization down to a target of 6.5 % or up to 8 % depending on duration of disease, life expectancy, complications, risk of hypoglycemia, and other comorbidities. See Table 8.1 for a comparison of the recommendations. The ADA and the European Association for the Study of Diabetes (EASD) advocates that glycemic control be individualized. Patients with special considerations, such as children, pregnant women, the elderly, or those with advanced chronic diseases, may require less or more intense goals for glycemic control [2].

Treatment efficacy can be assessed by performing an A1C test, which measures a patient's average glycemia over the preceding 2–3 months. The KDOQI work group suggests using standards set by the ADA when evaluating glycemic control in patients with CKD [40]. The A1C test should be

done quarterly in patients whose therapy has changed or who are not meeting blood glucose goals. In patients who are meeting treatment goals and who have stable blood glucose control, the A1C test should be performed at least twice yearly [2]. The limitations of A1C should be taken into consideration when monitoring glycemic control in patients with CKD, since this value may be reduced due to the shortened lifespan of erythrocytes and the presence of anemia [40]. Estimated average glucose (EAG) levels may be helpful in late stage CKD to better manage patients with declining kidney function. See http://professional.diabetes.org/GlucoseCalculator.aspx for conversion of EAG to approximate A1C levels.

Currently, it is estimated that among adults diagnosed with diabetes, 12 % take insulin only, 14 % take insulin and oral medications, 58 % take oral medications only, and 16 % follow lifestyle management with no insulin or oral medications [1]. Drug elimination occurs via the liver or the kidney and as a result, fluctuations in blood glucose levels can also occur due to alterations in insulin and medication metabolism with changing kidney function. Because of the reduced clearance, caution is required to ensure appropriate dosing. As CKD progresses, patients should be aware of the signs and symptoms of hypoglycemia and how to treat it [35]. Studies have shown that insulin reductions of up to 25–40 % may be necessary with moderate to severe kidney impairment [41]. Reduced kidney mass also decreases renal gluconeogenesis, which can compromise the ability of a patient to defend against hypoglycemia [40]. In summary, the management goals for CKD prevention include RAS blockade and treatment to target blood pressure, cholesterol, blood glucose, proteinuria, and dietary management.

Hypertension Management

Tight blood pressure control plays an important role in the treatment and prevention of diabetic nephropathy [3]. In patients with TIDM, the onset of HTN is frequently associated with the development of diabetic nephropathy. It is estimated that 65 % of patients with T2DM also have HTN, which is often present as part of their cardio-metabolic risk. Micro- and macrovascular complications of diabetes are exacerbated when HTN is present as a comorbidity [42]. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) and the ADA set a target blood pressure goal of <130/80 mmHg for patients with diabetes and kidney disease based on the findings of several large, randomized trials [2, 43]. Use of either ACEI or ARBs is routinely recommended because of their additional reno-protective effects. Of note, however is that in people with diabetes using ACE inhibitors or ARBs, drug associated hyperkalemia may occur at earlier stages of CKD than that traditionally seen in nondiabetic individuals. Due to the nephrotoxic effects of high dietary sodium intake, such as worsening albuminuria and increased blood pressure, the KDIGO guidelines recommend a sodium restriction of <90mmol/day (<2g) in CKD patients stages 1–4 [200]. The KDOQI Guidelines on Hypertension in CKD recommend the Dietary Approaches to Stop Hypertension (DASH) diet for patients with CKD stages 1–2 [44]. The DASH diet in generally not recommended for patients with a GFR <60 mL/min, due to its higher protein, phosphorus and potassium content [44]. Refer to Chap. 7 for more detail.

CVD Risk Management

While cardiovascular death rates have improved over the past decade, heart disease and stroke are still responsible for about 65 % of deaths in people with diabetes [2, 45]. According to the National Cholesterol Education Program (NCEP), patients with diabetes should achieve LDL-C levels less than 100 mg/dL [46]. Lifestyle strategies include a diet low in saturated fat, trans fat, and cholesterol.

The use of viscous fiber, n-3 fatty acids, plant sterols, and stanols, weight loss (if indicated) and physical activity is also recommended. Attention is then focused on achieving the secondary targets, namely TG less than 150 mg/dL, HDL-C greater that 40 mg/dL in men and greater than 50 mg/dL in women, and non-HDL less than 130 mg/dL [45]. Lipids should be screened at diagnosis and at least annually [2]. Refer to Chap. 7 for further information.

Medical Nutrition Therapy

Medical nutrition therapy is an integral component of diabetes management and in the context of CKD as a comorbid factor. Interventions should strive to balance the benefits of carbohydrate distribution and type with the need for dietary restriction of potassium, sodium, and phosphorus. General goals of medical nutrition therapy for diabetes to prevent acute and long-term complications include [2]:

1. Maintenance of target blood glucose levels by balancing food intake, activity level, and available insulin with stage of kidney function (caution for increasing risk of hypoglycemia as CKD advances and both medication clearance and dietary intake might be affected)
2. Achievement of optimal serum lipids and blood pressure to reduce the risk of CVD and for impact on progression of nephropathy
3. Adequate energy and protein intake to attain or maintain an acceptable body weight (BW) and nutritional status
4. Achievement of biochemical parameters and fluid status within defined standards

All nutrition goals should be considered within the context of patient-centered care including lifestyle, personal and cultural preferences, financial situation, and respect for the individual's willingness to make changes. Monitoring blood glucose, A1C, lipids, blood pressure, kidney function, and other biochemical parameters are essential to evaluate nutrition-related outcomes. If goals are not met, changes must be made in the overall management plan. The role of the dietitian is to help patients learn a problem-solving approach that evaluates diet as one of many factors that impact these goals [47].

Energy Needs and Weight Management

Among patients with diabetes, there is an association between obesity and risk for CKD. The KDOQI clinical practice guidelines for diabetes and CKD suggest that a normal BMI (15.5–24.9 kg/m^2) may reduce the risk of loss of kidney function and CVD [40]. Factors that may contribute to the relationship between obesity and CKD include physical compression of the kidneys by visceral obesity, renin-angiotensin system activation, hyperinsulinemia, and glomerular hyperfiltration, among others [40]. For overweight individuals with T2DM in Stages 1–3 CKD (Stage 1–2 for albuminuria ± GFR stage of 2–3a), moderate weight loss of 5–10 % improves insulin sensitivity, glycemic and blood pressure control, and proteinuria [13, 48–50].

The primary approach for achieving weight loss is therapeutic lifestyle change, which includes a moderate reduction in energy intake (500–1,000 kcal/day) and a moderate increase in physical activity (contributing approximately 200 or more kcal/day), which should result in a slow but progressive weight loss (1–2 lb/week) [2, 40]. The goal would be to mitigate loss of lean body or bone mass through use of an energy controlled, balanced, and slow approach to weight loss. Diets centered on food group exclusion or those that are overly restrictive carry the risk of excessive lean body mass (LBM) loss, nonadherence, and relapse. Furthermore, individuals with CKD and diabetes should use caution with low-carbohydrate/high-animal protein diets (>20 % of total daily calories) such as

Atkins, Protein Power, the Zone, South Beach, and Sugar Busters [40]. The Institute of Medicine (IOM) defines a low-carbohydrate diet as a restriction of total CHO to <130 g/day [51]. The efficacy and safety of low-carbohydrate diets in recent studies has led to a change in the recommendations related to the use of such diets. Updated recommendations promote weight loss through either a traditional low-fat calorie restriction or through the short-term (<2 year) use of a low-carbohydrate calorie-restricted diet. Recommendations include the careful monitoring of lipids, renal function, protein intake in those with nephropathy and attention to adjustment of anti-hyperglycemic therapy [2]. Greater adherence to weight loss diets is associated with greater weight loss and improvements in metabolic markers [52]. The weight loss plan should be selected with consideration for individual preferences, likely adherence, treatment goals, and long-term risk vs. benefit.

Recommendations for physical activity should be modest and based on the patient's willingness and ability. The ADA guidelines recommend a goal of at least 150 min/week of moderate intensity activity (50–70 % maximum heart rate) over at least 3 days/week. Resistance exercises three times per week are also encouraged [2, 53]. It is important to monitor blood glucose levels before exercising in people with T1DM because vigorous exercise could lead to hypo- or hyperglycemia, depending on the initial blood glucose levels and type of exercise. For planned exercise, a reduction in insulin dosage is the preferred method to prevent hypoglycemia. However, for unplanned exercise, an additional 10–15 g of CHO may be needed for every 60 min of moderate intensity exercise [53]. A greater amount of carbohydrate is required with more intensive exercise.

At all stages of CKD, a primary goal for MNT is to prevent protein and energy malnutrition (PEM), which increases the risk of poor clinical outcomes, morbidity, and mortality [54]. Uremia-associated anorexia is generally not seen until the later stages of CKD [55]; however other factors such as inflammatory cytokines and depression may also induce anorexia. The Academy of Nutrition and Dietetics (AND) guidelines for CKD in non-dialysis patients recommends 23–35 kcal/kg body weight (to prevent malnutrition) [56]. The NKF KDOQI Nutrition guidelines for Stage 4 CKD recommend a similar high caloric intake with 30–35 kcal/kg/day for individuals >60 years of age and 35 kcal/kg/day for those <60 years of age, using standard body weight (SBW) based on the second National Health and Nutrition Examination Survey data (NHANES II) [40]. In a review of emerging research since the year 2000, and after evidence-based guidelines were published, overall, non-dialyzed patients with CKD seem to have lower energy requirements in comparison to both healthy controls and maintenance dialysis patients [57, 58]. Suggested reasons for the depressed resting energy expenditure (REE) in non-dialyzed CKD patients include an adaptive response to low energy intake, impaired energy metabolism of skeletal muscle and impaired glucose oxidation. Comorbidities, including diabetes, may have a modest impact on increasing energy expenditure. Only one study by Avesani et al. [59] tried to determine whether the measured resting energy expenditure (MREE) of non-dialyzed patients with CKD ($n=24$) differed from that of non-dialyzed patients with CKD and diabetes ($n=24$, with only three T1DM). The MREE was based on indirect calorimetry using a metabolic cart. Outcomes showed that CKD patients with diabetes had higher MREE (12.5 % higher) than those without diabetes, with significant correlations to LBM and creatinine clearance. Multiple regression analysis showed that having diabetes added 182 kcal to the REE. Dietary energy intakes were not significantly different between those with diabetes (mean 23.4 ± 5.4 kcal/kg/day) and those CKD patients without diabetes (mean 24.8 ± 6.9 kcal/kg/day). Data related to the actual energy requirements in the pre-dialysis population are limited, but seem to suggest that the actual needs are much lower than that suggested by the guidelines. Analysis of the validity of prediction equations in this population is also limited. A recent study by Kamimura et al. [60] concluded that the Harris Benedict equation accurately predicted REE in patients with diabetes, when compared to indirect calorimetry as the standard. Interestingly, in CKD patients without diabetes, the Harris Benedict equation has been shown to significantly overestimate REE [60] although no studies have been completed on patients with diabetes and CKD. As a result, the Harris Benedict equation and the suggested 30–35 kcal/kg/day can be used to determine energy requirements, although both may tend towards overestimation in this patient population.

Dietary Strategies for Carbohydrate (CHO) Management

Careful management of CHO intake is essential to any diabetes meal-planning approach and focuses on distributing carbohydrate load throughout the day. Many dietary strategies can be used to achieve carbohydrate consistency, and the registered dietitian is well qualified to match the appropriate meal-planning strategy to each patient's lifestyle and capabilities.

A "constant carbohydrate" meal plan suits patients who use diet alone to control their blood glucose levels, those on fixed doses of insulin or oral diabetes medications, or patients who are not suitable for carbohydrate/exchange counting. Emphasis is placed on keeping the amount of CHO relatively constant for each meal, spacing meals throughout the day and maintaining consistency in meal timing and activity levels. Insulin should be adjusted around usual CHO intake as much as possible rather than CHO being altered to meet the insulin regimens. Some modifications in food choices may be needed to accommodate sodium, potassium, and phosphorus restrictions.

The "carbohydrate counting" method provides the most flexibility and is the preferred meal-planning approach for adjusting insulin around usual dietary intake. Initially, careful record-keeping by reading food labels and measuring portion sizes for CHO foods combined with both pre- and post-meal blood glucose readings is essential until an accurate ratio of insulin to grams of CHO (I/C ratio) is established. Once established, the patient counts the grams of available CHO to be eaten and then matches it with the proper amount of insulin. Ideally, blood glucose readings should be taken before each meal and the insulin dose decided based on the amount of carbohydrate to be consumed, the blood glucose reading at that time and based on any recent or upcoming activity. This concept requires motivation, skill in carbohydrate counting, and self-reflection to examine whether the patient's decisions on insulin dosing were correct. It is important to consider healthy eating with a balance of protein, fat, and other micronutrients so as to avoid excess energy intake and undesired weight gain at the expense of tight blood glucose control. Individuals who have pre-meal glucose values within target range but who are not meeting A1C targets should consider monitoring 2-h postprandial glucose (PPG) after the start of the meal. Treatment should be aimed at reducing PPG values to <180 mg/dL and thereby comparably reducing A1C [2].

Another means of either maintaining carbohydrate intake or counting carbohydrates is to use an Exchange List for Meal Planning [61]. Foods are categorized into food groups with similar amounts of CHO, protein, fats, and calories. Foods within each group (e.g., carbohydrate exchanges) can be traded, depending on the amounts consumed. Although the exchange lists can provide structure and a high degree of metabolic control, they also are complex and complicated for some individuals to understand.

Carbohydrates are an essential source of energy for optimal functioning of the brain and central nervous system and for exercise performance. Carbohydrates are the main source of dietary fiber and they supply important water-soluble vitamins, minerals, and other phytochemicals and antioxidants important for good health. The ADA recommends that CHO be derived primarily from whole grains, fruits, and vegetables, and non- or low-fat dairy products [2]. With decreasing kidney function however, food choices and portions may need to be adjusted based on serum potassium and phosphorus levels. Dietary guidelines for diabetes are often liberalized on the renal diet to provide adequate calories. See Fig. 8.1 for treatment algorithm.

Glycemic Index

Controlling high postprandial blood glucose levels is an ongoing challenge in diabetes management. People spend the majority of their day in a postprandial state and it is imperative for optimal glycemic control that they achieve target readings post meal [62]. Both the quantity and the quality of CHO

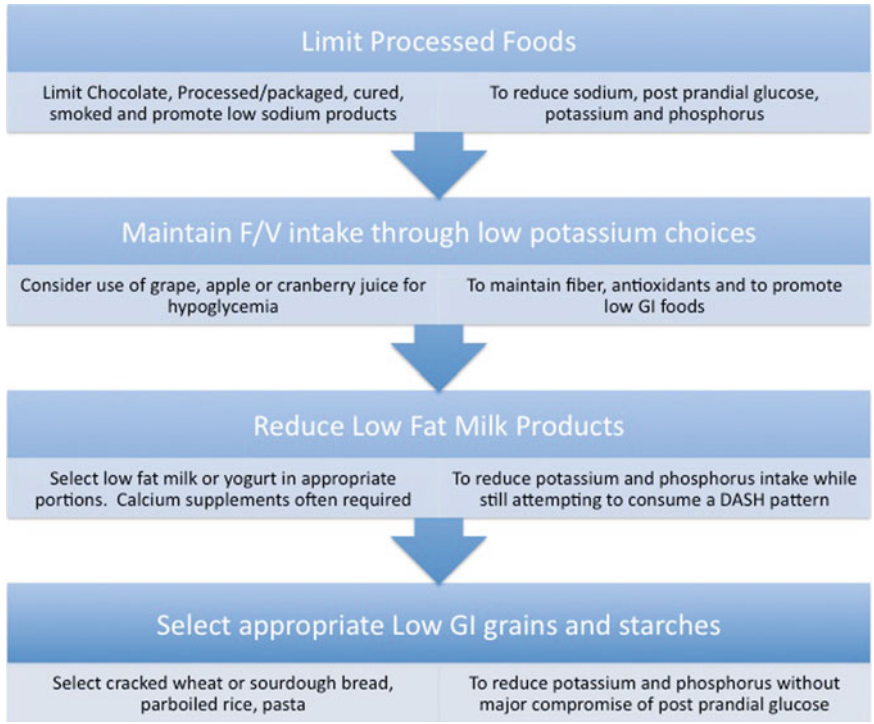

Fig. 8.1 Stepwise restriction protocol for MNT of diabetes complicated by CKD

found in foods influence PPG levels. Most experts agree, and the ADA's position is, that the evidence for total CHO intake from a meal or snack is a more reliable predictor of PPG [53, 63] and that the quality of carbohydrate has a smaller but still significant effect. The main method to categorize CHO-containing foods based on their glycemic response is the glycemic index (GI) [53, 63]. Significant improvements in postprandial glucose, total cholesterol, and markers of inflammation have been demonstrated in clinical trials [41, 64–66] using low-GI diets.

The GI ranks CHO foods based on the effect on postprandial glycemia. Some foods result in a marked increase followed by a more or less rapid fall in blood glucose, whereas others produce a smaller peak along with a more gradual decline in plasma glucose [53, 63]. Low-GI foods such as pasta, parboiled rice, barley, oats, beans, peas, lentils and pumpernickel, rye or whole grains breads are recommended in place of higher GI foods to aid in the management of postprandial glucose. The specific type of CHO (starch vs. sucrose) present in a particular food does not always predict its effect on blood glucose [41]. Foods ingested in 50 g portions are quantified in comparison to a reference food, either glucose or white bread, and the increase in blood glucose (over the fasting level) that is observed after 2 h determines the GI value for that food.

The GI of a food varies substantially depending on the CHO make up of the food, the length of time it was stored, how it was cooked, how it was processed, the acid content of the food, its ripeness and its variety (e.g., types of potatoes or rice) [41, 63, 64]. As such, to maintain the GI as low as possible, individuals should be counseled to cook pasta al dente and to choose foods that are less processed.

The International Tables of Glycemic Index [75], can be useful when a potassium or phosphorus restriction is warranted in the face of CKD. First, a number of highly processed convenience foods may be removed. Most fruit and vegetables are low GI (ranging from 55 or less on the glucose

references range); therefore, the second step towards reducing an elevated potassium level would be to examine the fruit and vegetable intake for modifications. Third, while most milk products are low GI, excessive intakes may lead to hyperkalemia. Reductions below the recommended intake may be necessary and as such calcium supplementation may be required. Lastly, many starches and grains contain varying levels of potassium and phosphorus and the GI list can assist in selecting foods that are low in potassium and phosphorus but also lower on the GI. Some examples include cracked wheat bread, sourdough bread, and parboiled rice. See Fig. 8.1 for a stepwise protocol. Alternatively, the addition of an acid source such as lemon juice or vinegar to a meal may assist with slowing gastric emptying and lowering the overall GI of the meal.

In summary, there appears to be a small but significant effect from a low-GI diet over a high-GI diet, primarily on PPG. The GI concept can be used as an adjunct to help "fine-tune" glycemic control and to provide some assistance on managing postprandial glucose levels in the face of a restricted diet.

Fiber

Fiber intake should be encouraged within the constraints of the progressing renal diet. High-fiber diets (50 g fiber/day) have been shown to reduce glycemia in subjects with T1DM and T2DM and to reduce hyperinsulinemia and lipemia in subjects with T2DM [53, 63] through delaying gastric emptying. Potential barriers to achieving such a high-fiber intake include gastrointestinal side effects and the high potassium and phosphorus content of high-fiber grains, fruits, and vegetables. The ADA position as a first priority encourages people with diabetes to aim for the same fiber intake goals set for the general population (14 g/1,000 kcal/day) [63]. Others recommend slightly higher intakes than that recommended for the general population (15–25 g/1,000 kcal) [67]. Where possible, fiber intake can be sought from increases in low-potassium fruits and vegetables and through the use of fiber supplements (Table 8.3).

Protein Guidelines for Diabetes and CKD

There is no evidence to suggest that protein needs in diabetes are different than that of the general population. Although glucose is the primary stimulus for insulin release, protein/amino acids enhance insulin release and thus when distributed throughout the day, have been shown to have an overall effect on the clearance of glucose from the blood [53, 63, 68]. As such, achieving ideal but not excessive protein intakes well distributed throughout the day are encouraged. The 2013 KDIGO guidelines for CKD suggest:

Lowering protein intake to 0.8 g/kg/day in adults with diabetes and a GFR <30 ml/min/1.73m^2 as well as the recommendation to avoid high protein intakes (>1.3 g/kg/day) in adults with CKD at risk of progression.

This is a change from previous KDOQI guidelines which recommend persons with diabetes consume a dietary protein intake of 0.8-0.9 g/kg/day, with at least 50% being from high biological value sources such as animal protein, soy and vegetable-based proteins. The KDIGO work group concluded that excess dietary protein leads to the accumulation of uremic toxins [200].

The benefits of limiting dietary protein intake are more evident in T1DM than in T2DM, but that may be due to fewer studies having been done in the latter population. Based on meta-analyses, low-protein diets had more pronounced benefits in diabetic than nondiabetic kidney disease [69, 70].

Table 8.3 Low potassium sources of fiber

Food item	Serving size	Amount of fiber (g)	Amount of potassium (mg)
Fruits			
Pear (with skin)	1 Medium	5.0	198
Raspberries	½ Cup	4.2	98
Blackberries	½ Cup	4.0	123
Apple (with skin)	1 Medium	2.6	148
Blueberries	½ Cup	2.0	59
Strawberries	½ Cup	1.7	117
Vegetables			
Green peas, canned, drained	½ Cup	4.0	93
Mixed vegetables, boiled	½ Cup	2.8	163
Carrots, boiled	½ Cup	2.2	194
Asparagus	6 Spears	1.8	202
Green and yellow snap beans, boiled	½ Cup	1.6	96
Cauliflower	½ Cup	1.5	93
Cabbage, boiled	½ Cup	1.3	155
Grains			
Popcorn, air popped	2 Cup	2.4	56
Whole wheat pasta, cooked	½ Cup	2.4	33
Cracked wheat bread	1 Slice	1.9	62
Instant cream of wheat	1 Cup	1.2	36

Created by authors
Source: Health Canada. The Canadian nutrient file, 2010 version. Ottawa, ONT. Available from www.healthcanada.gc.ca/cnf. Accessed October 24, 2012

Even modest limitations of dietary protein (0.89 g/kg BW/day vs. 1.02 g/kg BW/day) substantially reduced the risk of progressing to ESRD or death in persons with T1DM initially at stage 2 CKD [71]. A recent Cochrane systematic review, based on 12 studies, concluded that protein restriction has a small, nonsignificant effect on slowing the progression of diabetic nephropathy [72]. Prior to the widespread use of RAS blockade agents, protein restrictions were found to significantly reduce proteinuria; however in a recent meta-analysis, there was no significant improvement in GFR [73]. Due to individual variation, there may be a benefit on trialing the low-protein range (0.8 g/kg BW) and continuing in those who respond best [72]. Risks related to restricted protein diets (i.e., <0.7 g/kg/day) include potential for malnutrition [56]. As was evident in carbohydrates, both amount and type of protein are of importance.

The KDOQI Diabetes Work Group suggests that the DASH and DASH-Sodium diets [74] that emphasize sources of protein other than red meat may be an alternative to lower total protein intake in persons with HTN, diabetes, and in CKD stages 1–2. Diets that emphasize proteins from plant sources (vegetables, soy, whole grains, legumes, nuts) instead of animal sources (particularly red meat) may be renal-sparing [40, 73–78].

In summary, protein intakes should be carefully monitored and be maintained at 0.8 g/kg/BW/day. Excessive intakes may accelerate GFR declines and protein restrictions (below 0.7 g/kg/day) have demonstrated limited benefit and are not recommended based on the risk of malnutrition with declining renal function. Calculating protein requirements for a CKD patient can be accomplished as follows: (1) multiply the patient's actual body weight or ideal body weight (if the person is underweight or overweight) by 0.8. (2) Multiply the result by 0.5 to account for the percentage of HBV protein in grams that one should consume. (3) To convert the high biological value protein requirement from grams to ounces, divide the result by 7.

Dietary Fat Recommendations

Saturated fat and *trans* fatty acids are the principal dietary determinants of plasma LDL-C, the major risk factor for CVD. Because individuals with diabetes are considered to be at similar risk for CVD as those with a past history of CVD, the most recent guidelines for dietary fat intake (amount and type) from the NCEP and the American Heart Association (AHA) would apply. These recommendations state that total fat should be 25–35 % of total calories, with saturated fat <7 % and *trans* fat <1 % of calories [45, 79]. The KDOQI Diabetes Work Group suggests that increasing the intake of omega-3 and monounsaturated fatty acids (MUFAs) may provide favorable effects on progression of CKD. Few studies have examined the effects of fatty acid intake or supplements on the markers of kidney disease and the risk factors in patients with diabetes, and those studies have been short term and in small numbers [40, 80, 81]. Data from the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial in patients with or at risk of developing T2DM, demonstrated no significant impact of at least 900 mg of long chain n-3 daily on major cardiovascular effects, death from any cause or death from arrhythmia over a 6-year time period [82].

The IOM established guidelines for the intake of omega-3 fatty acids. Adequate Intake (AI) of alpha-linolenic acid was established at 1.6 g/day for men and 1.1 g/day for women. The more physiologically potent eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be substituted for up to 10 % of these amounts [51]. The AHA and the KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommends at least 8 oz of oily cold water fish weekly, which would provide EPA and DHA well within the recommended amounts [83]. Patients with documented CHD are advised by the AHA to consume 1 g of EPA and DHA daily, either from fish or supplements. Under a physician's care, supplements which provide 2–4 g of EPA + DHA daily are recommended for individuals with hypertriglyceridemia [79].

Special Considerations

Hypoglycemia/Uremia

As kidney function decreases, risk of hypoglycemia increases. Prolonged insulin action and decreased renal gluconeogenesis may be the two physiological mechanisms responsible for the increased propensity towards hypoglycemia in the earlier stages of CKD. As CKD progresses though, uremic factors start to play a greater role. Uremic gastroparesis, poor appetite, and taste changes now may add to the preexisting risk, combined even further with risk of depression, fatigue, and a progressively restrictive diet and the risk increases sharply. An A1C at target or below may indicate those patients with whom to be more cautious of hypoglycemia, but screening for symptoms of hypoglycemia in all patients is essential. The 15/15 rule should be used to treat hypoglycemia; namely, take 15 g of carbohydrate (CHO), wait 15 min, and retest the blood glucose. If necessary, repeat with another 15 g of CHO and continue the process until the blood glucose level normalizes [53, 63]. The usual methods for treating hypoglycemia may result in fluid overload and/or hyperkalemia in the oliguric patient with diabetes. Better choices that will provide 15 g of CHO are 10 jelly beans, 6 lifesavers, or commercial glucose tablets. Once the blood glucose returns to normal, if the next regular meal will be more than 1 h, then the patient should eat a snack with additional CHO to stabilize the glucose level [53, 63].

Hyperglycemia and Potassium

Hyperglycemia in the setting of a relative insulin deficiency can cause elevations in blood potassium levels. Management of hyperglycemia related to inadequate insulin/medication dosing may help to prevent hyperkalemia.

Dietary Changes

CKD in later stages most often requires strict dietary modification of sodium, potassium, fluids, and phosphorus. The progressive nature of these types of changes should be done while attempting to maximize nutritional status. Individuals should be counseled on the risks associated with nonadherence to the diet and that the dietary changes required to manage CKD should be prioritized over the previous education related to diabetes management. Focus has shifted to primarily rely on CHO amount and quality through different choices (see Fig. 8.1) while still attempting to maintain adequate fiber and micronutrients. Maintaining normal serum phosphate levels is key for the prevention of renal osteodystrophy. Phosphorus restrictions are not usually seen until the later stages of CKD however, counseling regarding a low-phosphorus diet may be required. See Chap. 15 for details.

Alcohol

General population guidelines recommend moderation in alcohol and further precautions should be considered within the context of diabetes and CKD. Consideration should be paid related to medication interactions, presence of HTN, lipid metabolism, fluid balance, and risk for hypoglycemia. The newest recommendations come from Health Canada, which allow a moderate amount of alcohol in low-risk individuals. A moderate amount of alcohol is considered to be less than two drinks per day for women and three drinks or less per day for men in Canada [84]. Previous recommendations and those still considered valid from the Centers for Disease Control and Prevention recommend less than one drink per day for women and two drinks per day for men [85]. A standard 15 g portion of alcohol is defined as 12 oz of beer, 5 oz wine and 1.5 oz distilled spirits. Moderate amounts of alcohol can be consumed with food without causing hyperglycemia or hypoglycemia [86, 87]. Furthermore, it has been associated with a lower risk of coronary death and shown to be protective against the development of coronary heart disease in patients with type 2 diabetes [88–90]. Light to moderate alcohol intake has been shown to have an inverse association with A1C [91] and one study demonstrated reno-protective effects and reductions in blood pressure in patients with nephropathy [92]. Excessive alcohol consumption should be avoided, and patients taking insulin or insulin secretagogues should consume alcohol with carbohydrate containing food to reduce the risk of nocturnal hypoglycemia [2]. Beer contains high amounts of phosphorus and should be discouraged for patients requiring a phosphate restriction. Alcohol should also be included in the total daily fluid allowance for patients requiring fluid restriction.

Nutritive and Non-nutritive Sweeteners

Nutritive sweeteners (also known as added sugars) contain carbohydrate and provide energy at appreciable levels (i.e., either 2 or 4 kcal/g) and includes glucose/dextrose, fructose, galactose, maltose, sucrose, cane juice and sugar, corn-based sweeteners, fruit juice concentrate, and fruit nectar [93].

Recent studies have demonstrated that in the setting of excess energy and fat intake, added sugars are linked to health conditions such as T2DM, inflammation, and CVD [94]. The IOM recommends that the intake of added sugars not exceed 25 % of energy, the AHA recommends no more than 100 kcal/day (25 g or 6 tsp for women) and 150 kcal/day (38 g or 10 tsp for men) [95]. The WHO, ADA, and CDA all recommend no more than 10 % of energy be provided by added sugars which could translate to overall intakes greater than that recommended by the AHA. Where possible, adherence to the AHA guidelines with an upper maximum limit of 10 % would be optimal.

The Food and Drug Administration (FDA) is responsible for evaluating the safety of non-nutritive sweeteners (NNS). The recommendations state that sugar alcohols and NNS are safe when consumed within the acceptable daily intakes established by the FDA [53]. Most NNS are excreted unchanged in either the urine or the feces meaning that they do not provide energy or of importance in the context of CKD, and they do not influence potassium levels [93]. NNS approved for use in the United States include Acesulfame K, Aspartame, Luo han guo, Neotame, Saccharin, Stevia, and Sucralose. NNS have demonstrated little to no impact in clinical trials on appetite or food intake and can be used as part of a weight loss or maintenance program in appropriate intake ranges.

Vitamin D

It has been generally thought that the kidneys were the only sites of 1-alpha-hydroxylation of calcidiol (25(OH)D) into calcitriol, therefore measurement of serum 25(OH)D levels were not as applicable in patients with CKD. However, recent data suggest that this conversion also occurs in extra-renal tissues, and therefore there is a role for measuring 25(OH)D levels in this patient population [96–99]. Many patients with diabetic nephropathy may have limited daily sun exposure and because of dietary restrictions may not consume enough foods fortified with vitamin D. Vitamin D deficiency is exceedingly prevalent in patients with CKD [100–102], and this may contribute to elevated parathyroid hormone levels [103]. There is little evidence regarding the treatment of vitamin D deficiency in predialysis patients. However, a few studies have demonstrated that treatment with ergocalciferol increases 25(OH)D levels and modestly decreases PTH levels [103, 104]. The 2009 KDIGO Guidelines recommend that 25(OH)D might be measured in patients with CKD stages 3–5D, with treatment similar to that of the general population [105]. The AND suggests vitamin D supplementation to maintain adequate levels of 25(OH)D at or above 75 nmol/L [56]. Routine supplementation for those without deficiency as per population recommendations is not contraindicated [105].

MNT Summary

Table 8.4 summarizes the nutrition recommendations for patients with diabetes and CKD. There is no evidence for additional vitamin and mineral supplements in persons with diabetes who do not have underlying deficiencies. Routine supplementation with antioxidants is not advised because of uncertainties related to long-term efficacy and safety [63]. A stepwise MNT protocol for CKD (non-dialysis) from the authors is presented in Fig. 8.1.

Table 8.4 Daily nutrition recommendations for diabetes and chronic kidney disease

Nutrient	CKD stages 1–2	CKD stages 3–5 (non-dialysis)	ESRD stage 5 (on dialysis)
Protein [40, 53, 56]	0.8 g/kg/day	0.8 g/kg/day	Hemo: 1.2 g/kg/day PD: 1.2–1.3 g/kg/day
Energy [54, 56, 60]	23–35 kcal/kg/day Or use HBE	23–35 kcal/kg/day Or use HBE	Hemo: 30–35 kcal/kg/day PD: 30–35 kcal/kg/day
CHO [40, 51]	Up to 60 % of energy	Up to 60 % of energy	Up to 60 % of energy
Fiber [53]	Minimum 14 g/1,000 kcal	Minimum 14 g/1,000 kcal	Minimum 14 g/1,000 kcal
Sodium [40, 56, 106]	<90 mmol/day (<2000 mg/day)		<100 mmol/day (<2,400 mg/day) *Further restriction to 1,500 mg/day may be required if fluid balance or hypertension are of concern*
Fluid	Usually unrestricted	Usually unrestricted	Hemo: 1 L + urine output PD: Individualized *Restriction may be required to optimize glucose control*
Potassium [56]	Individualized restriction required if elevated serum K	<2,400 mg/day if elevated serum K	Hemo: <2,400 mg/day PD: Individualized
Phosphorus [107]	Individualized restriction required if elevated serum PO_4	800–1,000 mg/day or	Hemo: 800–1,200 mg/day PD: 800–1,000 mg/day
Total fat [40, 51]	<30–35 % of energy	<30–35 % of energy	<30–35 % of energy
SFA [53]	<7 % of energy	<7 % of energy	<7 % of energy
PUFA [48]	~10 % of energy	~10 % of energy	~10 % of energy
Cholesterol [53, 65]	<200 mg/day	<200 mg/day	<200 mg/day

Adapted from multiple sources, 2012

Medicare Reimbursement for MNT

Effective January 1, 2002, Medicare beneficiaries diagnosed with diabetes and non-dialysis kidney disease inclusive of post-renal transplant were eligible for reimbursement of MNT. Beneficiaries must have a fasting glucose level >126 mg/dL to meet the diagnostic criterion for diabetes. Chronic renal insufficiency or non-dialysis kidney disease is defined as a GFR of 13–50 mL/min, not severe enough to require dialysis or renal transplantation. Effective February 27, 2001, Diabetes Self-Management Training (DSMT) services were eligible for Medicare reimbursement. Refer to the Centers for Medicare and Medicaid Services (CMS) guidelines published elsewhere for more detail [48, 108–110].

Pharmacological Management of Diabetes Within CKD

Oral Anti-hyperglycemic Agents

Oral anti-hyperglycemic agents (AHAs) now include six major classes of medications, all targeted at different or multiple metabolic defects of type 2 diabetes or to modify processes related to appetite, nutrient absorption, or excretion. The natural progression of T2DM is characterized by insulin

resistance and then moves to a progressive loss of beta cell function. At diagnosis, people with T2DM usually have less than 50 % of their normal insulin secretion and, after 6 years, less than 25 %. This progressive decline in beta cell function is the reason many fail oral therapy and require insulin [111]. It also highlights the importance of the need for dynamic pharmacological management of the disease.

There are many factors that should be considered during the selection of which agent to initiate treatment and which agents to add to an under-effective regimen. The degree of hyperglycemia, the risk of hypoglycemia, treatment efficacy, contraindications, side effects, and other comorbid conditions should be considered. Additionally an individual's age, access to food, personal preference, adherence, and their ability to make additional lifestyle modifications should be considered in the choice of medication. The AHAs can be divided into three main groups: (1) those targeting insulin resistance (biguanides, thiazolidinediones [TZDs]); (2) those targeting insulin secretion (sulphonylureas, meglitinides, incretin-based therapies); and (3) those targeting postprandial glycemia (alpha-glucosidase inhibitors). While incretin-based therapies act on multiple defects, their primary action relates to a blood glucose stimulated insulin response. To achieve the currently recommended evidence-based glycemic target A1C of 7 % or less, better control of postprandial hyperglycemia is needed. This is because as blood glucose control approaches target levels, postprandial blood glucose makes a proportionally greater contribution to overall glycemic exposure [112]. Metabolic clearance of many medications and their active metabolites is an issue with renal impairment that increases the risk of hypoglycemia. Along with reductions in medication clearance, there is also a reduction in renal gluconeogenesis, a progressive increase in uremic toxins and the potential for a decreased intake, all of which highlight that the selection and management of patients on AHAs should be done with the consideration of the risk of hypoglycemia [40]. See Table 8.5 for a summary of available therapies and Fig. 8.2 for safety considerations in CKD.

Medications Targeting Insulin Resistance

Metformin

Metformin, generally considered to be the drug of choice in T2DM in that it is an effective treatment of insulin resistance, has few side effects and does not cause hypoglycemia, is contraindicated in patients when renal function is not known, because of risk for lactic acidosis [113]. Prescribing guidelines in the United States warn against Metformin use at serum creatinine levels of >124 or 133 mmol/L in women and >1.4 or 1.5 mg/dL in men respectively. Many guidelines suggest that Metformin can be continued at a reduced dose in people with stable stage 3 CKD but that it should be stopped during times of acute illness especially in those patients who are also taking renin-angiotensin blockers or diuretics and discontinued completely in severe CKD.

Thiazolidinediones

TZDs are effective medications aimed at reducing insulin resistance as they are hepatically metabolized and do not cause hypoglycemia. As a result, there is no dose adjustment required for CKD; however, the side effects of TZDs, namely fluid retention, limit their usefulness in moderate to severe CKD. Rosiglitazone use is now highly restricted in many countries related to increased risk of myocardial infarction [114] and Pioglitazone has some data suggesting a link towards increased risk of bladder cancer [115].

Table 8.5 Medications

Class	Oral agent	Action	Efficacy (A1C %)	Side effects	CKD cautions
Secretagogues:					
Sulphonylureas	Glyburide Glipizide Glimepiride Gliclazide	↑ Insulin secretion	1–2	Minimal to significant hypoglycemia, weight gain	Hypoglycemia due to renal excretion (less risk with repaglinide)
Meglitinides	Repaglinide Nateglinide				
Biguanides	Metformin	↓Hepatic glucose production	1–2	GI side effects Vitamin B12 deficiency	Contraindicated if eGFR <30 mL/min and use with caution in those 30–60 mL/min
TZD	Pioglitazone Rosiglitazone	↑ Insulin sensitivity	1–2	Weight gain, edema, heart failure, Bone fractures	Caution with use in CKD related to fluid overload
Alpha-glucosidase inhibitors	Acarbose Miglitol Voglibose	Inhibits intestinal digestion/ absorption	0.5	GI side effects	Not recommended in severe CKD (<30 mL/min)
GLP-1 receptor agonists	Exenatide Liraglutide	↑Glucose dependent insulin secretion Slows gastric emptying and enhances satiety	1–2	GI side effects, weight loss	Exenatide is not recommended for use in GFR <30 mL/min and should be used with caution in GFR 30–50 mL/min. No long-term data on Liraglutide and therefore not recommended beyond mild renal insufficiency
DPP-4 inhibitors	Sitagliptin Vildagliptin Saxagliptin Linagliptin	Prolongs survival of endogenously released incretin hormones	1	Urticaria/ angioedema	Long-term safety unknown
Insulin	Basal: NPH Glargine Detemir Bolus: Regular Aspart Lispro Glulisine Pre-mixed	↑ Glucose disposal	Unlimited	Hypoglycemia Weight loss	Caution related to hypoglycemia risk

Adapted from multiple sources

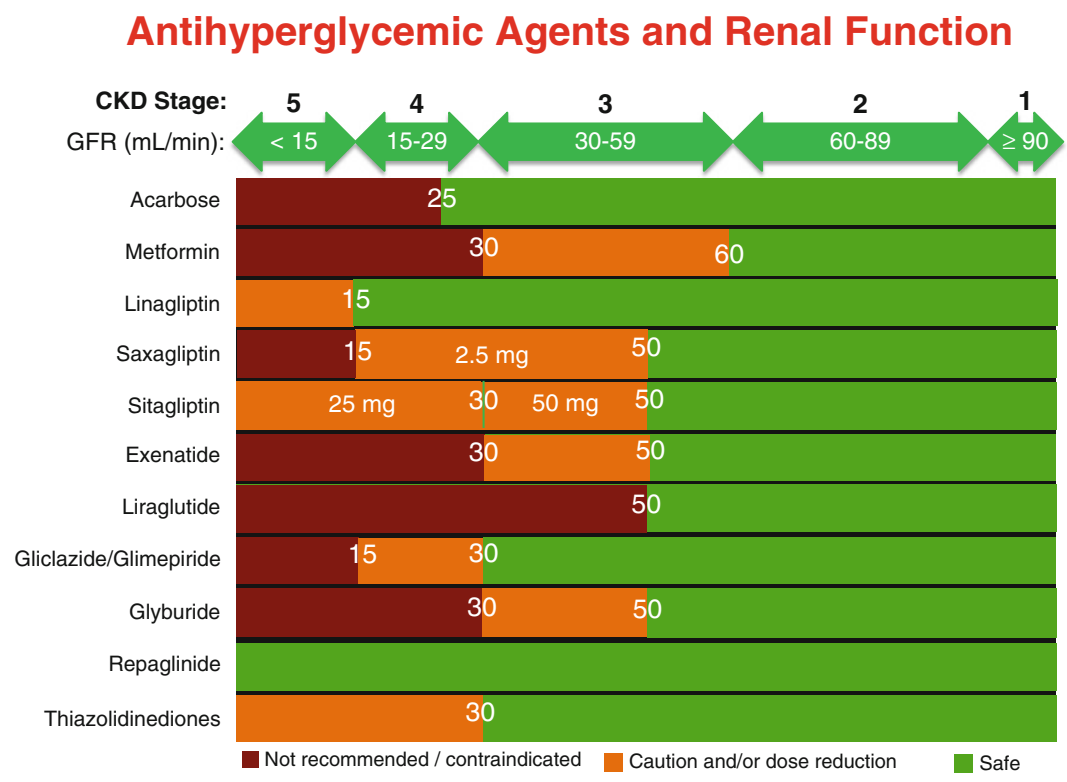

Fig. 8.2 Medication recommendations for use according to CKD stage. Reprinted from Can J Diabetes, 37(suppl 1), Harper W, Clement M, Goldenberg R, et al., Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. S61–S68, Copyright 2013, with permission from Elsevier

Medications Targeting Insulin Secretion

Sulphonylureas

Sulfonylureas should be avoided in patients with severe CKD because they rely on the kidney for elimination of the drug and active metabolites, which could result in prolonged action and a greater risk of hypoglycemia [40]. In earlier stages of CKD, sulfonylureas should be used with caution and may require dose adjustment to prevent hypoglycemia.

Meglitinides

Meglitinides have a shorter duration of action than sulphonylureas and low rates of renal excretion and as such have less risk of hypoglycemia. Generally, no dose adjustment is required for patients taking meglitinides through the progressive loss of renal function.

Incretin-Based Therapies

Incretins are hormones that enhance insulin secretion in response to elevated blood glucose levels from oral intake by stimulating the beta cells of the pancreas to produce insulin only during appropriate times. They also suppress the secretion of glucagon in the presence of hyperglycemia (which helps decrease hepatic glucose output) and slows gastric emptying, both of which help improve blood glucose regulation [116]. Glucagon-like peptide-1 (GLP-1), secreted by intestinal cells, appears to be the major mediator of the incretin effect as it binds to receptors in the pancreas, stomach, lung, and brain, and it also stimulates insulin secretion from the pancreas in response to high blood glucose levels [117]. Injectable GLP-1 receptor agonists include Exenatide (Byetta®) and Liraglutide (Victoza®) both of which consistently demonstrate an approximate 1 % reduction in A1C levels combined with weight loss in some individuals. Exenatide should not be used in patients with a GFR less than 30 mL/min and should be used with caution in patients with a GFR between 30 and 50 mL/min. No dose adjustment is required with Liraglutide in patients with renal insufficiency; however, there are few studies in patients with moderate and severe CKD and therefore it should be used with caution. Another member of the incretin family, DPP-4 Inhibitors, potentiates the postprandial GLP-1 response. Sitagliptin is not recommended in patients with moderate (GFR 30–50 mL/min) to severe CKD (GFR < 30 mL/min); linagliptin is not recommended in severe CKD and a 2.5 mg dose of saxagliptin is now allowed in moderate to severe renal insufficiency but it should not be used in hemodialysis patients. No dose adjustment is required for those DPP-4 inhibitors recommended for use in mild–moderate renal insufficiency.

Medications Targeting Postprandial Glucose

Active drug and metabolites of Alpha-glucosidase inhibitors have been found in patients with renal insufficiency and as such the drug is not recommended for use in patients with severe CKD [118].

Insulin

Insulin therapy with delivery through syringe, pen, or insulin pump technology remains the mainstay of treatment for people with T1DM and used frequently in patients with T2DM. Prandial (mealtime or bolus) insulin is classified according to the duration of action as either rapid or short acting insulin. Basal insulin is also classified in the same manner as either intermediate or long acting. Pre-mixed insulin is available and includes combinations of prandial insulin with an intermediate basal. Insulin selection and dosing is very patient specific and should be tailored to the individual's diet, lifestyle, motivation, and self-management skills in addition to the treatment goals, risk, and awareness of hypoglycemia. In individuals with T2DM, the progressive nature of the disease results in the frequent use of insulin upon failure of AHAs. In contrast to the traditional approach to insulin initiation, some studies have shown that beta cell function may be preserved with early insulin therapy which reduces the initial "glucose toxicity" [119]. Simply introducing a once daily injection of a basal insulin at bedtime, such as insulin glargine, detemir, or NPH, to an existing oral regimen can help reach glycemic goals [120].

Basal/bolus regimens using intermediate or long acting insulin once or twice daily with mealtime short or rapid acting insulin to cover the carbohydrate content of each meal are commonly prescribed. Such regimens increase flexibility in managing variable meal times, exercise and carbohydrate content and type. Hypoglycemia remains the most common side effect and barrier towards optimal glycemic

control with insulin. Insulin is both hepatically metabolized and renally excreted and as CKD progresses, the duration of insulin action may be extended thereby trending the patient towards hypoglycemia. Peakless basal insulin has demonstrated significant reductions in nocturnal hypoglycemia when used to replace intermediate insulin. Additionally, rapid acting insulin analogues have a reduced frequency of hypoglycemia and should be considered for use in individuals with diabetic nephropathy.

In consideration of patients with diabetic nephropathy, rapid acting insulin analogues can easily maintain postprandial glucose within target range even in the face of changes to meal compositions that have limited fiber and a higher GI. Management of blood glucose during times of poor or variable appetite, uremic gastroparesis, and delayed meal times can be best accomplished with a more physiological approach to insulin management through a long acting basal and rapid bolus regimen. Premixed insulin regimens in contrast require consistent meal times, carbohydrate intake, and snacks to reduce the risk of hypoglycemia.

Other Medications

Bile acid sequestrants that bind bile acids in the intestine and increase bile acid production in the liver may have some benefit in decreasing hepatic glucose production [121] and increasing incretin levels with modest effects on A1C [197]. Dopamine 2 agonists such as probably bromocriptine also have demonstrated some modest effects on A1C through activation of dopaminergic receptors and an effect on insulin sensitivity [198]. Amylin mimetics such as pramlintide activate amylin receptors with impact on gastric emptying and satiety levels and ultimately postprandial glucose excursions and weight [122].

Self-Monitoring of Blood Glucose

The frequency for Self-Monitoring of Blood Glucose (SMBG) should be determined by the self-management skills of the individual, the type of insulin regimen and the ability of the patient to adjust the dose of insulin, food intake, or exercise in response to the information obtained. The ADA recommends a minimum of once-daily monitoring for patients on insulin or insulin secretagogues to assist in the prevention of hypoglycemia [53]. However, to obtain optimal glucose control, it is necessary for a patient using insulin therapy to test a minimum of three times per day to detect variations in blood glucose levels that may require adjustments in insulin dosages [2].

The optimal frequency and timing of SMBG for patients with T2DM is not known, but should be sufficient to reach glucose goals [2]. Timing of the blood glucose test should take into account the potential for hypoglycemia that is higher in progressive CKD. As such, close examination of the effects of exercise and activity are necessary as would the concern for extended insulin action and peak with intermediate insulin.

ESRD and DM

Diabetes is the most common cause of end-stage renal disease (ESRD) and those dialysis patients with diabetes mellitus (DM) have a lower survival rate compared to non-diabetics with ESRD [121–124]. Furthermore, these patients have the poorest rehabilitation potential and the highest incidence of hospitalizations, mostly attributable to cardiovascular events [125–127].

Worsening insulin resistance is a recognized complication of advanced kidney disease. Although the causal mechanism remains unknown, factors such as inflammation, vitamin D deficiency, metabolic acidosis, increased fat mass, and accumulation of "uremic toxins" are thought to negatively affect insulin resistance [128].

Renal filtration of insulin is also affected as kidney disease progresses to its advanced stages. Once the GFR drops below 20 mL/min, the kidneys are unable to adequately metabolize insulin and there is a related decline in hepatic insulin metabolism [129]. This leads to a high risk of hypoglycemic events [130, 131]. Thus, as kidney function deteriorates further in ESRD, many patients require reduced amounts, or even cessation, of exogenous insulin, insulin secretagogues, and renally cleared medications [132, 133].

Therefore, the management of blood glucose in ESRD is complicated by various factors that either decrease or increase insulin requirements. Hence, glycemic control differs for each patient, and individualized therapy is required. To further complicate the issue of optimizing glycemic control, both hemodialysis and peritoneal dialysis (PD) are comprised of unique aspects that affect the management of DM.

Hemodialysis

Hemodialysis (HD) is the most common form of RRT used to treat people with DM [122, 125]. Poor glycemic control upon initiation of HD indicates worse survival [134, 135]. MNT for patients with diabetes on hemodialysis remain the same as that outlined by KDOQI [40] but with consideration for additional acute complications (e.g., hypoglycemia).

Dialysis treatment schedules may interfere with a patient's usual meal time, and posttreatment fatigue may impede intake. Furthermore, hemodialysis patients generally consume fewer calories on dialysis days, compared with non-dialysis days [136]. These factors can precipitate hypoglycemia; so a patient may need to eat before coming to treatment and/or bring a snack to consume after. It is important to encourage regular eating habits to promote consistent blood glucose patterns. In addition, insulin regimens which offer greater flexibility and insulin secretagogues with a shorter half life may have added benefits with the potential for variable dietary intakes.

There are varying concentrations of dialysate glucose that can be given during a dialysis session. In general, glucose-containing dialysate solutions may prevent glucose losses, and therefore reduce the risk of hypoglycemia [137–139].

Peritoneal Dialysis

The management of DM in peritoneal dialysis (PD) is especially challenged by the use of hypertonic dialysis solutions. Side effects related to intraperitoneal (IP) exposure to high glucose concentrations may include acute hyperglycemia, an inflammatory state, hyperlipidemia, fibrosis, enhanced protein loss, generalized intra-abdominal fat accumulations, increased risk of CVD, weight gain, and obesity; and the underlying diabetic state may compound or exacerbate these problems [140–142]. In addition, glucose degradation products or advanced glycation end product formation may directly or indirectly lead to peritoneal membrane alterations, such as peritoneal fibrosis, neoangiogenesis, and increased membrane permeability, which can lead to problems with ultrafiltration (UF) [141, 143, 144]. Strategies to reduce glucose-related toxicity include carbohydrate sparing dialytic regimens, such as amino acid-based fluids and icodextran. Icodextran is a glucose polymer-based solution which may

provide better glycemic control, increase UF volume, improve blood pressure control and be less hyperlipidemic [141, 144, 145].

Glycemic control is complex with PD, and poor glycemic control can increase thirst which may lead to fluid retention [146]. Sodium and fluid control is essential to adequate glycemic control in PD to optimize ultrafiltration, resulting in the use of lower percent glucose dialysate solutions which may subsequently lead to less IP glucose absorption and could minimize hyperglycemia.

The use of IP insulin has several advantages, including eliminating the need for subcutaneous insulin injections, providing a continuous and more rapid absorption directly into the portal vein and thus the potential for less hepatic glucose production. The latter may lead to improved glycemic control and insulin sensitivity [140, 142, 145, 147, 148–151]. Potential disadvantages with this form of therapy include increased insulin requirements due to insulin activity loss as there is dilution with the PD infusion [125]. In addition, there is an increased risk of bacterial contamination during injection of insulin into the dialysate bags, as well as peritoneal fibroblastic proliferation and hepatic subcapsular steatosis, which is associated with hypertriglyceridemia, obesity, fatty liver infiltration, and nonalcoholic steatohepatitis [142, 151, 152]. MNT intake targets are outlined within Table 8.4.

Monitoring Glycemic Control

The goals for monitoring glycemic control in people receiving maintenance dialysis are similar to those without RRT, but exact target levels for best outcomes have not been clearly established. Evidence exists to suggest that adequate monitoring of glucose in dialysis patients is uncommon despite the risk of additional diabetes-related complications [153, 154]. The Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Cardiovascular Disease in Dialysis Patients recommend that the ADA guidelines for monitoring glycemic control in people with DM be followed [155]. It is also important to monitor plasma glucose levels of patients without DM, as patients may develop DM after the initiation of dialysis, especially those receiving peritoneal dialysis [156]. Although current recommendations generally target an A1C of less than 7 %, there is concern about the accuracy and interpretation of the values in ESRD.

A1C levels may under-represent glycemic control due to decreased red blood cell survival, iron deficiency, recent transfusion, and metabolic acidosis [154, 156–161]. Conversely, carbamylated hemoglobin formation due to urea dissociation may falsely increase values. Recent data suggests that using multiple measurements of A1C, over extended periods of time is more reliable, and is associated with U- or J-shaped mortality outcomes [162–165]. Therefore, A1C can provide valid results for most patients with stage 5 CKD with appropriate methodology [166].

Other potential methods used to monitor glucose include fructosamine and glycated albumin. Fructosamine measures glycemia over a shorter 2–3 week period. A high protein turnover rate such as in dialysis may affect use of fructosamine, while a high urate level may interfere with assay results [154]. As such fructosamine is less reliable than A1C, especially with PD [154, 161, 165]. Glycated albumin measures the percentage of albumin that is glycated, and also measures glycemia over a 2–3 week period [167]. It has been suggested that glycated albumin may be more accurate in assessing glycemic control in dialysis patients [168]. However, its disadvantages include that it may be impacted by proteinuria and abnormal albumin levels, a common occurrence in dialysis patients [166, 169].

Given the perceived lack of accuracy with A1C, the paucity of data surrounding the optimal frequency and times to monitor blood glucose levels and the variability in treatment modalities and intake day to day, self-monitoring blood glucose (SMBG) should be encouraged. SMBG is especially indicated with insulin use to detect and deter asymptomatic hypoglycemia and hyperglycemia; it is usually recommended three to four times per day, with unknown optimal frequency when oral agents are

prescribed [170]. A single random test is a poor guide to overall glycemic control; and checking fasting values alone may be insufficient, as PPG reduction may significantly impact A1C, while lowering cardiovascular risk [154, 171, 172]. The inconvenience of SMBG to capture night time glucose control with PD signifies a potential role for continuous glucose monitoring [154, 173]. It is important to note that glucose polymer-based peritoneal dialysate solutions (icodextran) may interfere with glucose dehydrogenase-based glucometers giving false readings, so a compatible glucometer is needed [154]. In conclusion, glycemic control is best evaluated by monitoring regular measurements of both SMBG and A1C [170].

Medical Nutrition Therapy on Dialysis

The nutritional therapy of patients with DM who are receiving maintenance dialysis are similar to those in the later stages of CKD, with the exception of protein requirements, and generally stricter restrictions of phosphorus, potassium, and fluid. In the ESRD population, there is a high incidence of protein-energy malnutrition related to many factors, including but not limited to amino acid losses through dialysis, metabolic acidosis, and uremia-associated anorexia. Recommended protein intake is 1.2 g/kg/day for hemodialysis patients and 1.2–1.3 g/kg/day for peritoneal dialysis patients, with the source of protein being at least 50 % high biological value protein [174]. Optimizing carbohydrate distribution to achieve euglycemia, minimizing dyslipidemia, and attaining a total energy intake appropriate for weight management should continue to be encouraged. In addition, patients should be educated regarding appropriate hypoglycemia management with consideration of potassium and fluid restrictions.

The ADA promotes a diabetic diet that considers personal and cultural preferences, and the lifestyle of the patient while respecting the individual's desires and willingness to change [170]. It is unwise to assume that a good understanding of diabetes management already exists when a patient with diabetes begins dialysis. The patient is often overwhelmed by multiple dietary restrictions and food previously allowed may now need to be restricted. There may also be difficulty in coordinating the dietary recommendations into a cohesive meal plan. The ability to interchange carbohydrate units is complicated by the potassium and phosphorus content of the foods. Alternatives to traditional bedtime snacks and treatment for hypoglycemia may be indicated, although long-standing habits are not easy to change. Renal diabetic exchange lists can classify food groups for meal patterns, but it is important that the patient understands and is able to integrate the rationale and basic concepts of nutrition goals for DM and dialysis to further dietary acceptance and foster adherence.

Malnutrition

Diabetes is the most significant predictor of loss of LBM in dialysis patients, independent of inadequate dialysis dose, metabolic acidosis, and insufficient protein intake [127]. In comparison to ESRD patients without DM, patients with DM have increased muscle breakdown [128, 175, 176]. A higher incidence of protein malnutrition with dialysis and DM may not be a direct death risk [177], however, the association with other death risk factors cannot be dismissed.

Oral nutrition supplements (ONS) may be useful to increase protein and caloric intake. Specially formulated products for diabetes may not be necessary, as the ADA standards allow substitution of sucrose for other carbohydrates in the meal plan [170]. The choice of an ONS should be based on overall nutrient profile to meet the individual's metabolic needs and the palatability and affordability of the product.

Fluid Control

Fluid control may be more difficult in patients with DM because hyperglycemia may increase thirst and urination. In those with diabetic neuropathy, symptoms of dry mouth, decreased salivary flow rates, and the effects of xerogenic drugs may worsen control [178–182]. Fluid intake may be higher if dental problems impair chewing or if gastroparesis is severe and solid food is not tolerated. Patients should be educated on tips to control thirst without further exacerbating hyperglycemia. Tips may include, brushing or rinsing teeth more often, sucking on a lemon or lime wedges, using ice chips in limited quantities, and using sugar-free gum or candies.

Gastroparesis

Gastroparesis is defined as non-obstructive delayed gastric emptying with impaired gastric acid secretion and GI motility [183]. It is a common complication in patients with long-standing diabetes due to autonomic neuropathy; however it can also occur in non-diabetics [184, 185]. Although the prevalence of gastroparesis in ESRD is unknown, it has been estimated that diabetic gastroparesis can affect up to 30 % of patients with ESRD [186]. Furthermore, some studies have identified delayed gastric emptying in approximately 50 % of patients undergoing peritoneal dialysis [187–189].

Symptoms include early satiety, postprandial fullness, anorexia, nausea, bloating, belching, epigastric discomfort, abdominal pain, and emesis of undigested food [47, 183, 190–193]. Unexplained and erratic blood glucose levels may often lead to the diagnosis of gastroparesis. Although normalization of blood glucose levels may improve gastric emptying, gastroparesis complicates the balance between insulin timing and food absorption. Less insulin may be required with decreased gastric emptying to maintain euglycemia, and rapid acting insulin may increase the risk of hypoglycemia with delayed absorption, inability to consume full anticipated meal or with loss of meal due to emesis [194, 195]. Prolonged insulin action with stage 5 CKD further complicates this scenario.

Patients with gastroparesis may be at risk for fluid, electrolyte and nutrient deficits, anorexia and malnutrition, especially if they experience frequent nausea and vomiting [196]. Dialysis patients with diabetes who complain of early satiety, bloating and/or nausea and have weight loss, should be screened for gastroparesis [196]. ONS may be considered, as liquid supplements are energy and nutrient dense, and empty more easily from the stomach compared to solid foods. Solid foods may be better tolerated earlier in the day, while liquids can be consumed later in the day as early satiety worsens [196].

Fat delays gastric emptying, while high-fiber foods may lead to the formation of bezoars. Food remaining in the stomach for a long period of time can lead to fermentation and bacterial overgrowth or hardening into solid masses, known as bezoars, which can cause nausea, vomiting, and obstruction of the small intestine. Therefore, a low-fat and low-fiber diet is recommended for patients with gastroparesis [183, 196].

Since large-volume meals can delay gastric emptying as well, small, frequent meals should be encouraged [183, 196]. Patients should be advised to eat high protein foods first and to minimize fluids with food to combat early satiety. Meals should be as consistent as possible in carbohydrate content and food should be chewed thoroughly [47, 196].

Summary

The incidence of both diabetes and CKD is on the rise. Living with either diabetes or CKD is challenging for anyone. Managing diabetes in the presence of CKD requires additional effort on the part of the patient and the health-care team to improve outcomes and to decrease morbidity and mortality

in this population. Because of the complexity of diabetes and CKD and their comorbidities, multiple drug therapies, in conjunction with MNT, are necessary to achieve the goals of therapy; therefore, patient adherence becomes a serious concern. The nutrition needs of patients with diabetes and CKD change as the progression and treatment of the disease changes. Understanding the treatment goals at each stage is crucial to optimize the nutritional status of patients throughout the course of their disease and to individualize their education and meal plans accordingly [47].

Case Study

E.C. is a 58-year-old woman initially referred for MNT due to hyperkalemia and seen for 1 month follow up today. Her past medical history reveals T2DM × 19 years, HTN, hyperlipidemia, CKD, anemia, gout, arthritis, obesity, retinopathy, and proteinuria.

Current medications include Humalog Mix 25: 80 U a.m. and 90 U with supper; Crestor 20 mg; Lasix 80 mg; Vasotec 40 mg bid; Atenelol 100 mg; Losartin 100 mg; Norvasc 10 mg; Allopurinol 100 mg; Cardura 4 mg; Colchicine 0.6 mg; Procrit 8,000 U SC q wk; MVI daily.

Her physical exam presents with Ht: 5′4″; Wt: 208 lb (today); Wt: 205 lb (1 month ago); BP 140/90 mmHg; pedal edema 2+. Laboratory data included: A1C 8.5, Glucose 193 mg/dL (fasting); SCr. 2.6 mg/dL; MAC 123 mm; Hgb 10.1 g/dL; TC 201 mg/dL; TG 671 mg/dL; HDL 32 mg/dL; LDL unable to calculate; ACR 7.4; GFR 32 mL/min, K 5.5 mmol/L. She routinely only checks BG 2× per day at a.m. and before supper; reports 6–8 episodes of hypoglycemia in the past month; did not bring meter or BG log with her.

She is married; works 7 a.m. to 3 p.m. as a computer analyst for a large company; quit smoking 18 years ago; no alcohol consumed. She complains of swelling in feet and does not regularly exercise; reports balance/stability problems with gout and excess weight.

Dietary history revealed that she eats out daily on weekdays for lunch although the time varies daily. Upon receiving information on the foods high in potassium at her previous visit and from information she found on the internet E.C. has cut all whole grains from her diet.

Questions

1. What is the patient's estimated CKD stage?
   Answer: 32 mL/min = Stage 3 CKD.
2. Since the patient did not bring a meter or SMBG records with her, what is her average blood sugar based on her A1C?
   Answer: Mean plasma glucose 197.
3. What factors may be involved in the poor glycemic control she is experiencing?
   Answer: Weight gain; symptoms from chronic disease including fatigue, taste changes, waste build up, hyperglycemia; insufficient insulin dose; inadequate insulin type; poor clearance of insulin; poor or variable dietary intake with potassium restrictions.
4. What dietary protein intake would you recommend?
   Answer: Based on 0.8 g if using actual body wt (94.5 kg) = 76 g/day.
5. What diet/medication strategies would you suggest to E.C. to manage her erratic blood glucose patterns and her hyperkalemia?
   Answer: Change insulin to multiple daily injection regimen with long acting basal; modify to low-potassium fruit and vegetables to minimize hyperkalemia and encourage her to consider appropriate carbohydrate choices to prevent hypoglycemia.

References

1. American Diabetes Association Web site. http://www.diabetes.org. Diabetes Statistics and National Diabetes Fact Sheet, 2011. Accessed 4 June 2012.
2. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care. 2012;35 Suppl 1:S11–63.
3. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW. American Diabetes Association: nephropathy in diabetes (position statement). Diabetes Care. 2004;27 Suppl 1:S79–83.
4. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–53.
5. Nesbitt KN. An overview of diabetic nephropathy. J Pharmacy Practice. 2004;17(1):75–9.
6. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1:825–31.
7. Adler S. Diabetic nephropathy: linking histology, cell biology and genetics. Kidney Int. 2004;66:2095.
8. Krolewski AS. Genetics of diabetic nephropathy: evidence for major and minor gene effects. Kidney Int. 1999;55:1582.
9. Cooper ME. Pathogenesis, prevention and treatment of diabetic nephropathy. Lancet. 1998;352:213.
10. Nelson RG, Knowler WC, Pettitt DJ, et al. Diabetic kidney disease in Pima Indians. Diabetes Care. 1993;16:335.
11. Brancati FL, Whittle JC, Whelton PK, et al. The excess incidence of diabetic end stage renal disease among blacks. A population based study of potential explanatory factors. JAMA. 1992;268:3079.
12. Smith SR, Svetky LP, Dennis VW. Racial differences in the incidence and progression of renal diseases. Kidney Int. 1991;40:815.
13. Morales E, Valero MA, León M, Hernández E, Praga M. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. Am J Kidney Dis. 2003;41(2):319.
14. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence and complications of IDDM by sex and duration. Pittsburg Epidemiology of Diabetes Complications Study II. Diabetes. 1990;39:116.
15. Newman DJ, Mattock MB, Dawnay AB, et al. Systematic review on early albumin testing for early detection of diabetic complications. Health Technol Assess. 2005;9:iii.
16. DCCT/EDIC Research Group, Nathan DM, Zinman B, et al. Modern day clinical course of type 1 diabetes after 30 years duration: the DCCT/EDIC and Pittsburg Epidemiology of Diabetes Complications Experience (1983–2005). Arch Intern Med. 2009;169:1307.
17. Schering D, Kasten S. The link between diabetes and cardiovascular disease. J Pharmacy Practice. 2004;17(1):61–5.
18. Ritz E, Stefanski A. Diabetic nephropathy in type 2 diabetes. Am J Kidney Dis. 1996;27:167.
19. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80(1):17.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro III AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604.
21. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J, Levey AS. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations for estimating GFR levels above 60 mL/min/1.73 m^2. Am J Kidney Dis. 2010;56(3):486.
22. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39 Suppl 1:S1–266.
23. Namyi Y, Milite CP, Inzucchi SE. Evidence-based treatment of diabetic nephropathy. Pract Diabetol. 2005;December:36–41.
24. Peppa M, Raptis SA. Advanced glycation end products and cardiovascular disease. Curr Diabetes Rev. 2008;4(2):92–100.
25. Stirban A, Negrean M, Götting C, Uribarri J, Gawlowski T, Stratmann B, Kleesiek K, Koschinsky T, Vlassara H, Tschoepe D. Dietary advanced glycation end products and oxidative stress: in vivo effects on endothelial function and adipokines. Ann N Y Acad Sci. 2008;1126:276–9.
26. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
27. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–65.

28. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: (UKPDS 38). BMJ. 1998;317(7160):703–13.
29. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000;321:412–9.
30. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
31. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol. 2010;55:1310–7.
32. Gerstein HC, Miller ME, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–59.
33. Duckworth W, Abraira C, Moritz T, et al. Glucose control and Vascular Complications in Veterans with Type 2 Diabetes (VADT). N Engl J Med. 2009;360:129–39.
34. Patel A, MacMahon S, Chalmers J, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72.
35. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–85.
36. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsärinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S; ONTARGET Investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372(9638):547–53.
37. Gaede P, Lund-Anderson H, Parving HH, Pederson O. Effect of a multi-factorial intervention on mortality in T2DM (Steno-2). N Engl J Med. 2008;358:580–91.
38. Delahanty LM. Implications of the Diabetes Control and Complications Trial for renal outcomes and medical nutrition therapy. J Ren Nutr. 1998;8:59–63.
39. American Diabetes Association. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364–79.
40. National Kidney Foundation. KDOQI clinical practice guidelines for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49 Suppl 2:S1–179.
41. Brand-Miller J, Hayne S, Petocz P, et al. Low glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care. 2003;26:2261–7.
42. Durst SW, Schering D. Hypertension management in the diabetes patient. J Pharmacy Practice. 2004;17(1):55–60.
43. National High Blood Pressure Education Program. The seventh report of the Joint National Committee on Detection, Evaluation, and Treatment. JAMA. 2003;289:2560–72.
44. National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43 Suppl 1:S115–9.
45. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
46. American Diabetes Association. Dyslipidemia management in adults with diabetes (position statement). Diabetes Care. 2004;27 Suppl 1:S68–71.
47. Pagenkemper JJ. Nutrition management of diabetes in chronic kidney disease. In: Byham-Gray L, Wiesen K, editors. A clinical guide to nutrition care in kidney disease. Chicago IL: American Dietetic Association; 2004.
48. Ross TA, Boucher JL, O'Connell BS, editors. American dietetic association guide to diabetes medical nutrition therapy and education by the Diabetes Care and Education Dietetic Practice Group. Chicago, IL: American Dietetic Association; 2005.
49. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. Endocrinol Metab Clin North Am. 2003;32:805–22.
50. Saiki A, Nagayama D, Ohhira M, Endoh K, Ohtsuka M, Koide N, Oyama T, Miyashita Y, Shirai K. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. Int J Obes (Lond). 2005;29(9):1115.
51. National Academy of Sciences, Institute of Medicine. Dietary reference intakes: energy, carbohydrate, fiber, fat, fatty acids cholesterol, protein, and amino acids. Washington, DC: National Academy Press; 2002.
52. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA. 2005;293:43–53.
53. American Diabetes Association. Nutrition recommendation and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2008;31 Suppl 1:S61–72.

54. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35:S40–5, S58–61.
55. Kopple JD, Chumlea W, Gassman J. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57:1688–703.
56. Evidence-Based Nutrition Practice Guideline on Chronic Kidney Disease. July 2010. http://andevidencelibrary.com. Copyrighted by the Academy of Nutrition and Dietetics. Accessed 10 Dec 2012.
57. Byham-Gray LD. Weighing the evidence: energy determinations across the spectrum of kidney disease. J Ren Nutr. 2006;16(1):17–26.
58. Cuppari L, Ikizler TA. Energy balance in advanced chronic kidney disease and end-stage renal disease. Semin Dial. 2010;23(4):373–7.
59. Avesani CM, Cuppari L, Silva AC, et al. Resting energy expenditure in pre-dialysis diabetic patients. Nephrol Dial Transplant. 2001;16:556–60.
60. Kamimura MA, Avesani CM, Bazanelli AP, Baria F, Draibe SA, Cuppari L. Are prediction equations reliable for estimating resting energy expenditure in chronic kidney disease patients. Nephrol Dial Transplant. 2011;26(2):544–50.
61. http://www.diabetes.ca/for-professionals/resources/nutrition/beyond-basics/
62. Monnier L, Colette C. Targeting prandial hyperglycemia: how important is it and how best to do this? Curr Diab Rep. 2008;8(5):368–74.
63. Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, Kulkarni K, Geil P. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement of the American Diabetes Association. Diabetes Care. 2004;27:2226–71.
64. Thomas DE, Elliott EJ. The use of low-glycaemic index diets in diabetes control. Br J Nutr. 2010;104:797–802.
65. Opperman AM, Venter CS, Oosthusizen W, et al. Meta-analysis of the health effects of using the glycaemic index in meal planning. Br J Nutr. 2004;92:367–81.
66. Wolever TM, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 2008;87:114–25.
67. Anderson JW, Randles KM, Kendall CW, et al. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. J Am Coll Nutr. 2004;23:5–17.
68. Nuttall FQ, Gannon MC. Metabolic response of people with type 2 diabetes to a high protein diet. Nutr Metab. 2004;1(1):6.
69. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis. 1998;31:954–61.
70. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal disease: a meta-analysis. Ann Intern Med. 1996;124:627–32.
71. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int. 2002;62:220–8.
72. Robertson LM, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev. 2007;(4):CD002181.
73. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2008;88:660–6.
74. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller III ER, Simons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3–10.
75. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values. Diabetes Care. 2008;31:2281–3.
76. Azadbakht L, Atabak S, Esmaillzadeh A. Soy protein intake, cardio-renal indices and C-reactive protein indices, and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial. Diabetes Care. 2008;31(4):648–54.
77. Aabadakht L, Esmaillzadeh A. Soy protein consumption and kidney related biomarkers among type 2 diabetics: a crossover randomized clinical trial. J Ren Nutr. 2009;19(6):479–86.
78. Teixeira SR, Tappenden KA, Carson L, Jones R, Prabhudesai M, Marshall WP, Erdman JW. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile n men with type 2 diabetes mellitus and nephropathy. J Nutr. 2004;134(8):1874–80.
79. American Heart Association. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114:82–96.
80. Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S. Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. Lipids. 1990;9:541–5.
81. Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH. Fish oil in diabetic nephropathy. Diabetes Care. 1996;19:1214–9.

82. The ORIGIN Trial Investigators. N-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367(4):309–18.
83. National Kidney Foundation. KDOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 Suppl 3:S90–5.
84. Butt P, Bierness D, Cesa F, Gliksman L, Paradis C, Stockwell T. Alcohol and health in Canada: a summary of evidence and guidelines for low-risk drinking. Ottawa, ON: Canadian Centre on Substance Abuse; 2011.
85. Centres for Disease Control and Prevention (CDC). Alcohol-related disease impact (ARDI). Atlanta, GA: CDC. http://www.cdc.gov/alcohol/ardi.htm. Accessed 15 June 2012.
86. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med. 2004;140:211–9.
87. Bantle AE, Thomas W, Bantle JP. Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus. Metabolism. 2008;57:241–5.
88. Ajani UA, Gaziano JM, Lotufo PA, Liu S, Hennekens CH, Buring JE, Manson JE. Alcohol consumption and risk of coronary heart disease by diabetes status. Circulation. 2000;102(5):500.
89. Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, Willett WC, Manson JE. Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. Circulation. 2000;102(5):494.
90. Tanasescu M, Hu FB, Willett WC, Stampfer MJ, Rimm EB. Alcohol consumption and risk of coronary heart disease among men with type 2 diabetes mellitus. J Am Coll Cardiol. 2001;38(7):1836.
91. Ahmed AT, Karter AJ, Warton M, Doan JU, Weisner CM. The relationship between alcohol consumption and glycemic control among patients with diabetes: The Kaiser Permanente Northern California Diabetes Registry. J Gen Intern Med. 2008;23:275–82.
92. Nakamura T, Fujiwara N, Sugaya T, Ueda Y, Koide H. Effect of red wine on urinary protein, 8 hydroxydeoxyguanosine, and liver-type fatty acid binding protein excretion in patients with diabetic nephropathy. Metabolism. 2009;58:1185–90.
93. Fitch C, Keim KS, Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. J Acad Nutr Diet. 2012;112:739–58.
94. US Departments of Agriculture and Health and Human Services. Dietary guidelines for Americans. 7th ed. Washington, DC: US Government Printing Office; 2010.
95. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health. A scientific statement from the American Heart Association. Circulation. 2009;120(11):1011–20.
96. Segersten U, Holm PK, Bjorklund P, et al. 25-Hydroxyvitamin D31alpha-hydroxylase expression in breast cancer and use of non-1alphahydroxylated vitamin D analogue. Breast Cancer Res. 2005;7:R980–6.
97. Van Driel M, Koedam M, Buurman CJ, et al. Evidence for auto/paracrine actions of vitamin D in bone: 1alpha-hydroxylase expression and activity in human bone cells. FASEB J. 2006;20:2417–9.
98. Somjen D, Weisman Y, Kohen F, et al. 25-Hydroxyvitamin D3-1alphahydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation. 2005;111:1666–71.
99. Segersten U, Correa P, Hewison M, et al. 25-Hydroxyvitamin D(3)-1alphahydroxylase expression in normal and pathological parathyroid glands. J Clin Endocrinol Metab. 2002;87:2967–72.
100. Gonzalez EA, Sachdeva A, Oliver DA, et al. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol. 2004;24:503–10.
101. LaClair RE, Hellman RN, Karp SL, et al. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. Am J Kidney Dis. 2005;45:1026–33.
102. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71:31–8.
103. Zisman AL, Hristova M, Ho LT, et al. Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. Am J Nephrol. 2007;27:36–43.
104. Al-Aly Z, Qazi RA, González EA, Zeringue A, Martin KJ. Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment with ergocalciferol in patients with CKD. Am J Kidney Dis. 2007;50(1):59.
105. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guidelines for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009;76 Suppl 113:1.
106. Daskalopoulou SS, Khan NA, Quinn RR. The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. Can J Cardiol. 2012;28(3):270–87.
107. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42 Suppl 3:S1–201.

108. Medicare program; revisions to payment policies and five-year review of and adjustments to the relative value units under the physician fee schedule for calendar year 2002; final rule, 66 Federal Register 55246-55332 (2001) (codified at 42 CFR 405).
109. Additional clarification for medical nutrition therapy (MNT) services. CMS Program Memorandum Intermediaries/Carriers. Transmittal AB-02-059. 1 May 2002. Change request 2142. http://www.cms.hhs.gov/manuals/pm_trans/AB02059.pdf. Accessed 3 April 2006.
110. Medicare program, expanded coverage for outpatient diabetes self-management training and diabetes outcome measurements; final rule and notice. 65 Federal Register 83130-83154 (2000) (codified at 42 CFR 410, 414,424,480, 498).
111. Daugherty KK. Review of insulin therapy. J Pharmacy Practice. 2004;17(1):10–9.
112. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1C. Diabetes Care. 2003;26:881–5.
113. Holstein A, Stumvoll M. Contraindications can damage your health: is metformin a case in point? Diabetologia. 2005;48:2454–9.
114. Nissen SE, Wolski K. Rosiglitazone re-visited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170:1191–201.
115. Kermode-Scott B. Meta-analysis confirms raised risk of bladder cancer from pioglitazone. BMJ. 2012;345:e4541.
116. Drucker DJ. Incretin-based therapies: a clinical need filled by unique metabolic effects. Diabetes Educ. 2006;32 Suppl 2:S65–71.
117. Kruger DF, Martin CL, Sadler CE. New insights into glucose regulation. Diabetes Educ. 2006;32:221–8.
118. Hanefeld M. Cardiovascular benefits and safety profile of acarbose therapy in prediabetes and established type 2 diabetes. Cardiovasc Diabetol. 2007;6:20.
119. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289:2254–64.
120. Cornell S, Briggs A. Newer treatment strategies for the management of type 2 diabetes mellitus. J Pharmacy Practice. 2004;17(1):49–54.
121. Centers for Disease Control and Prevention (CDC). Incidence of end-stage renal disease attributed to diabetes among persons with diagnosed diabetes—United States and Puerto Rico, 1996–2007. MMWR Morb Mortal Wkly Rep. 2010;59(42):1361.
122. National Institute of Diabetes and Digestive and Kidney Diseases. United States Renal Data System: USRDS 2005 annual data report. Bethesda, MD: National Institutes of Health; 2005.
123. Wolfe RA, Gaylin DS, Port FK, Held PJ, Wood CL. Using USRDS generated mortality tables to compare local ESRD mortality rates to national rates. Kidney Int. 1992;42(4):991.
124. United States Renal Data System. Excerpts from the USRDS 2005 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2006;47 Suppl 1:S1.
125. Locatelli F, Pozzoni P, DelVecchio L. Renal replacement therapy in patients with diabetes and ESRD. J Am Soc Nephrol. 2004;15:S25–9.
126. Lok CE, Oliver MJ, Rothwell DM, Hux JE. The growing volume of diabetes related dialysis: a population based study. Nephrol Dial Transplant. 2004;19:3098–103.
127. Pumim LB, Heimburger O, Qureshi AR, et al. Accelerated lean body mass loss in incidence chronic dialysis patients with diabetes mellitus. Kidney Int. 2005;3:2368–74.
128. Siew ED, Ikizler TA. Insulin resistance and protein energy metabolism in patients with advanced chronic kidney disease. Semin Dial. 2010;23(4):378–82.
129. Mak RD, DeFronzo RA. Glucose and insulin metabolism in uremia. Nephron. 1993;61:377.
130. Mak RH. Impact of end-stage renal disease and dialysis on glycemic control. Semin Dial. 2000;13:4–8.
131. Shrishrimal K, Hart P, Michota F. Managing diabetes in hemodialysis patients: observations and recommendations. Cleve Clin J Med. 2009;76(11):649–55.
132. Biesenback G, Raml A, Schmekal B, et al. Decreased insulin requirement in relation to GFR in nephropathy in type 1 and insulin-treated type 2 diabetic patients. Diabet Med. 2003;20:642–5.
133. Kovesdy CP, Park JC, Kalantar-Zadeh K. Glycemic control and burnt-out diabetes in ESRD. Semin Dial. 2010;23:148–56.
134. Akmal M. Hemodialysis in diabetic patients. Am J Kidney Dis. 2001;38:S195–9.
135. Morioka T, Emoto M, Tabata T, et al. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care. 2001;24:909–13.
136. Burrowes JD, et al. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross-sectional results from the HEMO study. J Ren Nutr. 2003;13(3):191–8.
137. Burmeister JE, Scapini A, da Rosa Miltersteiner D, et al. Glucose added dialysis fluid prevents asymptomatic hypoglycaemia in regular hemodialysis. Nephrol Dial Transplant. 2007;22:1184–9.

138. Jackson MA, Holland MR, Nicholas J, et al. Hemodialysis-induced hypoglycemia in diabetic patients. Clin Nephrol. 2000;54:30–4.
139. Jackson MA, Holland MR, Nicholas J, et al. Occult hypoglycaemia caused by hemodialysis. Clin Nephrol. 1999;51:242–7.
140. Sitter T, Sauter M. Impact of glucose in PD: saint or sinner? Perit Dial Int. 2005;25:415–25.
141. Torun D, Ogurzkurt L, Sezer S, et al. Hepatic subcapsular steatosis as a complication associated with intraperitoneal insulin treatment in diabetic peritoneal dialysis patients. Perit Dial Int. 2005;25:595–600.
142. Strid H, Simren M, Johansson A, et al. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological well-being. Nephrol Dial Transplant. 2002;17:1434.
143. Gokal R. Peritoneal dialysis in the 21st century: an analysis of current problems and future developments. J Am Soc Nephrol. 2002;12:S104–16.
144. Yao Q, Lindholm B, Heimburger O. Peritoneal dialysis prescription for diabetic patients. Perit Dial Int. 2005;25:S76–9.
145. Liu J, Rosner MH. Lipid abnormalities associated with end-stage renal disease. Semin Dial. 2006;19:32–40.
146. Wong Y-H, Szeto C-C, Chow K-M, et al. Rosiglitazone reduces insulin requirements and c-reactive protein levels in type 2 diabetes patients receiving peritoneal dialysis. Am J Kidney Dis. 2005;46:713–9.
147. Quellhorst E. Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration. J Am Soc Nephrol. 2002;12:S92–6.
148. Diaz-Buxo JA. Blood glucose control in diabetics: I. Semin Dial. 1993;6:392.
149. Daniels ID, Markell MS. Blood glucose control in diabetics: II. Semin Dial. 1993;6:394.
150. Tzamaloukas AH, Oreopoulos DG. Subcutaneous versus intraperitoneal insulin in the management of diabetics on CAPD: a review. In: Khanna R, Nolph KD, Prowant B, et al., editors. Advances in peritoneal dialysis, vol. 7. Toronto: University of Toronto Press; 1991. p. 81–5.
151. Khalili KI, Lan FP, Hanbridge AE, et al. Hepatic subcapsular steatosis in response to intraperitoneal insulin delivery: CT findings and prevalence. AJR Am J Roentgenol. 2003;180:1601–4.
152. Selgas R, Lopez-Riva A, Alvaro F, et al. Insulin influence on the mitogenic-induced effect of the peritoneal effluent in CAPD patients. In: Khanna R, Nolph KD, Prowant B, et al., editors. Advances in peritoneal dialysis, vol. 7. Toronto: University of Toronto Press; 1991. p. 161–4.
153. Ansari A, Thomas S, Goldsmith D. Assessing glycemic control with diabetes and end-stage renal disease. Am J Kidney Dis. 2004;41:523–31.
154. Uhlig K, Levey AS, Sarnak MJ. Traditional cardiac risk factors in individuals and chronic kidney disease. Semin Dial. 2003;16:116–27.
155. KDOQI clinical practice guidelines and clinical recommendations for cardiovascular disease in dialysis patients. http://www.kidney.org/professionals/kdoqi/guidelines_cvd/guide11.htm. Accessed 2 Dec 2012.
156. Szeto CC, Chow KM, Kwan BC, et al. New-onset hyperglycemia in non-diabetic Chinese patients started on peritoneal dialysis. Am J Kidney Dis. 2007;49:524.
157. De Boer MJ, Miedema K, Casparie AF. Glycosylated haemoglobin in renal failure. Diabetologia. 1980;18(6):437.
158. Scott MG, Hoffmann JW, Meltzer VN, Siegfried BA, Chan KM. Effects of azotemia on results of the boronate-agarose affinity and ion-exchange methods for glycated hemoglobin. Clin Chem. 1984;30(6):896.
159. Wettre S, Lundberg M. Kinetics of glycosylated haemoglobin in uraemia determined on ion-exchange and affinity chromatography: no increase in the rate of glycosylation. Diabetes Res. 1986;3(2):107.
160. Paisey R, Banks R, Holton R, Young K, Hopton M, White D, Hartog M. Glycosylated haemoglobin in uraemia. Diabet Med. 1986;3(5):445.
161. Joy MS, Cefalu WT, Hogan SL, Nachman PH. Long-term glycemic control measurements in diabetic patients receiving hemodialysis. Am J Kidney Dis. 2002;39(2):297.
162. Williams ME, Lacson Jr E, Wang W, et al. Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. Clin J Am Soc Nephrol. 2010;5:1595–601.
163. Duong U, Mehrotra R, Molnar MZ, et al. Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. Clin J Am Soc Nephrol. 2011;6:1041–8.
164. Ricks J, Molnar MZ, Kovesdy CP, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. Diabetes. 2012;61:708–15.
165. Kalantar-Zadeh K. A critical evaluation of glycated protein parameters in advanced nephropathy: a matter of life or death. Diabetes Care. 2012;35:1625–8.
166. KDOQI. KDOQI clinical practice guidelines and clinical recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49:S62–73.
167. Mehrotra R, Kalantar-Zadeh K, Adler S. Assessment of glycemic control in dialysis patients with diabetes: glycosylated haemoglobin or glycated albumin? Clin J Am Soc Nephrol. 2011;6:1520–2.
168. Freedman BI, Shenoy RN, Planer JA, et al. Comparison of glycated albumin and haemoglobin A1c concentration in diabetic subjects on peritoneal and hemodialysis. Perit Dial Int. 2010;30:72–9.

169. Peacock TP, Shihabi ZK, Bleyer AJ, et al. Comparison of glycated albumin and haemoglobin A1c levels in diabetic subjects on hemodialysis. Kidney Int. 2008;73:1062.
170. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2007;20 Suppl 1:S4–41.
171. Gerich JE. The importance of controlling postprandial hyperglycemia. Pract Diabetol. 2005;24:22–6.
172. Hirsch IB, Bergenstal RM, Parkin CG, et al. A real-world approach to insulin therapy in primary care practice. Clin Diabetes. 2005;23:78–86.
173. Klonoff DC. Continuous glucose monitoring. Diabetes Care. 2005;28:1231–9.
174. National Kidney Foundation. KDOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35 Suppl 1:S1–140.
175. Pupim LB, Flakoll PJ, Majchrzak KM, et al. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. Kidney Int. 2005;68:1857–65.
176. Noori N, Kopple JD. Effect of diabetes mellitus on protein-energy wasting and protein wasting in end-stage renal disease. Semin Dial. 2010;23(2):178–84.
177. Cano NJM, Roth H, Aparicio M, et al. Malnutrition in hemodialysis diabetic patients: evaluation and prognostic influence. Kidney Int. 2002;62:593–601.
178. Chavez EM, Taylor GW, Borrel LN, Ship JA. A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;92:281–91.
179. Moore PA, Guggenheimer J, Etzel KR, et al. Type 1 diabetes mellitus, xerostomia and salivary flow rates. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92:281–91.
180. Meurman JH, Collin HL, Niskanen L, et al. Saliva in non-insulin-dependent diabetic patients and control subjects. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86:69–76.
181. Chavez EM, Borrell LN, Taylor GW, et al. A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91:166–73.
182. Sreebny LM, Yu A, Green A, et al. Xerostomia in diabetes mellitus. Diabetes Care. 1992;15:900–4.
183. Vinik AI, Freeman R, Erbas T. Diabetic autonomic neuropathy. Semin Neurol. 2003;23:365–72.
184. Grodstein G, Harrison A, Roberts C, et al. Impaired gastric emptying in hemodialysis patients (abstract). Kidney Int. 1979;16:952.
185. Schoenmakere G, Vanholder R, Rottey S, Duym P, Lameire N. Relationship between gastric emptying and clinical and biochemical factors in chronic haemodialysis patients. Nephrol Dial Transplant. 2001;16(9):1850.
186. Rothstein RD, Alavi A. The evaluation of the patient with gastroparesis secondary to insulin-dependent diabetes mellitus. J Nucl Med. 1992;33(9):1707.
187. Brown-Cartwright D, Smith HJ, Feldman M. Gastric emptying of an indigestible solid in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. Gastroenterology. 1988;95(1):49.
188. Bird NJ, Streather CP, O'Doherty MJ, Barton IK, Gaunt JI, Nunan TO. Gastric emptying in patients with chronic renal failure on continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant. 1994;9(3):287.
189. Fernström A, Hylander B, Grybäck P, Jacobsson H, Hellström PM. Gastric emptying and electrogastrography in patients on CAPD. Perit Dial Int. 1999;19(5):429.
190. Duby JJ, Campbell RK, Setter SM, et al. Diabetic neuropathy: an intensive review. Am J Health Syst Pharm. 2004;61:160–76.
191. Vinik AI, Master R, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553–74.
192. Syed AA, Rattansingh A, Furtado SD. Current perspectives on the management of gastroparesis. J Postgrad Med. 2005;51:54–60.
193. Lin Z, Forster J, Sarosiek I, et al. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. Diabetes Care. 2004;27:1071–6.
194. Rayner CK, Samson M, Jones KL, Horowitz M. Relationship of upper gastrointestinal motor and sensory function with glycemic control. Diabetes Care. 2001;24L:371–81.
195. Funnell MM, Greene DA. Diabetic neuropathy. In: Funnell MM, Hunt C, Kulkarni K, Rubin RR, Yarborough PC, editors. A core curriculum for diabetes education. 3rd ed. Chicago: American Association of Diabetes Educators; 1998. p. 709–43.
196. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. Diabetes Spectrum. 2007;20(4):231–4.
197. Staels B, Handelsman Y, Fonseca V. Bile acid sequestrants for lipid and glucose control. Curr Diab Rep. 2010;10(1):70–7.
198. Karl DM. Learning to use pramlintide. Pract Diabetol. 2006;25:43–6.
199. Uribarri J, Cai W, Ramdas M, Goodman S, Pyzik R, Chen X, Zhu L, Striker GE, Vlassara H. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care. 2011;34(7):1610–6.
200. KDIGO. 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:5–14. doi:10.1038/kisup.2012.77.

Chapter 9
Dyslipidemias

Judith A. Beto, Vinod K. Bansal, and Wendy E. Ramirez

Key Points

- Define dyslipidemia in CKD from a pathophysiological and metabolic perspective.
- Review current clinical practice guidelines, evidence-based literature, and peer-reviewed recommendations.
- Identify key assessment and intervention strategies.
- Outline parameters of dietary and non-dietary treatment to reduce lipidemia.

Keywords Dyslipidemia • Nutrition • Diet • Chronic kidney disease

Introduction

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) has produced a cohort of clinical practice guidelines directed toward improving the quality and breadth of care given to patients with chronic kidney disease (CKD) [1]. The KDOQI Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification created a clinical action plan that defined five stages of kidney disease by estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease (MDRD) equation [2]. This classification system redirected the existing focus when patients were near or at kidney failure (stage 5 requiring renal replacement therapy such as hemodialysis or transplantation) to earlier clinical intervention during stages 1–4 which might delay or retard progression. By applying the KDOQI classification system to existing population surveys, it is now conservatively estimated that more than 20 million Americans (one out of nine adults) have some risk factors for CKD [2].

Recent analyses have suggested an increase in cardiovascular disease (CVD) as high as 100 % greater in CKD compared to the general population even when matching for gender, race, age, and

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other confounding risk factors. Control of dyslipidemia in earlier stages of CVD may help lower or prevent cardiovascular risk [3, 4].

Lipid screening was added to the expanded activities for the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) beginning in 2006 [5]. The American Kidney Fund's multiple screening projects [6] and the National Institute of Diabetes and Digestive and Kidney Disease's National Kidney Disease Education Program (NKDEP) [7] both include lipid levels as part of their CKD risk factor evaluation. The KDOQI Clinical Practice Guidelines for managing dyslipidemia in CKD focus on patients undergoing renal replacement therapy in stage 5 [4]. This chapter will focus on the definition and treatment of dyslipidemia in stages 1–5 of CKD.

Pathophysiology

Dyslipidemia is defined as elevated serum levels of lipid components in the blood: total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and other lipid particles such as triglycerides [8]. Abnormal lipid profiles are seen in kidney function impairment and particularly in protein-losing nephropathies such as nephrotic syndrome [4].

Lipid metabolism, specifically cholesterol synthesis, takes place in the liver. The liver produces bile which is the primary lipid-reducing agent stored in the gallbladder. Cholesterol can be synthesized in the liver, cholesterol can be removed from circulating lipoproteins, and cholesterol can also be directly absorbed from the small intestine from cholesterol secreted in the bile or from dietary cholesterol. Excess circulating cholesterol results in hyperlipidemia. Individual variation in lipid response comprises differences in absorption or biosynthesis of primary and receptor-mediated lipid products that may or may not be CKD related. Chronic elevation may lead to deposits on inner arterial walls (fatty plaque) resulting in accumulation and atherosclerosis.

The process of reverse cholesterol transport also exists whereby cholesterol may be removed from areas of lipid accumulation and returned to circulation. The exact mechanisms responsible, however, are still being understood. HDL, as the primary carrier, transports cholesterol back to the liver where it is either reused or excreted. This metabolic process uses a cohort of enzymes and protein pathways to decrease monocyte penetration of wall sites. Macrophages attract oxidized LDL which appears to increase inflammatory effects [8].

Serum triglycerides, represented primarily as chylomicrons, move into the lymphatic system. From this point, they enter directly into blood circulation at the internal jugular and subclavian vein junction. The exact role of triglycerides in the CVD process is still evolving. CKD patients often have elevated levels in conjunction with other abnormal lipid values. A distinct combined profile of elevated triglycerides, low HDL, and elevated LDL may represent a more accurate risk scenario [9].

Existing Clinical Practice Guidelines and Peer-Reviewed Recommendations

KDOQI suggests that all CKD patients should be managed as high risk using existing lipid guidelines for non-CKD high-risk patients. Specific KDOQI guidelines have been published for dyslipidemias in CKD and are discussed in this chapter [4, 10]. Currently, there are no long-term studies of lipid management in CKD patients that provide any additional information to direct care. Two systematic reviews and meta-analyses supported the beneficial, low-risk effect of dietary and pharmaceutical modifications to reduce level of serum lipids in CKD stages 1–4 but reported no clear benefit in stage 5 [11, 12]. The role of lowering serum lipids in stage 5 patients currently on hemodialysis remains unclear. Two major randomized clinical trials in the dialysis population showed mixed results with

cardiovascular outcome. The use of the statin rosuvastatin did lower LDL significantly but did not have any benefit in the combined primary endpoint of death from cardiovascular cases, nonfatal myocardial infarct, or nonfatal strokes in a cohort of over 3,000 hemodialysis patients [13]. In the SHARP trial (Study of Heart and Renal Protection), a combination therapy of simvastatin plus ezetimibe was used. The overall conclusion was that this therapy was effective in reducing atherosclerotic events by 17 % in moderate to advanced CKD patients, but the effect on patients already on dialysis was hard to determine [14]. In a recent observational replication of the 4D study on a large historical dialysis organization database, hemodialysis diabetic patients on statin ($n=5,144$) matched to similar patients not treated with a statin ($n=5,144$) were compared for cardiovascular outcomes. Statin use was associated with some decrease in outcomes, but the size of the benefit was considerably smaller than reported in the general population with statin use [15].

Assessment

Biochemical

Serum lipids should be assessed at the first office visit. Patients may have been screened for TC with a non-fasting sample as part of general risk assessment. Ideally, a fasting lipid profile should be obtained. The lipid profile should include TC, HDL, LDL, and triglycerides. Goal ranges as shown in Table 9.1 are the same as the general population [9, 16]. Values reported outside of reasonable laboratory parameters should be repeated for reliability. Instructions for at least a 12-h fast should be reinforced with the patient prior to blood draws for highest accuracy [9, 16].

Serum lipids should be drawn annually or whenever a treatment change warrants reassessment of effect. Serum lipid patterns may change during CKD stages. The ramifications of the duration of lipid abnormalities and their relationship to later CVD risk are unknown. When hyperlipidemia is particularly resistant to standard treatment, the clinician may consider additional biochemical testing for contributory inflammatory markers such as high sensitivity (C-reactive protein) [4, 10, 16]. Hidden sources of infection should be investigated (i.e., foot and nail infection particularly in diabetics) and advanced periodontal disease.

Physical

Measured, rather than self-reported, height and weight should be recorded. The body mass index should be calculated and compared to standardized tables for baseline assessment. Patients with fluid accumulation such as edema, amputees, or other body composition imbalances need special adaptations to standardized formulas [17]. Newer emphasis has been placed on waist-hip circumference as

Table 9.1 Goals for fasting serum profiles from the National Institute of Health's National Cholesterol Education Program

Fasting parameter (mg/dL)	Optimal	Borderline	High
Total cholesterol	<200	200–230	≥240
LDL cholesterol	<100–129	130–159	≥160
HDL cholesterol	≥60	41–59	<40
Triglycerides	<150	150–199	≥200

Adapted from [13]

a more predictive measure of body composition. General adult guidelines are a maximum waist circumference of 102 cm (40 in.) for men and 88 cm (35 in.) for women [16]. Physical assessment should include an evaluation of recommended cardiac activity level and intensity based on American Heart Association guidelines in preparation for lifestyle intervention [15, 16].

Patterns of body composition have received some attention in the literature. Ideally, individuals should have optimal lean muscle lean mass in proper proportion to adipose tissue to achieve a body mass index comparable to healthy body weight. Serum triglycerides are often elevated in conjunction with obesity and metabolic syndrome [9, 15, 16]. There are several handheld instruments that can be used to estimate lean body mass with individual strengths and weaknesses on reliability and validity of data over time. Employing a single instrument to track changes of an individual over time using their own baseline to measure progress may be more consistent and reliable rather than comparing to a heterogeneous group mean or trend. Adipose tissue location, particularly abdominal fat stores estimated by waist circumference, has also been used in cardiovascular risk factor evaluation.

A detailed medical history should be taken including but not limited to prior laboratory values, family history of associated lipid or vascular disorders, comorbid conditions, and current medications [4, 10, 17, 18].

Nutritional

A registered dietitian will be most able to evaluate the dietary intake and recommend specific food changes to promote lower serum lipids. Dietary intake patterns can be assessed by one of several methods (see Chap. 3). Specific attention should be given to the type of fat consumed by saturation level, pattern of fat consumption throughout day, and use of fat in food preparation. Detailed information from a computer analysis of nutrient content should guide dietary changes [4, 16–18].

The Dietary Approach to Stop Hypertension (DASH) study provided evidence to support weight reduction as an evidence-based strategy to aid in blood pressure control. As part of this plan, emphasis is placed on choosing sources of unsaturated dietary fat to support reduction of serum lipids as well [19]. Adaptations may be required in CKD. The reduction in protein portions may aid in slowing progression of CKD. The increase in dairy products may increase serum phosphorus. The increase in fruits and vegetables may decrease serum triglycerides by reducing simple sugars but may increase dietary potassium. Serum electrolytes should be monitored in later stages of CKD (stage 4).

A single educational session will not be sufficient to enact dietary change. Routinely scheduled long-term monitoring is required. The services of a registered dietitian delivered to Medicare-eligible patients diagnosed with diabetes and kidney disease prior to dialysis are reimbursable with a referral from their treating physician [20]. Patients undergoing dialysis therapy are covered for nutritional services within the center where they receive treatment. This professional assessment and ongoing monitoring are essential to attain the dietary goals.

Intervention

Lifestyle

The American Heart Association recommends establishing a consistent daily physical activity pattern for all adults. Sustained cardiac activity will promote the use of circulating lipids for energy, rather than storage as atherosclerotic deposits. Also regular exercise to achieve a sustained cardiovascular

benefit heart rate level may reduce serum fat particle size [21]. Patients can visually understand this exercise principle if a bottle of salad oil combined with red vinegar is shown first in a resting state of separated layers and then shaken (as in exercise) to distribute and reduce the fat particle size.

The increased cardiac output and corresponding muscle strength generally have minimal risk when undertaken within the context of daily activities found in the home (climbing stairs, walking, vacuuming, carrying groceries). CKD patients should be evaluated for anemia and potential deficiencies (i.e., iron, folic acid, vitamin B_{12}) which can reduce oxygen-carrying capacity of the blood and exhibit symptoms of fatigue. The use of erythropoietin, the kidney hormone decreased in CKD, should be administered and monitored using updated KDIGO guidelines [22].

The American Heart Association recommends a minimum of 10,000 steps per day to achieve basic cardiac health [21]. A simple pedometer can be used to record steps taken per day. Complicated models monitoring stride distances are not necessary. Although the accuracy between pedometers has been shown to be variable, the use of the same pedometer by the same patient on a daily basis minimizes variability and provides a consistent baseline measurement upon which to monitor physical activity. Physical activity can be increased by small increments of as few as 100–250 steps per day until the minimal goal has been reached or as higher goals are attained. The use of a pedometer should become routine over time. The placement of the pedometer in relation to the hip flex movement is important to obtain accurate and consistent results.

To sustain motivation, many individuals benefit from pairing with a "walking buddy" or walking group to provide continuous support and activity opportunities. For example, individuals who own dogs often increase their daily walking frequency and distance when compared to individuals who do not. Social support generally has been shown to decrease relative risks of death in both the general and chronic disease populations.

Dietary

The general dietary principles to treat dyslipidemia by diet in CKD stages 1–5 are shown in Table 9.2. The key component of dietary intervention is type and amount of fat consumed with emphasis on reducing saturated and *trans*-fatty acid content. The type and amount of simple carbohydrate is also important when treating elevated serum triglycerides [9]. These general population goals are appropriate for both healthy and CKD individuals [4, 10, 16–18, 21]. As such, the integration of diet modifications can be beneficial to both the individual as well as other individuals living within that household, potentially maximizing the benefit and compliance to everyone.

Determination of Nutrition Prescription

General guidelines suggest reducing total fat calories but also assume individuals will not consume more calories per day than they need to attain or sustain a healthy weight. The estimation of the amount of daily dietary fat to be consumed should be based on a reasonable body weight. Obesity will be promoted or sustained using the current body weight if presently at obese or overweight levels. Body mass index of 25–29.9 kg/m^2 is considered overweight by government guidelines. The consumption of "empty" calories will contribute to overall non-lean body mass. The definition of "healthy" weight in many patients within the context of chronic disease has challenges of its own and the use of formulas contained in KDOQI guidelines have been shown to be used inconsistently in practice [23].

Recent literature from the chronic dialysis population (CKD stage 5) has shown a trend toward greater survival at higher body weight levels compared to normal and underweight levels. Although

Table 9.2 Summary of dietary recommendations to address dyslipidemia in CKD stages 1–5

Dietary modification	Intervention method	Anticipated change
Match energy intake to energy output	Calculate and implement amount of calories required using goal body weight	Attain and maintain healthy body weight
Match caloric distribution among diet components	Provide adequate dietary protein while providing sufficient total calories	Maintain normal serum albumin
	Emphasize quality of protein when quantity limited to potentially retard progression	Decrease risk of protein-calorie malnutrition
Decrease total fat calories to ≤30 % of total calories	Decrease total fat calories consumed from all dietary sources	Normalize serum lipids
Decrease total cholesterol intake <300 mg/day	Reduce intake of dietary cholesterol (i.e., egg yolks, animal fats); substitute whole milk dairy products with skim and low-fat alternatives; replace egg yolks with egg substitute products	Normalize serum cholesterol
Decrease saturated fat calories <7 % of total calories	Decrease intake or avoid saturated fats (i.e., animal fats, butter, full fat dairy products, mayonnaise, avocado, tropical oils such as palm and coconut)	Decrease LDL
Change type of fats used in food preparation	Promote intake of non-hydrogenated vegetable oils (peanut, canola, olive) or nut oils (walnut, flaxseed)	Decrease LDL
Increase use of monounsaturated fats within total fat intake amount	Promote use of olive oil, sunflower oil, canola oil	Increase HDL
Increase use of omega-3 fatty acids within total fat intake amount	Increase consumption of green leafy vegetables, flaxseed, nuts (almonds, walnuts), and use of fatty fish 1–2 servings/week	Increase HDL
Avoid use of *trans*-unsaturated fatty acids	Avoid commercially fried foods, hydrogenated fats, partially hydrogenated vegetable oils and margarines, and processed foods containing these fats	Decrease LDL Increase HDL
Decrease total calories to achieve weight loss	Calculate and implement amount of calories required to achieve reduction in current body weight to goal body weight	Decrease in body weight Decrease in serum triglycerides
Decrease intake of simple sugars and alcohol consumption	Promote consumption of low glycemic intake foods; reduce or eliminate alcohol consumption	Decrease in serum triglycerides

Adapted from [4, 9, 10, 16, 18]

the exact mechanism is not fully understood, this "J-curve" observation may be related to the cushion of additional body fat stores available for energy during concurrent hospitalization or stress periods. It is important to maintain a reasonable body weight during CKD stages 1–4 and avoid malnutrition when progressing to CKD stage 5. The exact benefit or need for a "cushion" of fat stores and muscle mass, however, has yet to be determined [24].

Amount and Type of Dietary Fat

A typical 2,000 cal per day diet should contain ≤30 % total fat. This is calculated as 600 cal (30 % of 2,000 cal and 600/9 cal/g of fat) which equals approximately 66 g or less of total fat per day. No more than 7 % of total calories (140 cal or 16 g of fat) should come from saturated fat [4, 16, 17].

Saturated fat has more hydrogen bonds than polyunsaturated and monounsaturated fat. Typically, saturated fat remains solid at room temperature (such as animal fat from meat, lard, butter), whereas unsaturated fat is softer or liquid at room temperature (such as vegetable oils or tub compared to stick margarine). These hydrogen bonds are more difficult to break down and metabolize, thus circulating as larger fat particles in the serum. The composition of the diet should be changed to encourage the intake of predominantly polyunsaturated and monounsaturated sources within the total daily fat intake.

Trans-fatty acids have been altered during processing to change the natural *cis* configuration (the most unsaturated version) to the *trans* configuration (primarily to increase shelf life). *Trans*-fatty acids function as saturated fatty acids during metabolism and have been implicated in reducing HDL and increasing LDL cholesterol [8]. They are found predominantly in processed foods (cookies, crackers, baked goods). Many fast-food restaurants use frying oils that may contain a high content of *trans*-fatty acids. Several major cities are increasing dietary far awareness to the general public by mandating bans of *trans*-fatty acids in restaurants.

Nutrition labels allow for rounding of fat grams on a label to 0.5 g or zero if that food contains less than 5 g of fat per portion and rounding to the nearest 1 g if containing more than 5 g of fat per portion. If a consumer uses the nutrition label as the general guide to counting fat grams per day, the accuracy of their estimate can be proportionate to the number of food items they consume each day. Nutrition labels in the United States must now also contain *trans*-fatty acid composition [25]. The American Heart Association has a Heart-Check Mark Food Certification Program [26] with specific nutritional guidelines that aid consumers in selecting a wide variety of foods that meet the nutrition prescription discussed in this chapter.

Incorporation of Type of Carbohydrate, Dietary Fiber, and Plant Sterols

Replacement of simple carbohydrates with more complex dietary sources in conjunction with weight reduction has been shown to decrease serum triglycerides [9, 16]. The level of dietary fiber has generally decreased in the Western diet pattern with the increased consumption of refined foods, higher animal protein, and lower plant sources. Increasing dietary fiber and including plant sterols in the diet have also been identified as effective dietary interventions to address hyperlipidemia [16, 18].

Increasing the consumption of dietary fiber to levels of 20–30 g/day has been linked to lower LDL levels. Soluble fiber binds to bile acids which may decrease the absorption of cholesterol. Both soluble and insoluble fiber may also decrease gastrointestinal transit time which may improve insulin sensitivity by slowing carbohydrate absorption. Insoluble fiber is found primarily in wheat products but has shown less LDL effect than soluble. Soluble fiber is found in a wide variety of foods including barley, bran, raw or partially cooked fruits and vegetables, nuts and seeds, and oats and oatmeal. A wide variety of over-the-counter psyllium capsules and soft fiber equivalents are available as alternatives or supplements to dietary modification. Fiber intake should be increased gradually over time in conjunction with liberal fluid intake to decrease gastrointestinal symptoms until gut adapts to higher load [16, 18]. Excess dietary fiber intake by diet or supplements can result in negative effects of gastrointestinal symptoms and potential malabsorption of selected nutrients. Dietary fluid and potassium restrictions may require adaptations when progression to CKD stage 5 is eminent.

Plant sterols and their stanol esters are naturally present in small quantities in plant sources. Most research has been done in soybean derivatives where they have been chemically concentrated to produce commercial products marketed as butter or margarine substitutes. Plant sterol esters in this new format which exceed what can be consumed by diet alone have been shown to potentially lower LDL in the general population. Clinical trials have included more than 1,800 people with doses of up to 25 g/day. No clinical studies have been done in CKD patients, but they are rated as a safe food-grade additive. A daily intake of approximately two tablespoons consumed as part of two separate meals per day (total 2–3 g/day) is the recommended dose with no evidence that higher levels produce a greater effect [16].

Pharmacological

There are several classes of drugs used for reducing serum lipids as shown in Table 9.3. Two recent systematic reviews and meta-analysis have shown moderate to high evidence that statin (HMG CoA reductase inhibitor) use in CKD stages 1–4 decreases risk for all-risk and CVD mortality while preserving existing kidney function [11, 12]. Other recent studies in dialysis, patients have shown limited benefit in the context of minimal risk [13–15]. Each drug has a unique mechanism by which it changes lipid metabolism or absorption. The most common mechanism is metabolically blocking of the enzymes that aid in the manufacturer of cholesterol. Others use a variety of mechanisms to change the way in which dietary cholesterol is absorbed. All are taken orally and use the gastrointestinal tract as an important metabolic medium. A complete drug interaction analysis should be performed by a registered pharmacist at regular intervals to monitor potential problems. For example, some statins interfere with the absorption of drugs such as immunosuppressive agents such as cyclosporine [27].

Regular bowel habits will promote the efficacy of many of these drugs. The gastrointestinal tract can increase absorption of specific dietary components such as potassium in CKD as a compensatory mechanism to decreased absorption–reabsorption by the kidneys. Constipation may be a problem due to lower fluid intake and binding features of concurrent drugs such as phosphate binders in later stages of CKD.

The type of pharmacological intervention used is not as important as the attainment of the overall goal of lipid reduction. Each drug has specific potency effects, doses, and safety data. A variety of options may be necessary to achieve compliance within financial and administration issues while avoiding side effects and potential complications. Dietary and pharmacological intervention should be used together to maximize lipid reduction effect as their mechanisms of action are complementary, not competitive [4, 16, 18].

Table 9.3 Summary of selected pharmacological agents to address dyslipidemia in CKD stages 1–5

Mechanism of action/drug class	Selected pharmacological agent by generic name	Brand name
Bile acid sequestrants	Cholestyramine	Questran
	Cholestipol	Colestid
	Colesevelam	Welchol
Fibric acid	Fenofibrate	Tricor
	Gemfibrozil	Lopid
Statins	Atorvastatin	Lipitor
HMC-CoA reductase inhibitors	Fluvastatin	Lescol
	Lovastatin	Mevacor, Altoprev (extend release)
	Pitavastatin	Livalo
	Pravastatin	Pravachol
	Rosuvastatin	Crestor
	Simvastatin	Zocor
Cholesterol inhibitor	Ezetimibe	Zetia
Nicotinic acid	Niacin	Niacor, Slo-niacin (sustained release), Niaspan (extended release)
Combinations	Ezetimibe and simvastatin	Vytorin
	Niaspan and lovastatin	Advicor

Adapted from [4, 10–15, 28]
Strongest evidence for use of statins (HMG CoA reductase inhibitors) in CKD stages 1–4, [11, 12]
All agents should be evaluated and monitored for drug–nutrient interactions, side effects, and tolerance in CKD stages 1–5

Summary

The achievement and reduction of dyslipidemia to optimal levels in CKD stages 1–5 is a multifactorial approach. Practitioners need to use comprehensive assessment techniques to evaluate the status of the individual. Intervention strategies that include physical activity, dietary changes, and pharmacological options need to be continually monitored to achieve goals. The use of a registered dietitian is necessary to provide the support and continuous monitoring of daily food intake to modify existing habits and promote new patterns. The individual should attain a healthy body weight while maintaining optimal nutrition status in preparation for progression to stage 5 CKD. A strong integrated health team approach is necessary to diagnose, evaluate, and treat dyslipidemia throughout the CKD stages. KDOQI guidelines provide a template upon which to plan and coordinate quality care.

References

1. Eknoyan G, Levin NW. An overview of the National Kidney Foundation-Dialysis Outcomes Quality Initiative implementation. Adv Ren Replace Ther. 1999;6:3–6.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(S1):S1–266.
3. Guidelines and Protocols Advisory Committee. Chronic kidney disease—identification, evaluation, and management of patients. British Columbia Medical Council, 2008. www.BCGuidelines.ca. Accessed 15 July 2012.
4. National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Dis. 2003;41:S1–92.
5. National Kidney Foundation. Advances in CKD detection and determination of prognosis: Executive summary of the National Kidney Foundation Kidney Early Evaluation Program (KEEP) 2012 annual data report. Am J Kidney Dis. 2013;61(4):S1–S3.
6. American Kidney Fund. Take charge: protect your kidneys. http://www.kidneyfund.org. Accessed 15 Feb 2012.
7. National Institutes of Health. National Kidney Disease Education Program. http://nkdep.nih.gov. Accessed 15 July 2012.
8. Gropper SS, Smith JL. Advanced nutrition and human metabolism. 5th ed. Belmont, CA: Thomson Wadsworth; 2011. p. 137–82.
9. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui M, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2252–332.
10. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2002;39(S3):S1–266.
11. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease. Ann Intern Med. 2012;157:251–62.
12. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrinin F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease. Ann Intern Med. 2012;157:263–75.
13. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
14. Barigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease: study of heart and renal protection: a randomised placebo-controlled trial. Lancet. 2001;377:2181–92.
15. Chan KE, Thadhani R, Lazarus JM, Hakim RM. Modeling the 4D study: statins and cardiovascular outcomes in long-term hemodialysis patients with diabetes. Clin J Am Soc Nephrol. 2010;5:856–66.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program [NCEP]. www.nih.gov. Accessed 15 July 2012.
17. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35(S2):S1–140.
18. Gidding SS, Lichtenstein AH, Faith MS, Karpyn A, Mennella JA, Popkin B, Rowe J, Van Horn L, Whitsel L. Implementing American Heart Association pediatric 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,

Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. Circulation. 2009;119:1161–75.
19. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation. 2010;122:406–41.
20. National Heart Lung Blood Institute. Your guide to lowering you blood pressure with DASH. http://www.nhlbi.gov/health/public/dash/new_dash.pdf. Accessed 15 July 2012.
21. Medical nutrition services: an overview. http://questions.cms.gov. Accessed 15 Feb 2012.
22. National Kidney Foundation. K/DOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. http://www.kidney.org/professionals/KDOQI/guidelines_anemiaUP/index.htm. Accessed 15 July 2012.
23. Harvey KS. Methods for determining health body weight in end stage renal disease. J Ren Nutr. 2006;16:269–76.
24. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, McAllister CJ, Shinaberger CS, Gjertson DW, Greenland S. Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. Am J Kidney Dis. 2005;46(3):489–500.
25. Food and Drug Administration. Food labeling guide. www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocument/default.htm. Accessed 15 July 2012.
26. American Heart Association. Heart-check mark nutritional guidelines. http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HeartSmartShopping/Heart-Check-Mark-Food-Certification_UCM_300914_article.jsp. Accessed 15 July 2012.
27. Drug Effectiveness Review Project. Oregon Health & Science University Evidence-Based Practice Center. Statins. http://derp.ohsu.edu/about/final-document-display.cfm. Accessed 15 Aug 2012.
28. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: Update. Am J Kidney Dis. 2012;60(5):850–866.

Chapter 10
Implications and Management of Obesity in Kidney Disease

Allon N. Friedman

Key Points

- A variety of anthropometric measurements can be used to estimate body fat in the kidney disease population.
- Glomerular filtration rate-estimating equations should be used cautiously in obese individuals.
- Obesity rates in patients with kidney disease and failure and post-kidney transplantation are increasing at least as rapidly as in the general population.
- The observation that obesity is associated with improved clinical outcomes in dialysis patients does not necessarily impute causality.
- Obesity is linked to structural, functional, hemodynamic, and molecular changes in the kidney that can often be reversed with weight loss.
- The pathophysiology of obesity-related kidney disease is complex and likely multifactorial.
- Reduced nephron mass may explain why certain individuals develop obesity-related kidney disease.
- Short-term studies suggest weight loss may improve markers of kidney health such as proteinuria.

Keywords Obesity • Kidney • Proteinuria • Glomerular filtration rate • Dialysis • Transplant • Weight • Bariatric surgery • Diet

Introduction

The obesity crisis sweeping the globe in recent decades has not spared the chronic kidney disease (CKD) population, and both patients and their nephrologists are now struggling with this formidable challenge. Of all the problems facing kidney disease patients, few have arisen with such rapidity to the forefront of health care, have the capacity to adversely influence health in such a wide variety of ways, and are as modifiable as obesity.

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This chapter is designed to give the reader a broad familiarity with the epidemiology, basic science, and clinical aspects of obesity as it relates to patients throughout the spectrum of kidney disease. Various controversies surrounding this topic will also be addressed. In doing so, this chapter will equip the reader with a comprehensive understanding of this important and rapidly evolving area.

Case Scenario

A 46-year old obese black female with a history of moderate hypertension, obstructive sleep apnea, and osteoarthritis was referred to nephrology clinic for evaluation of proteinuria. She was noted to have persistent proteinuria since she began seeing her internist 2 years ago. There is no prior history of diabetes and kidney disease or a family history of kidney disease. Review of systems revealed only chronic achiness in the knees and lower back. Medications included amlodipine, pravastatin, atenolol, and hydrocodone/acetaminophen as needed for arthritis. The patient denied tobacco, ethanol, illicit drugs, or nonsteroidal anti-inflammatory medication use. On exam the patient was comfortable and very obese appearing. Blood pressure was 152/78 mmHg, heart rate 67 beats/min, respirations 19 per minute, afebrile, weight 113.8 kg, height 160 cm, and body mass index (BMI) 43 kg/m^2. Physical exam revealed a bull neck precluding jugular venous pressure measurement, clear lung fields, pendulous breasts, normal heart sounds, obese abdomen, and 1+ pitting edema over both tibias. Urinalysis revealed a specific gravity of 1.020, pH 6, 2+ protein, and no blood. Urine sediment was bland. Spot urine protein/creatinine ratio was 2.2, blood urea nitrogen was 30, and serum creatinine was 1.7 mg/dL (estimated GFR [eGFR] of 42 mL/min/1.73 m^2). All other laboratory values were normal. The patient was initiated on lisinopril for blood pressure and proteinuria reduction and instructed to lose weight. With the addition of lisinopril, the proteinuria fell modestly (to a spot urine protein/creatinine ratio of 1.7). One year later the patient underwent a Roux-en-Y gastric bypass. Her weight 1 year postoperatively was 170 lb (BMI 29 kg/m^2). On her most recent visit 15 months post-surgery, her spot urine protein/creatinine ratio was 0.3 and serum creatinine 1.2 mg/dL (eGFR of 62 mL/min/1.73 m^2).

Defining Obesity

The definition of "excess" body fat is somewhat arbitrary, and there is no currently validated threshold to define obesity [1]. While a number of techniques can be used to accurately measure body fat content and/or patterns of unhealthy fat deposition—among them neutron activation analysis, dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance, air displacement plethysmography, computed tomography, and the like—their use is typically limited to the research environment.

In clinical practice and medical epidemiology, obesity is determined by simple measurements that "define" excess body fat, which themselves are partly derived from their associations with clinical risk (see Table 10.1). Perhaps the most commonly used marker for obesity in CKD patients is the BMI, a ratio of weight to height (i.e., weight (kg) divided by height (m^2)). Simple to calculate and easy to employ, the BMI is a reasonably good indicator of total body fat content in the general population as well as in CKD and dialysis patients [2–4]. One study of 77 patients with an eGFR of 40 mL/min found that a BMI greater than 30 kg/m^2 had a 100 % positive predictive value for detecting obesity compared with a reference body composition method, though its negative predictive value was only 30 % [3]. That is, a high BMI confirmed obesity while a low BMI did not exclude obesity. This study highlights some of the limitations of the BMI, which include the fact that it cannot distinguish lean from fat mass, peripheral from central/visceral fat, or derangements in volume status that may be misinterpreted as

Table 10.1 Classifying overweight and obesity according to BMI, waist circumference, and associated disease risk

			Disease risk[a] relative to normal weight and waist circumference	
			Men ≤102 cm	Men >102 cm
Classification	BMI (kg/m^2)	Obesity class	Women ≤88 cm	Women >88 cm
Underweight	<18.5		–	–
Normal weight[b]	18.5–24.9		–	–
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

Adapted from [2]

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease

[b]Increased waist circumference can increase risk even in persons of normal weight

excess adiposity. These limitations have spurred interest in alternative anthropometric measurements such as waist circumference and waist-to-hip ratio that detect excess visceral fat in a manner that the BMI does not. Visceral fat is currently considered an important causal risk factor for insulin resistance, the metabolic syndrome, and cardiovascular disease [5]. Recent studies suggest that these alternative metrics add important prognostic information in both kidney disease and dialysis populations [6–8].

In summary, commonly used anthropometric measurements have been demonstrated to provide useful information about adiposity status in kidney disease patients. However, their limitations should be kept in mind.

Measuring Kidney Parameters in Obese Individuals

The two most important clinical indicators of kidney function and health are the glomerular filtration rate and proteinuria [9, 10]. The glomerular filtration rate can be directly measured using various techniques such as plasma or urinary clearance of inulin or other exogenous markers. Of note, there is sparse information on the use of such methods in obese populations [11]. Because direct measurement is usually too cumbersome, time consuming, and costly for routine use, most clinicians and many researchers rely on creatinine-based formulas—including the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations—to estimate the glomerular filtration rate. However, such equations should be used with caution in individuals who are obese or whose weights are fluctuating for the following reasons: First, estimating equations work reasonably well in the populations they were derived in, but none of the equations were derived in primarily obese populations, which explains why their accuracy is reduced in that setting [12–15] or in the setting of weight gain or loss. Second, estimating equations rely heavily on serum creatinine as an endogenous filtration marker. However, serum creatinine is generated directly from muscle; the greater the muscle mass, the greater the creatinine generated. Therefore, any change in muscle mass as a result of weight gain or loss will also influence serum creatinine generation, making it difficult to differentiate changes in glomerular filtration from changes in muscle mass. Third, a number of these equations (e.g., MDRD, CKD-EPI) include an adjustment for body surface area in order to equalize differences in body size between individuals. This adjustment is based upon the observed relationship in mammals that glomerular filtration rate is proportional to body size [16], which is itself premised upon the fact that the kidney modifies its excretory (e.g., filtration) capabilities based upon the amount of metabolic by-products generated by the body [17, 18]. The use of such adjustments in obese individuals is problematic because it is lean, not fat,

mass that primarily generates metabolic waste, so adjusting for lean *and* fat mass introduces systemic bias and error into the process [19, 20].

Serum cystatin C is a relatively new endogenous marker of glomerular filtration that has been proposed as an alternative to serum creatinine. Originally believed to be unaffected by body mass, it now appears that this may not be the case [21, 22].

Proteinuria can be measured from a 24 h urine collection or, alternatively, estimated from a spot urine protein to creatinine ratio. Either method is acceptable in obese individuals. However, the latter is susceptible to bias when used for serial measurements during weight change because urine creatinine is dependent upon muscle mass, which will change with weight gain or loss. It will therefore be difficult to distinguish whether a rise in the urine protein to creatinine ratio in an obese individual after weight loss represents a true increase in proteinuria or simply a reduction of urinary creatinine from loss of lean mass. In the setting of changes in weight, a 24 h urine collection is therefore the preferred method of measurement.

Epidemiology and Trends in Obesity

Obesity is undoubtedly a scourge of modern times. Though it has traditionally been identified as a problem of affluent, Western societies, this is rapidly changing as underdeveloped regions of the world experience economic progress. According to the World Health Organization, in 2008 over one billion individuals were currently overweight, with at least 300 million being obese [23].

The obesity problem has also affected individuals in every phase of CKD. Though data specifically examining the prevalence of obesity in CKD stages 1 through 4 is not available, it is reasonable to assume that this is a common problem, given that over one-third of US adults in the general populace are obese [24]. This assumption is buttressed by the unsettling data about the prevalence of obesity in CKD patients at the point of initiating dialysis. A recent analysis of information collected between 1995 and 2002 in incident US dialysis patients found that the mean BMI steadily increased year after year at a rate twice as steep as what was observed in the general US population (8 % vs. 4 %) [25]. By 2002, nearly one-third of incident dialysis patients were obese. Especially disturbing is that the fastest rate of growth was observed in patients with more severe obesity (stage 2 or greater). The limited available data suggest that hemodialysis and peritoneal dialysis patients are equally at risk for being obese [26]. The increased prevalence of obesity extends even to kidney transplant recipients. In 2000, 25 % and 59 % of patients at time of kidney transplantation were obese or overweight, respectively, by BMI criteria, and the proportion of obese individuals rose by 116 % over the preceding decade and a half [27]. Further significant weight gain after transplantation (e.g., greater than 10 kg) is not uncommon [28].

An obvious explanation for such trends is that social factors making available an abundance of inexpensive, calorie-dense foodstuffs and the promotion of increasingly sedentary lifestyles affect individuals with kidney disease at least as much as they do the general populace. The fact that kidney disease patients are perhaps more than ever burdened by comorbid illnesses may further limit their ability to live healthier lifestyles. It is perhaps no coincidence that patients with diabetes who start dialysis (over 40 % of all such patients [29]) are more obese and have a greater trajectory of growth in obesity than their nondiabetic peers [25]. Specific renal-related factors may also play a role. One retrospective study of weight gain in peritoneal dialysis patients suggested that absorption of glucose in the dialysate plays an important role in certain predisposed patients [30]. A number of risk factors for weight gain after kidney transplantation have been identified [28] and are shown in Table 10.2. Of particular interest is steroid use, long considered to stimulate the appetite. In fact, the role of steroid use in weight gain is unclear [31]. While increasingly common steroid-free immunosuppressive regimens have been associated with reduced weight gain, patients still gain weight over time [32].

Table 10.2 Risk factors for weight gain post-kidney transplant

Traditional risk factors
• Younger age
• Female sex
• Black ethnicity
• Low socioeconomic status
• Preexisting obesity
Nontraditional risk factors
• Steroid use
• Number of rejection episodes
• Living donor kidney transplant
• Other immunosuppressive medications

From Potluri K, Hou S. Obesity in kidney transplant recipients and candidates. Am J Kidney Dis 2010;56:143–56. Reprinted with permission from Elsevier Limited

Obesity and Clinical Risk

Chronic Kidney Disease Stages 1–4

The relationship between obesity and the development and progression of chronic kidney disease has been intensely studied in recent years. A consensus is slowly beginning to emerge that obesity may be responsible for a large proportion of chronic kidney disease in the population. Using population attributable risk analyses, one group estimated that approximately one-fifth to one-fourth of kidney disease cases could be prevented by eliminating overweight and obesity [33].

A series of epidemiologic studies report that weight gain and/or obesity is an independent predictor of the development of proteinuria, kidney stones, acute kidney injury, and chronic kidney disease in the general population [34–40] or in higher-risk groups such as pre-hypertensive individuals [41]. These observations extend beyond ethnic and national lines to include Asians, Europeans, and Americans, as well as older adults. The risk that obesity confers is heightened in the presence of additional risk factors such as elevated blood pressure, lipid, or glucose levels that in combination are referred to as "the metabolic syndrome" [42, 43]. A high BMI has also been linked to the progression of preexisting glomerulonephritis and nondiabetic kidney disease [44, 45]. Limitations to such analyses include residual confounding and the estimation, rather than direct measurement, of the glomerular filtration rate.

However, obesity also appears to be an independent risk factor for progression to end-stage renal disease, an outcome that is not dependent upon the eGFR [46, 47]. In a population of over 300,000 healthy adult members of Kaiser Permanente, a higher BMI was a risk factor for the development of future kidney failure even after adjusting for baseline blood pressure and the presence of diabetes. Compared to individuals with normal weight, the adjusted relative risk for end-stage renal disease was 1.87 (95 % confidence interval (CI), 1.64–2.14) for overweight individuals, 3.57 (CI, 3.05–4.18) with a BMI between 30 and 34.9 kg/m^2, 6.12 (CI, 4.97–7.54) with a BMI between 35 and 39.9 kg/m^2, and 7.07 (CI, 5.37–9.31) with a BMI $\geq$ 40 kg/m^2 (see Fig. 10.1). Interestingly, the presence of obesity at time of initiation of dialysis has also associated with a more rapid decline in residual kidney function [48] as well as a family history of end-stage renal disease [49]. Whether this is due to environmental or genetic factors is not known. Finally, obesity as measured by waist-to-hip ratio but not BMI has been independently associated with a higher risk of cardiovascular events in persons with chronic kidney disease [7].

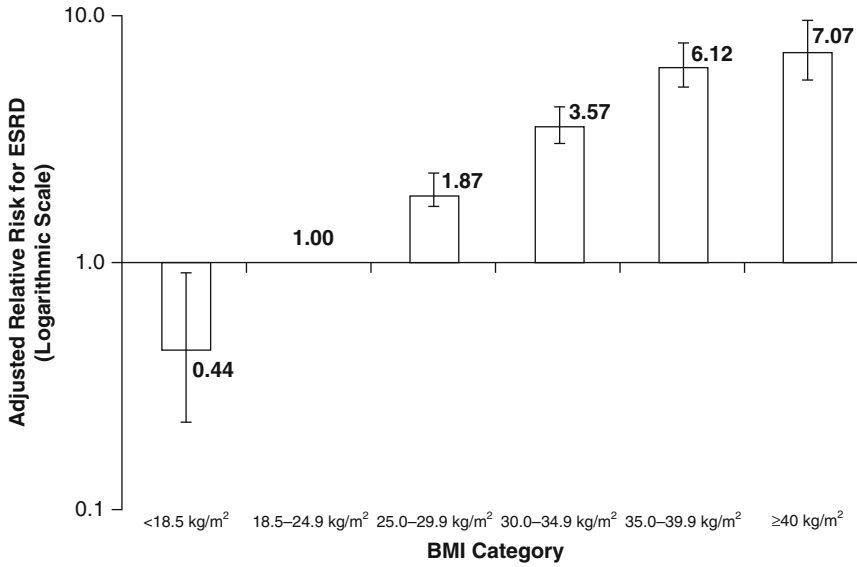

Fig. 10.1 Adjusted relative risk for end-stage renal disease by body mass index. From Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21–8. Reprinted with permission from American College of Physicians

End-Stage Renal Disease (Stage 5)

Numerous observations suggest that obesity has protective, rather than harmful, effects on survival in dialysis patients. This phenomenon, sometimes known as "reverse epidemiology" or "the obesity paradox," is a controversial one [50–52]. A more nuanced understanding of this topic requires familiarity with the relationship between adiposity and mortality in the general population [53].

In the general populace, the relationship between adiposity (as measured by BMI) and mortality is influenced by a number of factors, including demographics, concurrent illnesses, and cause of death. For example, the risk of death from excess fat is higher in whites (vs. blacks), lower at extreme ages, and differs between men and women [54]. In analyses that adjust for multiple factors, the death rates of healthy nonsmokers usually increase at either extreme of BMI, although the risk is greater at higher BMI. Thus a "J-shaped" relationship between BMI and risk of death is formed. In contrast, in persons who smoke or are ill, mortality risk increases equally at both ends of the spectrum (a "U-shaped" curve), with absolute risk being attenuated overall [54]. It is clear that for the end-stage renal disease population, with all its complexities and multiple competing factors, the relationship between BMI and mortality may not be a straightforward one.

The first study analyzing the relationship between adiposity and outcomes reported that in a French hemodialysis cohort, a BMI of 23.3 kg/m^2 was associated with a 29 % reduction in overall, cardiovascular, and non-cardiovascular mortality when compared to a BMI between 20.4 and 23.3 kg/m^2 [55]. Since then, dozens of similar studies have been performed in varied populations of hemo- and peritoneal dialysis patients using disparate markers of adiposity, though BMI remains by far the most commonly used. One systematic review found that 60 % of such studies in hemodialysis patients reported a significant inverse relationship between all-cause mortality and BMI, though the relationship between BMI and cardiovascular mortality was less strong [56]. Such studies in peritoneal dialysis patients are less common, tend to be smaller, and have mixed results. The largest such study noted in over 40,000 patients that excess adiposity did not confer an increased mortality risk, whereas having a BMI less than 18.5 kg/m^2 did [57]. The largest studies of the relationship between adiposity and

mortality involve mixed populations of hemodialysis and peritoneal dialysis patients. With the occasional exception, they support a neutral or protective relationship between excess adiposity and death in the hemodialysis population, with less convincing results in peritoneal dialysis patients [53].

There are many similarities between the dialysis and general population in terms of the relationship between adiposity and mortality. Age, sex, race, and comorbid risk factors modify the relationship in both groups [54, 58–63]. Yet the striking difference involves the key issue of how excess adiposity associates with death. Can it be possible that being fatter actually improves one's chance of survival while on dialysis? A number of concerns need to be addressed prior to fully accepting that conclusion.

The fact that many of the studies include patients who have already started dialysis (i.e., prevalent patients) introduces the possibility of survival bias because of the possibility that fatter subjects may have died earlier on dialysis. However, survival bias cannot explain why large studies of incident patients also find a protective association [26, 57, 59–61, 64]. Incompletely accounting for known mortality risk factors such as smoking, blood pressure, and medications due to database limitations also exists in some of the analyses. Censoring patients who are transplant or switch dialysis modalities does not always occur as it should. Yet consistent results across studies make it unlikely that these factors explain why adiposity has a protective benefit.

One major limitation involves the fact that BMI does not distinguish between different body compartments (e.g., fat mass, lean body mass). This important issue has been tackled in a series of epidemiological experiments. In a cohort of over 70,000 hemodialysis patients, urine creatinine excretion was used as a surrogate for muscle mass, and the predominant predictor of survival was found to be muscle, not fat, mass, where greater muscle mass had a protective effect [65]. This finding was soon challenged by an analysis involving over 400,000 dialysis patients that found no influential effect of lean mass when using equations to estimate body mass compartments [64]. More recent studies using other proxies for muscle and fat mass including serum creatinine [66], mid-arm muscle circumference [67], and triceps skinfold thickness [67] indicate that greater muscle mass (and perhaps fat mass) has a protective association with overall mortality.

But perhaps the major reason to remain cautious about the premise that the presence of obese reduces mortality risk is that the supportive evidence is entirely associative (as opposed to causal) in nature. In fact, no study exists demonstrating that weight gain is beneficial for dialysis patients or that the converse is true. Moreover, the implications of intentional versus unintentional weight loss are clearly distinct. One retrospective analysis found unintentional weight to be associated with higher rates of death, an unsurprising conclusion [68].

If the assumption that excess adiposity is beneficial, what could account for this? One possible explanation is that end-stage renal disease patients are a select group in that they alone have survived years of chronic kidney disease and multiple comorbid illnesses. They may be genotypically or phenotypically different from obese individuals in the general population. Additionally, obese dialysis patients have lower rates of certain risk factors such as smoking or hypertension compared to their peers with lower BMI [61, 69]. An abundance of stored fat may also serve as a well-needed reservoir of energy during acute illnesses or the wasting effects of dialysis, though it is difficult to explain why severe obesity (BMI > 37 kg/m^2), with all its associated risks, is more protective than a less severe but still unquestionable excess in adiposity (28–31 kg/m^2) [64]. A more speculative mechanism may be the influence of biologically active molecules secreted by adipocytes such as adiponectin or leptin [70].

While great attention has been given to studying how obesity influences mortality in dialysis patients, far less interest has been shown in documenting how it affects other important outcomes. This is especially true in light of the very poor long-term survival in this population [29], making the preservation of quality of life and the avoidance of hospitalization arguably as important as lowering the death rate. Investigators have already begun to study how obesity affects dialysis access. Successfully working dialysis accesses (e.g., arteriovenous fistulas, peritoneal dialysis catheters) are critical to the well-being of both hemodialysis and peritoneal patients. Accesses that fail to work well typically require great expenditure of resources and expose the patient to discomfort and

inconvenience, if not outright danger. Whether obesity limits the successful placement and/or function of arteriovenous fistulas, which are usually formed surgically in a subcutaneous fashion in either arm, is a controversial issue [71–73]. It may be that only the most obese of individuals are at elevated risk for hemodialysis access failure, perhaps because excessive adipose tissue is physically compressing the access and impending normal blood flow [71, 74].

Peritoneal dialysis catheters are inserted by tunneling through the abdominal wall to place the catheter tip in the peritoneal cavity. A reasonable concern is that obese individuals may suffer complications with catheter insertion or function due to excessive abdominal wall adiposity or be more predisposed to catheter tunnel infections or outright infectious peritonitis from difficulties inherent in performing aseptic technique when connecting or disconnecting to the peritoneal dialysate tubing. In fact, the preponderance of the data suggests that obesity confers an increased risk of catheter infections and peritonitis that can lead to catheter loss [59, 75–77]. For obese individuals in whom traditional abdominal peritoneal dialysis catheter use is not an option, alternative strategies exist such as the use of presternal dialysis catheters [78]. Aside from dialysis access issues, future topics ripe for research include whether obesity adversely affects quality of life indicators, arthritis, ambulation, comfort during dialysis, mood, and hospitalization rates, among others.

Kidney Transplant Recipients

The presence of obesity in transplant candidates and recipients has a number of important implications. Because of concern regarding higher perioperative complications such as wound dehiscence or infections in obese individuals [79], many transplant centers exclude individuals with BMI greater than 30 or 35 kg/m^2. In fact, the existence of obesity in a potential recipient may reduce the likelihood of their receiving a kidney transplant [80].

Similar to the pre-dialysis and dialysis populations, the prevalence of obesity as measured by BMI among kidney transplant recipients has grown by over 40 % in the past decade to reach 33 % [81]. Whether obesity at time of transplantation impacts negatively on patient or allograft outcomes is a hotly debated topic. A number of reports in kidney transplant recipients describe an association between a higher BMI and greater risk of delayed graft function, long-term renal allograft and patient survival [82–84], though others have challenged this finding [79, 85, 86]. What is becoming increasingly clear is that alternative proxies for obesity other than BMI can yield valuable information. Waist circumference provides additional prognostic information when added to BMI [87], and muscle mass may be even more useful than BMI as a predictive marker [88, 89].

The impact of weight loss on patient outcomes has also just begun to be explored. Recent observational studies have noted that weight loss in individuals on the transplant waiting list was not protective but actually linked to a higher rate of death [89, 90]. The implications of these findings are unclear, since neither study was able to determine if the weight loss was intentional, a critical issue. Finally, limited research has not found that the presence of obesity in kidney donors places them at higher risk for long-term renal and other complications [91], though functional hemodynamic changes have been noted [92].

Influence of Obesity on Kidney Function, Structure, and Health

The concept that obesity affects kidney function and health has existed for nearly a century. In 1923, Boston practitioner William Preble published his observations in 1,000 obese patients that found high rates of albuminuria and kidney impairment [93]. Subsequent reports from the 1970s onward reported an association between obesity and the nephrotic syndrome that disappeared with weight loss [94–99].

Kidney biopsies in many but not all of these patients demonstrated focal segmental glomerulosclerosis, but other findings including enlargement of the glomerulus (i.e., glomerulomegaly), intraglomerular fibrin deposition, and mesangial glomerulopathy were also observed. A number of patients manifested venous hypertension likely as a result of the sleep apnea syndrome [94, 99]. From these early descriptive reports, our understanding of how obesity influences the kidney has grown to encompass a much larger variety of functional, anatomic, and molecular effects.

Kidney Mass

Kidney mass has been demonstrated to grow with weight gain and high-protein diet consumption as described in animal models (see below), cross-sectional studies in children and adults, and weight-loss trials [100–104]. This is generally believed to occur because the kidney adapts to growing metabolic demand.

Renal Hemodynamics

Data obtained from cross-sectional analyses and studies of (primarily) bariatric surgery-related weight loss report significant effects on renal hemodynamics. Most, though not all, studies find that obesity is associated with an elevated glomerular filtration rate, renal plasma/blood flow, and filtration fraction (i.e., glomerular filtration rate divided by renal plasma flow) when compared to controls [13, 105–111]. The concept that kidney hemodynamics, similar to kidney mass, is influenced by metabolic requirements is supported by the observation that even in the BMI range of less than 30 kg/m^2, the BMI and filtration fraction are strongly associated [112]. By carefully studying the urinary clearance of tiny dextran molecules and applying the results to theoretical sieving models, one group of researchers concluded that the higher glomerular filtration rate documented in obese individuals was most likely the result of increased intraglomerular hydraulic pressure caused by dilated glomerular afferent arterioles [105]. Of note, weight loss after bariatric surgery appears to reverse the elevations in renal hemodynamic parameters [106, 113].

Proteinuria

Along with the glomerular filtration rate, proteinuria is one of the strongest clinical markers of kidney disease, with a higher level of proteinuria (or albuminuria, the most common measured fraction of proteinuria) usually indicating kidney damage [9, 10]. A strong and consistent positive relationship has been demonstrated between obesity and the likelihood of urinary protein or albumin excretion (see Fig. 10.2). This finding is consistent across race, sex, and ethnicity and exists in healthy individuals as well as nondiabetic and diabetic patients [114–118]. As with the hemodynamic indices, weight loss lowers proteinuria [119].

Histologic Changes

Analyses of kidney tissue obtained under differing circumstances (e.g., during gastric bypass surgery, at time of kidney transplant implantation, or for medical diagnostic reasons) and patient populations

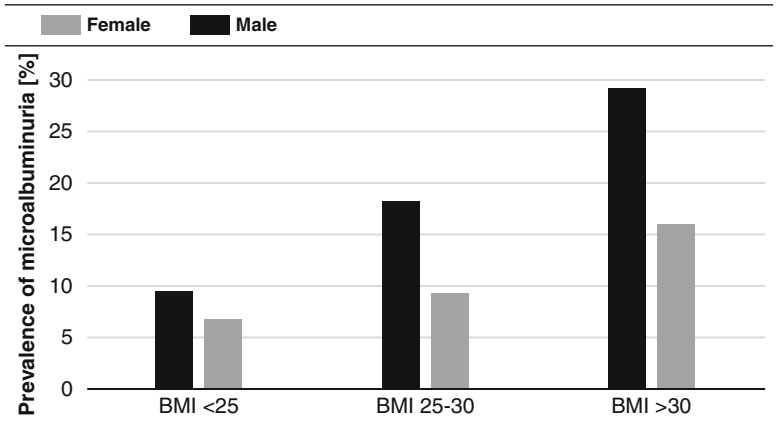

Fig. 10.2 Percentage of men and women with microalbuminuria according to BMI. From de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL. Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord 2002;26 Suppl 4:S21–4. Reprinted with permission from Nature Publishing Group

(e.g., kidney donors, bariatric surgery patients, IgA nephropathy, or other kidney diseases) reveal common findings such as glomerulomegaly and a thickened glomerular basement membrane [120–125]. However, a variety of other abnormalities, including increased glomerular planar surface area, podocyte hypertrophy, expanded mesangial matrix with or without paramesangial deposits, decreased slit diaphragm frequency, tubular atrophy, arterial hyperplasia, and sclerosis, have additionally been noted. Of importance, focal segmental glomerular sclerosis was a rare finding, if observed at all. One limitation of this literature involves the heterogeneity of the populations studied, the reasons for which the biopsy was obtained, the quality of the biopsy sample, and the studies performed.

Molecular Findings

RNA gene expression profiles have been measured in kidney biopsy samples from obese patients with proteinuria and glomerulomegaly with or without focal segmental glomerulosclerosis. Compared to the control samples, expression was upregulated for a variety of key genes involved in lipid metabolism, the inflammatory cascade, and insulin homeostasis/resistance [126].

Obesity-Related Glomerulopathy and Glomerulosclerosis

In 2001 obesity-related glomerulopathy (ORG) was first defined morphologically in obese individuals as the presence of either focal segmental glomerulosclerosis with glomerulomegaly or glomerulomegaly alone without secondary causes such as diabetic kidney disease or hypertensive nephrosclerosis [127]. ORG was characterized by proteinuria, often nephrotic in range, without overt nephrotic syndrome, and usually mild-to-moderate kidney disease. When compared to a cohort of patients with idiopathic focal segmental glomerulosclerosis, persons with ORG were more likely to be white and older with a lower rate of nephrotic syndrome (and consequently higher serum albumin and lower cholesterol levels). ORG patients also had fewer areas of segmental sclerosis and less podocyte foot-process effacement but a greater incidence of glomerulomegaly. Reduced podocyte density and greater

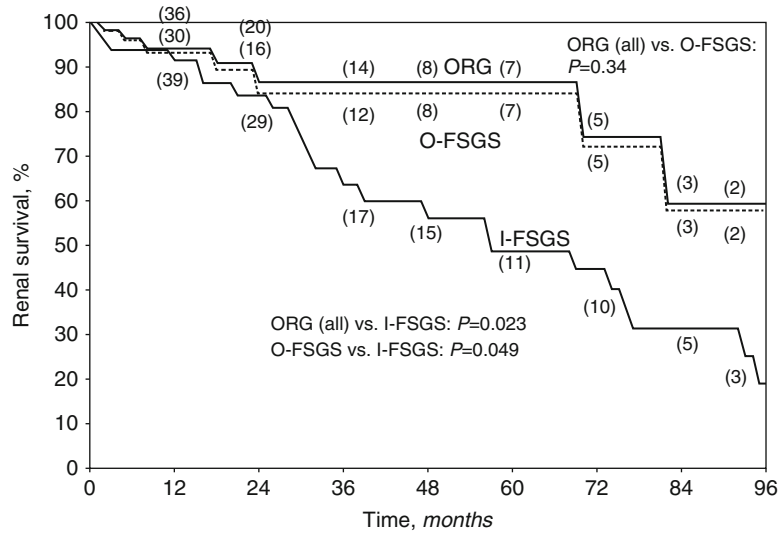

Fig. 10.3 Renal survival (endpoints defined as doubling of serum creatinine or ESRD) over time in ORG, O-FSGS, and control I-FSGS. Analysis by the method of Kaplan and Meier with comparison by the log rank test. Symbols are (*bottom solid line*) I-FSGS, (*top solid line*) ORG (all), and (*dotted line*) O-FSGS. ORG (all) vs. O-FSGS, $P=0.34$; ORG (all) vs. I-FSGS, $P=0.023$; O-FSGS vs. I-FSGS, $P=0.049$. From Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 2001;59:1498–509. Reprinted with permission from Nature Publishing Group

podocyte foot-process width has also been reported in ORG [128]. In terms of clinical outcomes, ORG was associated with a more benign course that was less likely to lead to kidney failure (see Fig. 10.3). The incidence of ORG was also reported to have increased tenfold between the years 1986 and 2000 [127].

Since the publication of its original description, reports of ORG have cropped up in other regions of the world [129, 130]. Yet the precise prevalence of obesity in the community and asymptomatic obese individuals remains unknown.

Animal Models of Weight Gain and Loss

The effects of obesity have been examined in a number of rodent models, many of which have specific genetic mutations that make them susceptible to obesity and diabetes [131–139]. The consensus finds that obesity leads to increases in kidney size, blood pressure, serum insulin, glucose, low-density lipoprotein, and triglyceride levels, albuminuria, and an initial elevation and subsequent decline in the glomerular filtration rate. Histological analyses demonstrate enlargement of the glomerular tuft area with mesangial expansion, thickening of the glomerular basement membrane, progressive glomerulosclerosis, and tubulointerstitial damage. In addition, type IV collagen and lipid deposition in the glomerulus and macrophage infiltration in the medulla are also observed. All these changes can be prevented or stopped by restricting caloric intake.

Because rodent models may have limited applicability to humans, it is useful to examine other animal models. In one such model, obesity was induced in dogs by feeding of beef fat for up to 24 weeks [140]. Compared to lean controls, the obese dogs manifested relative hypertension, tachycardia, elevations in the glomerular filtration rate and renal plasma flow, kidney weight, and plasma

glucose and insulin levels. Similar to what was seen in rodents, the obese dogs exhibited a marked expansion of the glomerular tuft area and Bowman's capsule space, a thickening of the glomerular basement membrane, and mesangial expansion. Kidneys from the obese dogs also exhibited more transforming growth factor-β1 (TGF-β1), a marker for fibrosis. Unlike in the rodent models, there was no difference between lean and obese dogs in terms of detectable glomerulosclerosis, a key indicator of irreversible kidney damage. This may represent a fundamental difference in the effects of obesity between animal species. A separate study using the obese dog model reported that obese (vs. lean) dogs had upregulation of a host of genes within the kidney related to sympathetic activation, the inflammatory response, matrix formation, angiogenesis, and endothelial dysfunction, with downregulation of genes associated with the leptin receptor and attenuation of cell survival [141].

Pathophysiology of Obesity-Related Kidney Disease

Aside from its promotion of diabetes and hypertension, obesity may adversely affect kidney health through multiple distinct but often interrelated mechanisms. A number of putative pathophysiologic mechanisms are discussed here.

Dietary Protein

Increased dietary protein consumption significantly modulates both renal hemodynamics and proteinuria/albuminuria [142]. Acute oral or intravenous protein intake can increase the glomerular filtration by upwards of 50 %, while more chronic ingestion has similar effects [143–145]. Likewise, oral protein consumption increases [146–148] albuminuria levels in randomized controlled human studies. These well-established physiologic responses to protein consumption are behind a large body of research demonstrating that high-protein intake in the setting of reduced kidney mass leads to further injury possibly through intraglomerular hypertension, glomerulosclerosis, and ultimately kidney failure [149]. Is it possible that increased consumption of dietary protein (along with all other nutrients) in individuals who are obese contributes to the development and/or progression of kidney disease in these patients? Observational data in subjects with one kidney support this premise [150, 151]. Yet protein intake by itself, while possibly contributing to the glomerular hyperfiltration observed in obesity, does not fully explain it [152].

Podocyte Depletion

Podocytes are cells that support and maintain the glomerular basement membrane filtration mechanism with limited capacity for cell division and replacement [153]. As previously noted, compared to a calorie-intake-restricted group, rats allowed to freely consume calories develop progressive glomerular enlargement [154]. This sets into motion a series of steps during which podocytes hypertrophy to cover the ever growing glomerular area they must cover. Over time, this compensatory mechanism fails, leading to widened podocyte foot processes, decreased filter efficiency, further loss of podocytes, and ultimately focal segmental glomerulosclerosis. In humans, increased glomerular volume in ORG patients has been associated with decreased podocyte density and greater foot-process width, each of which correlates with greater proteinuria [128]. Aside from glomerular enlargement, angiotensin II, aldosterone, plasminogen activator inhibitor-1 (PAI-1), hyperlipidemia, and adiponectin, each of which is upregulated by obesity, have all been hypothesized to lead to podocyte depletion [155–159].

Intraglomerular Hemodynamics

It has been hypothesized that obese individuals have increased sodium absorption in the proximal tubule from upregulated sympathetic activity, circulating angiotensin II, or other mechanisms. This leads to suppression of the tubuloglomerular feedback mechanism, perhaps via effects on the macula densa mineralocorticoid receptors [160], thereby causing afferent arteriolar dilation and direct transmission of higher (and ultimately detrimental) systemic blood pressures to the glomerulus [161]. The higher glomerular filtration rate and filtration fraction observed in obese humans lead to increased oncotic pressure in the peritubular capillaries, which can also promote proximal sodium absorption [162]. Taken together, these concepts describe a vicious cycle in which glomerular hyperfiltration promotes proximal tubule absorption which in turn suppresses the tubuloglomerular feedback mechanism and causes further glomerular hyperfiltration, intraglomerular hypertension, and salt reabsorption.

Renin-Angiotensin-Aldosterone Axis

The deleterious effects on the kidney of the renin-aldosterone axis, which is upregulated in obesity [163], are well established and explain why inhibitors of this axis may be effective treatments for kidney disease in overweight patients [164]. Experimental data in animals and observational data in humans suggest that angiotensin II and aldosterone may play a role in the onset of obesity-related hypertension and kidney disease [165–167]. Possible mechanisms include sympathetic nerve stimulation, insulin resistance, and hemodynamic alterations that promote renal cellular toxicity and fibrosis [167].

Sympathetic Activation

Sympathetic nerve activation is upregulated with increased feeding [168]. In a dog model of obesity, kidney denervation resulted in lack of a rise in arterial blood pressure and greatly reduced sodium retention, though there was no difference between denervated dogs and controls in terms of renal hemodynamics [169]. The significance of this finding requires further study.

Obstructive Sleep Apnea

Obstructive sleep apnea is strongly associated with obesity and has been linked to obesity-related focal segmental glomerulosclerosis [94] and proteinuria [99, 170, 171], though the association is controversial [172]. One recent case report described how initiation of BiPAP ventilation in an obese patient with obesity hypoventilation syndrome and biopsy-proven focal segmental glomerulosclerosis preceded the rapid disappearance of his nephrotic-range proteinuria [171]. Possible mechanisms involve improvement of pulmonary hypertension and associated venous congestion that could affect blood flow within the kidney and upregulation of sympathetic nerve activity.

Insulin Resistance and the Metabolic Syndrome

The link between insulin resistance, a hallmark of obesity and the metabolic syndrome, and kidney disease is primarily based on associative data in humans [173, 174]. Indeed, it is very difficult to tease

out the specific effects of insulin resistance from the cluster of other abnormalities observed in patients with the metabolic syndrome.

Lipotoxicity

There is a body of literature demonstrating that lipid accumulation may induce damage in glomerular cells and promote the progression of kidney disease, though the mechanisms are not fully elucidated [175]. Possible culprits include free fatty acids, either albumin bound or unbound, and triglyceride-rich lipoproteins.

Fatty Kidney

Fat accumulation in the kidney sinuses in the setting of obesity has been observed in animal models and humans [176, 177] and has been associated with hypertension and kidney disease [162, 163]. This may be due to direct compression of vessels within the kidney resulting in increased renal interstitial pressure, sodium reabsorption, and other adverse effects.

Adipocyte Secretory Products

In recent years fat cells (adipocytes) have been increasingly recognized not simply as passive reservoirs of energy but actual endocrine organs, secreting a host of biologically active molecules. Some of these molecules, known as adipokines, have been implicated as possibly playing a role in obesity-related kidney disease. Adiponectin and leptin, two such adipokines, will be reviewed here.

Leptin, one of the first of the adipokines to have been identified, plays an important role in regulating food intake. Its circulating levels are proportional to body fat. In vitro and in vivo studies in rat glomerular cells and a mice model lacking the leptin receptor reported that exposure to leptin induced glomerular endothelial cell proliferation and upregulated TGF-β1 and collagen deposition within the glomerulus. Based on these findings and its effects on sympathetic nerve activation and insulin resistance [178], leptin is hypothesized to contribute to the glomerulosclerosis of obesity.

Adiponectin is a small molecule secreted by adipocytes that has insulin-sensitizing effects [179]. For unclear reasons, circulating levels of adiponectin fall with obesity. Mice that cannot express adiponectin manifest increased levels of albuminuria and podocyte foot-process fusion while treatment with adiponectin reverses these effects [159]. In observational studies, adiponectin is inversely correlated with proteinuria [159, 180]. A direct effect of adiponectin on podocytes is postulated to occur at least in part through stimulation of the AMP-activated protein kinase (AMPK) pathway that inhibits reactive oxygen species [181].

Prevalence of Obesity-Related Kidney Disease

Though there are no population data available on the prevalence of ORG or similar obesity-associated kidney illnesses, it is clear from clinical practice and the medical literature that such complications are relatively uncommon. Given the ubiquitousness of obesity, why are so few people affected and what predisposes them? One answer may be found in the observation that individuals born with reduced

nephron mass and relatively low nephron numbers, such as with small for gestational age (SGA) or preterm births, are especially susceptible to developing hypertension and in certain circumstances kidney disease [182]. Similarly, the presence of obesity in persons with low nephron mass may lead to changes that promote kidney damage and failure [183]. One report describes how obese children born either preterm or term had similar rates of proteinuria and glomerulosclerosis on kidney biopsy (and much higher rates than nonobese children), though preterm children had nearly a two and a half times greater risk of kidney failure [184]. Further work is needed to confirm the hypothesis that low nephron numbers predispose toward the development of obesity-related kidney disease.

Weight-Loss Strategies and Benefits

The idea that weight loss in overweight or obese kidney disease patients is beneficial for kidney health is a topic of growing interest. Kidney disease patients are as interested in losing weight as are people in the general population [185]. The optimal weight range for patients with chronic kidney disease is not well defined, though evidence suggests that even modest weight loss in overweight and obese individuals has beneficial effects on surrogate clinical outcomes such as proteinuria [119, 186]. This section will review weight-loss goals, medical and surgical strategies for weight loss, and kidney-related benefits as stratified by stage of kidney disease.

Chronic Kidney Disease Stages 1–4

One systematic review of 13 controlled and uncontrolled medical and surgical weight-loss studies found that each kilogram of weight lost was associated with a reduction in 110 mg of proteinuria and 1.1 g of albuminuria [119]. While the methodology of lumping controlled and uncontrolled trials together is problematic, the findings are consistent across groups and disease processes (diabetic vs. nondiabetic) and also observed in patients without overt kidney disease. The effects of weight loss on long-term kidney and other outcomes such as progression to end-stage renal disease have not been studied, though short-term data report a reduction in the glomerular filtration rate or surrogate measurements [119, 186]. However, this may not necessarily reflect damage to the kidney and may simply be a result of reduced metabolic demand.

Strategies to reduce weight include behavioral modification (i.e., diet and exercise), pharmacologic interventions, and bariatric surgery. Medications that are used to reduce weight are limited by dosing and other toxicities in chronic kidney disease, as described in Table 10.3. Sustained weight loss is typically difficult to attain and a combination of the three strategies may be necessary. One open-label study recruited 44 mostly nondiabetic overweight or obese kidney disease patients to a weight-loss regimen involving a low-fat diet, exercise, and orlistat [187]. Over a period of 2 years, this intervention led to approximately 5 kg greater weight loss than standard care. Proteinuria and measured glomerular filtration rate were not measured, though the latter (estimated by equations) dropped to a lesser extent in the intervention group. Whether more profound weight loss by bariatric surgery stabilizes or improves kidney function has been investigated in small case series, but the lack of long-term follow-up and the previously reviewed limitations of using estimating equations to assess filtration make interpretation difficult [188–191]. Of note, an infrequent complication that needs to be considered when contemplating certain bariatric surgeries includes increased oxalate reabsorption with resultant hyperoxaluria, kidney stones, renal oxalosis, and irreversible kidney failure [192]. The presence of kidney disease in patients undergoing bariatric surgery is also associated with a modest increase in perioperative complications [193].

Table 10.3 Long-term pharmacologic treatment for weight loss approved in the United States

Drug	Mechanism of action	Potential side effects	Drug interactions	Safety in kidney disease
Orlistat (Xenical, Alli)	Lipase inhibitor	Fecal incontinence, fat-soluble vitamin deficiency	Cyclosporine, amiodarone	May be a risk factor for acute kidney injury possibly from oxalate nephropathy [201]
Lorcaserin (Belviq)	Serotonin agonist, anorexic	Headache, upper respiratory infections, nasopharyngitis	Avoid with other serotonergic drugs (SSRI, TCA, MAO, etc)	Avoid if creatinine clearance <50 mL/min
Phentermine/topiramate (Qsymia)	Sympathomimetic, anorexic	Dry mouth, constipation, parasthesias, proximal (type 2) renal tubular acidosis, calcium kidney stones	Numerous interactions	Reduce dose in stage 3–5 CKD. Not recommended in dialysis patients

Adapted with permission from [202]
CKD chronic kidney disease, *CNS* central nervous system, *SSRI* selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressant, *MAO* monoamine oxidase

End-Stage Renal Disease (Stage 5)

Perhaps because of the positive association between a higher BMI and reduced mortality (reviewed in a previous section), there has been a reluctance to perform weight reduction trials in this population. Of note, many of the pharmacologic weight-lowering agents are contraindicated in end-stage renal disease (Table 10.3). Preliminary evidence suggests that bariatric surgery in dialysis patients offers comparable weight loss to non-dialysis patients, though the risk of perioperative mortality may be slightly higher [194]. It may also improve opportunities for kidney transplantation by lowering the BMI to more acceptable levels [195, 196].

Kidney Transplant Recipients

According to two small studies using historical controls, dietary management programs in incident or prevalent transplant patients reduce weight gain post-surgery [197, 198]. Weight-loss medications in kidney transplant recipients should be used cautiously, as many of them alter the pharmacokinetic profile of commonly used immunosuppressive drugs (see Table 10.3). Interestingly, gastric bypass may have similar effects, so drug levels should be followed carefully post-surgery [199]. Similar to dialysis patients, bariatric surgery is very effective in inducing weight loss in transplant recipients, though it is associated with a higher complication rate compared to the general population [200].

References

1. Ho-Pham LT, Campbell LV, Nguyen TV. More on body fat cutoff points. Mayo Clin Proc. 2011;86:584; author reply 584–5.
2. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: National Institutes of Health; 1998.
3. Agarwal R, Bills JE, Light RP. Diagnosing obesity by body mass index in chronic kidney disease: an explanation for the "obesity paradox?". Hypertension. 2010;56:893–900.

4. Leinig C, Pecoits-Filho R, Nascimento MM, Goncalves S, Riella MC, Martins C. Association between body mass index and body fat in chronic kidney disease stages 3 to 5, hemodialysis, and peritoneal dialysis patients. J Ren Nutr. 2008;18:424–9.
5. Bergman RN, Kim SP, Catalano KJ, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity (Silver Spring). 2006;14 Suppl 1:16S–9.
6. Kramer H, Shoham D, McClure LA, et al. Association of waist circumference and body mass index with all-cause mortality in CKD: the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. Am J Kidney Dis. 2011;58:177–85.
7. Elsayed EF, Tighiouart H, Weiner DE, et al. Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. Am J Kidney Dis. 2008;52:49–57.
8. Postorino M, Marino C, Tripepi G, Zoccali C. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardiol. 2009;53:1265–72.
9. Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. Am J Kidney Dis. 2007;50:169–80.
10. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39:S1–000.
11. Jesudason DR, Clifton P. Interpreting different measures of glomerular filtration rate in obesity and weight loss: pitfalls for the clinician. Int J Obes (Lond). 2012;36(11):1421–7.
12. Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis. 2005;46:233–41.
13. Friedman AN, Strother M, Quinney SK, et al. Measuring the glomerular filtration rate in obese individuals without overt kidney disease. Nephron Clin Pract. 2010;116:c224–34.
14. Wuerzner G, Bochud M, Giusti V, Burnier M. Measurement of glomerular filtration rate in obese patients: pitfalls and potential consequences on drug therapy. Obes Facts. 2011;4:238–43.
15. Nair S, Mishra V, Hayden K, et al. The four-variable modification of diet in renal disease formula underestimates glomerular filtration rate in obese type 2 diabetic individuals with chronic kidney disease. Diabetologia. 2011;54:1304–7.
16. Edwards NA. Scaling of renal functions in mammals. Comp Biochem Physiol A Comp Physiol. 1975;52:63–6.
17. Friedman A. The importance of considering metabolism when indexing the glomerular filtration rate. Am J Kidney Dis. 2010;56(6):1218.
18. Singer MA. Of mice and men and elephants: metabolic rate sets glomerular filtration rate. Am J Kidney Dis. 2001;37:164–78.
19. Delanaye P, Radermecker RP, Rorive M, Depas G, Krzesinski JM. Indexing glomerular filtration rate for body surface area in obese patients is misleading: concept and example. Nephrol Dial Transplant. 2005;20:2024–8.
20. Livingston EH, Lee S. Body surface area prediction in normal-weight and obese patients. Am J Physiol Endocrinol Metab. 2001;281:E586–91.
21. Macdonald J, Marcora S, Jibani M, et al. GFR estimation using cystatin C is not independent of body composition. Am J Kidney Dis. 2006;48:712–9.
22. Vupputuri S, Fox CS, Coresh J, Woodward M, Muntner P. Differential estimation of CKD using creatinine- versus cystatin C-based estimating equations by category of body mass index. Am J Kidney Dis. 2009;53:993–1001.
23. World Health Organization. Preventing and managing the global epidemic of obesity. Report of the World Health Organization Consultation of Obesity; 2000;894:1–253.
24. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307(5):491–7.
25. Kramer HJ, Saranathan A, Luke A, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol. 2006;17:1453–9.
26. Abbott KC, Glanton CW, Trespalacios FC, et al. Body mass index, dialysis modality, and survival: analysis of the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study. Kidney Int. 2004;65:597–605.
27. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis. 2003;41:480–7.
28. Potluri K, Hou S. Obesity in kidney transplant recipients and candidates. Am J Kidney Dis. 2010;56:143–56.
29. U.S. Renal Data System. USRDS 2011 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2011.
30. Jolly S, Chatatalsingh C, Bargman J, Vas S, Chu M, Oreopoulos DG. Excessive weight gain during peritoneal dialysis. Int J Artif Organs. 2001;24:197–202.
31. Elster EA, Leeser DB, Morrissette C, et al. Obesity following kidney transplantation and steroid avoidance immunosuppression. Clin Transplant. 2008;22:354–9.
32. Rogers CC, Alloway RR, Buell JF, et al. Body weight alterations under early corticosteroid withdrawal and chronic corticosteroid therapy with modern immunosuppression. Transplantation. 2005;80:26–33.

33. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int. 2008;73:19–33.
34. Druml W, Metnitz B, Schaden E, Bauer P, Metnitz PG. Impact of body mass on incidence and prognosis of acute kidney injury requiring renal replacement therapy. Intensive Care Med. 2010;36:1221–8.
35. Ryu S, Chang Y, Woo HY, et al. Changes in body weight predict CKD in healthy men. J Am Soc Nephrol. 2008;19:1798–805.
36. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004;291:844–50.
37. de Boer IH, Katz R, Fried LF, et al. Obesity and change in estimated GFR among older adults. Am J Kidney Dis. 2009;54:1043–51.
38. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17:1695–702.
39. Bello AK, de Zeeuw D, El Nahas M, et al. Impact of weight change on albuminuria in the general population. Nephrol Dial Transplant. 2007;22:1619–27.
40. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293:455–62.
41. Munkhaugen J, Lydersen S, Wideroe TE, Hallan S. Prehypertension, obesity, and risk of kidney disease: 20-year follow-up of the HUNT I study in Norway. Am J Kidney Dis. 2009;54:638–46.
42. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2011;6:2364–73.
43. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med. 2004;140:167–74.
44. Bonnet F, Deprele C, Sassolas A, et al. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. Am J Kidney Dis. 2001;37:720–7.
45. Othman M, Kawar B, El Nahas AM. Influence of obesity on progression of non-diabetic chronic kidney disease: a retrospective cohort study. Nephron Clin Pract. 2009;113:c16–23.
46. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65:1870–6.
47. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144:21–8.
48. Drechsler C, de Mutsert R, Grootendorst DC, et al. Association of body mass index with decline in residual kidney function after initiation of dialysis. Am J Kidney Dis. 2009;53:1014–23.
49. Speckman RA, McClellan WM, Volkova NV, et al. Obesity is associated with family history of ESRD in incident dialysis patients. Am J Kidney Dis. 2006;48:50–8.
50. Ikizler TA. Resolved: being fat is good for dialysis patients: the Godzilla effect: pro. J Am Soc Nephrol. 2008;19:1059–62.
51. Stenvinkel P, Lindholm B. Resolved: being fat is good for dialysis patients: the Godzilla effect: con. J Am Soc Nephrol. 2008;19:1062–4.
52. Levin NW, Handelman GJ, Coresh J, Port FK, Kaysen GA. Reverse epidemiology: a confusing, confounding, and inaccurate term. Semin Dial. 2007;20:586–92.
53. Friedman AN. Adiposity in dialysis: good or bad? Semin Dial. 2006;19:136–40.
54. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath Jr CW. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999;341:1097–105.
55. Degoulet P, Legrain M, Reach I, et al. Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. Nephron. 1982;31:103–10.
56. Herselman M, Esau N, Kruger JM, Labadarios D, Moosa MR. Relationship between body mass index and mortality in adults on maintenance hemodialysis: a systematic review. J Ren Nutr. 2010;20:281–92, 7 p following 292.
57. Snyder JJ, Foley RN, Gilbertson DT, Vonesh EF, Collins AJ. Body size and outcomes on peritoneal dialysis in the United States. Kidney Int. 2003;64:1838–44.
58. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int. 1999;55:1560–7.
59. McDonald SP, Collins JF, Johnson DW. Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. J Am Soc Nephrol. 2003;14:2894–901.
60. Wong JS, Port FK, Hulbert-Shearon TE, et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int. 1999;55:2515–23.
61. Stack AG, Murthy BV, Molony DA. Survival differences between peritoneal dialysis and hemodialysis among "large" ESRD patients in the United States. Kidney Int. 2004;65:2398–408.
62. Ricks J, Molnar MZ, Kovesdy CP, et al. Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. Am J Kidney Dis. 2011;58:574–82.

63. Hoogeveen EK, Halbesma N, Rothman KJ, et al. Obesity and mortality risk among younger dialysis patients. Clin J Am Soc Nephrol. 2012;7(2):280–8.
64. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr. 2004;80:324–32.
65. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003;14:2366–72.
66. Kalantar-Zadeh K, Streja E, Kovesdy CP, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc. 2010;85:991–1001.
67. Huang CX, Tighiouart H, Beddhu S, et al. Both low muscle mass and low fat are associated with higher all-cause mortality in hemodialysis patients. Kidney Int. 2010;77:624–9.
68. Campbell KL, MacLaughlin HL. Unintentional weight loss is an independent predictor of mortality in a hemodialysis population. J Ren Nutr. 2010;20:414–8.
69. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. JAMA. 2005;293:1868–74.
70. Zoccali C, Postorino M, Marino C, Pizzini P, Cutrupi S, Tripepi G. Waist circumference modifies the relationship between the adipose tissue cytokines leptin and adiponectin and all-cause and cardiovascular mortality in haemodialysis patients. J Intern Med. 2011;269:172–81.
71. Chan MR, Young HN, Becker YT, Yevzlin AS. Obesity as a predictor of vascular access outcomes: analysis of the USRDS DMMS Wave II study. Semin Dial. 2008;21:274–9.
72. Kats M, Hawxby AM, Barker J, Allon M. Impact of obesity on arteriovenous fistula outcomes in dialysis patients. Kidney Int. 2007;71:39–43.
73. Weyde W, Krajewska M, Letachowicz W, et al. Obesity is not an obstacle for successful autogenous arteriovenous fistula creation in haemodialysis. Nephrol Dial Transplant. 2008;23:1318–22.
74. Plumb TJ, Adelson AB, Groggel GC, Johanning JM, Lynch TG, Lund B. Obesity and hemodialysis vascular access failure. Am J Kidney Dis. 2007;50:450–4.
75. Aslam N, Bernardini J, Fried L, Piraino B. Large body mass index does not predict short-term survival in peritoneal dialysis patients. Perit Dial Int. 2002;22:191–6.
76. Piraino B, Bernardini J, Centa PK, Johnston JR, Sorkin MI. The effect of body weight on CAPD related infections and catheter loss. Perit Dial Int. 1991;11:64–8.
77. McDonald SP, Collins JF, Rumpsfeld M, Johnson DW. Obesity is a risk factor for peritonitis in the Australian and New Zealand peritoneal dialysis patient populations. Perit Dial Int. 2004;24:340–6.
78. Twardowski ZJ. Presternal peritoneal catheter. Adv Ren Replace Ther. 2002;9:125–32.
79. Johnson DW, Isbel NM, Brown AM, et al. The effect of obesity on renal transplant outcomes. Transplantation. 2002;74:675–81.
80. Segev DL, Simpkins CE, Thompson RE, Locke JE, Warren DS, Montgomery RA. Obesity impacts access to kidney transplantation. J Am Soc Nephrol. 2008;19:349–55.
81. Lentine KL, Axelrod D, Abbott KC. Interpreting body composition in kidney transplantation: weighing candidate selection, prognostication, and interventional strategies to optimize health. Clin J Am Soc Nephrol. 2011;6:1238–40.
82. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation. 2002;73:70–4.
83. Meier-Kriesche HU, Vaghela M, Thambuganipalle R, Friedman G, Jacobs M, Kaplan B. The effect of body mass index on long-term renal allograft survival. Transplantation. 1999;68:1294–7.
84. Molnar MZ, Kovesdy CP, Mucsi I, et al. Higher recipient body mass index is associated with post-transplant delayed kidney graft function. Kidney Int. 2011;80:218–24.
85. Glanton CW, Kao TC, Cruess D, Agodoa LY, Abbott KC. Impact of renal transplantation on survival in end-stage renal disease patients with elevated body mass index. Kidney Int. 2003;63:647–53.
86. Howard RJ, Thai VB, Patton PR, et al. Obesity does not portend a bad outcome for kidney transplant recipients. Transplantation. 2002;73:53–5.
87. Kovesdy CP, Czira ME, Rudas A, et al. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant. 2010;10:2644–51.
88. Streja E, Molnar MZ, Kovesdy CP, et al. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. Clin J Am Soc Nephrol. 2011;6:1463–73.
89. Molnar MZ, Streja E, Kovesdy CP, et al. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant. 2011;11:725–36.
90. Schold JD, Srinivas TR, Guerra G, et al. A "weight-listing" paradox for candidates of renal transplantation? Am J Transplant. 2007;7:550–9.
91. Tavakol MM, Vincenti FG, Assadi H, et al. Long-term renal function and cardiovascular disease risk in obese kidney donors. Clin J Am Soc Nephrol. 2009;4:1230–8.

92. Rook M, Bosma RJ, van Son WJ, et al. Nephrectomy elicits impact of age and BMI on renal hemodynamics: lower postdonation reserve capacity in older or overweight kidney donors. Am J Transplant. 2008;8:2077–85.
93. Preble W. Obesity: observations on one thousand cases. Boston Med Surg J. 1923;188:617–21.
94. Jennette JC, Charles L, Grubb W. Glomerulomegaly and focal segmental glomerulosclerosis associated with obesity and sleep-apnea syndrome. Am J Kidney Dis. 1987;10:470–2.
95. Verani RR. Obesity-associated focal segmental glomerulosclerosis: pathological features of the lesion and relationship with cardiomegaly and hyperlipidemia. Am J Kidney Dis. 1992;20:629–34.
96. Kasiske BL, Crosson JT. Renal disease in patients with massive obesity. Arch Intern Med. 1986;146:1105–9.
97. Wesson DE, Kurtzman NA, Frommer JP. Massive obesity and nephrotic proteinuria with a normal renal biopsy. Nephron. 1985;40:235–7.
98. Warnke RA, Kempson RL. The nephrotic syndrome in massive obesity: a study by light, immunofluorescence, and electron microscopy. Arch Pathol Lab Med. 1978;102:431–8.
99. Weisinger JR, Kempson RL, Eldridge FL, Swenson RS. The nephrotic syndrome: a complication of massive obesity. Ann Intern Med. 1974;81:440–7.
100. Peters A, Bosy-Westphal A, Kubera B, et al. Why doesn't the brain lose weight, when obese people diet? Obes Facts. 2011;4:151–7.
101. Skov AR, Toubro S, Bulow J, Krabbe K, Parving HH, Astrup A. Changes in renal function during weight loss induced by high vs low-protein low-fat diets in overweight subjects. Int J Obes Relat Metab Disord. 1999;23:1170–7.
102. Pantoja Zuzuarregui JR, Mallios R, Murphy J. The effect of obesity on kidney length in a healthy pediatric population. Pediatr Nephrol. 2009;24:2023–7.
103. Paivansalo MJ, Merikanto J, Savolainen MJ, et al. Effect of hypertension, diabetes and other cardiovascular risk factors on kidney size in middle-aged adults. Clin Nephrol. 1998;50:161–8.
104. Johnson S, Rishi R, Andone A, et al. Determinants and functional significance of renal parenchymal volume in adults. Clin J Am Soc Nephrol. 2011;6:70–6.
105. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol. 2000;278:F817–22.
106. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol. 2003;14:1480–6.
107. Anastasio P, Spitali L, Frangiosa A, et al. Glomerular filtration rate in severely overweight normotensive humans. Am J Kidney Dis. 2000;35:1144–8.
108. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995;26:610–5.
109. Scaglione R, Ganguzza A, Corrao S, et al. Central obesity and hypertension: pathophysiologic role of renal haemodynamics and function. Int J Obes Relat Metab Disord. 1995;19:403–9.
110. Wuerzner G, Pruijm M, Maillard M, et al. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. Am J Kidney Dis. 2010;56:303–12.
111. Janmahasatian S, Duffull SB, Chagnac A, Kirkpatrick CM, Green B. Lean body mass normalizes the effect of obesity on renal function. Br J Clin Pharmacol. 2008;65:964–5.
112. Bosma RJ, van der Heide JJ, Oosterop EJ, de Jong PE, Navis G. Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. Kidney Int. 2004;65:259–65.
113. Brochner-Mortensen J, Rickers H, Balslev I. Renal function and body composition before and after intestinal bypass operation in obese patients. Scand J Clin Lab Invest. 1980;40:695–702.
114. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S. Influence of smoking and obesity on the development of proteinuria. Kidney Int. 2002;62:956–62.
115. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL. Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord. 2002;26 Suppl 4:S21–4.
116. Cirillo M, Senigalliesi L, Laurenzi M, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Arch Intern Med. 1998;158:1933–9.
117. Toto RD, Greene T, Hebert LA, et al. Relationship between body mass index and proteinuria in hypertensive nephrosclerosis: results from the African American Study of Kidney Disease and Hypertension (AASK) cohort. Am J Kidney Dis. 2010;56:896–906.
118. Kramer H, Reboussin D, Bertoni AG, et al. Obesity and albuminuria among adults with type 2 diabetes: the Look AHEAD (Action for Health in Diabetes) Study. Diabetes Care. 2009;32:851–3.
119. Afshinnia F, Wilt TJ, Duval S, Esmaeili A, Ibrahim HN. Weight loss and proteinuria: systematic review of clinical trials and comparative cohorts. Nephrol Dial Transplant. 2010;25:1173–83.
120. Tanaka M, Yamada S, Iwasaki Y, et al. Impact of obesity on IgA nephropathy: comparative ultrastructural study between obese and non-obese patients. Nephron Clin Pract. 2009;112:c71–8.

121. Goumenos DS, Kawar B, El Nahas M, et al. Early histological changes in the kidney of people with morbid obesity. Nephrol Dial Transplant. 2009;24:3732–8.
122. Serra A, Romero R, Lopez D, et al. Renal injury in the extremely obese patients with normal renal function. Kidney Int. 2008;73:947–55.
123. Rea DJ, Heimbach JK, Grande JP, et al. Glomerular volume and renal histology in obese and non-obese living kidney donors. Kidney Int. 2006;70:1636–41.
124. Alexander MP, Patel TV, Farag YM, Florez A, Rennke HG, Singh AK. Kidney pathological changes in metabolic syndrome: a cross-sectional study. Am J Kidney Dis. 2009;53:751–9.
125. Kato S, Nazneen A, Nakashima Y, et al. Pathological influence of obesity on renal structural changes in chronic kidney disease. Clin Exp Nephrol. 2009;13:332–40.
126. Wu Y, Liu Z, Xiang Z, et al. Obesity-related glomerulopathy: insights from gene expression profiles of the glomeruli derived from renal biopsy samples. Endocrinology. 2006;147:44–50.
127. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int. 2001;59:1498–509.
128. Chen HM, Liu ZH, Zeng CH, Li SJ, Wang QW, Li LS. Podocyte lesions in patients with obesity-related glomerulopathy. Am J Kidney Dis. 2006;48:772–9.
129. Chen HM, Li SJ, Chen HP, Wang QW, Li LS, Liu ZH. Obesity-related glomerulopathy in China: a case series of 90 patients. Am J Kidney Dis. 2008;52:58–65.
130. Praga M, Hernandez E, Morales E, et al. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2001;16:1790–8.
131. Maddox DA, Alavi FK, Santella RN, Zawada Jr ET. Prevention of obesity-linked renal disease: age-dependent effects of dietary food restriction. Kidney Int. 2002;62:208–19.
132. Gades MD, Van Goor H, Kaysen GA, Johnson PR, Horwitz BA, Stern JS. Brief periods of hyperphagia cause renal injury in the obese Zucker rat. Kidney Int. 1999;56:1779–87.
133. Kasiske BL, Cleary MP, O'Donnell MP, Keane WF. Effects of carbohydrate restriction on renal injury in the obese Zucker rat. Am J Clin Nutr. 1986;44:56–65.
134. Alavi FK, Zawada ET, Hoff KK. Renal hemodynamic effects of chronic ketorolac tromethamine treatment in aged lean and obese Zucker rats. Clin Nephrol. 1995;43:318–23.
135. Kasiske BL, Cleary MP, O'Donnell MP, Keane WF. Effects of genetic obesity on renal structure and function in the Zucker rat. J Lab Clin Med. 1985;106:598–604.
136. Coimbra TM, Janssen U, Grone HJ, et al. Early events leading to renal injury in obese Zucker (fatty) rats with type II diabetes. Kidney Int. 2000;57:167–82.
137. Johnson PR, Stern JS, Horwitz BA, Harris Jr RE, Greene SF. Longevity in obese and lean male and female rats of the Zucker strain: prevention of hyperphagia. Am J Clin Nutr. 1997;66:890–903.
138. Stern JS, Gades MD, Wheeldon CM, Borchers AT. Calorie restriction in obesity: prevention of kidney disease in rodents. J Nutr. 2001;131:913S–7.
139. Keenan KP, Coleman JB, McCoy CL, Hoe CM, Soper KA, Laroque P. Chronic nephropathy in ad libitum overfed Sprague-Dawley rats and its early attenuation by increasing degrees of dietary (caloric) restriction to control growth. Toxicol Pathol. 2000;28:788–98.
140. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001;12:1211–7.
141. Gu JW, Wang J, Stockton A, Lokitz B, Henegar L, Hall JE. Cytokine gene expression profiles in kidney medulla and cortex of obese hypertensive dogs. Kidney Int. 2004;66:713–21.
142. Friedman AN. High-protein diets: potential effects on the kidney in renal health and disease. Am J Kidney Dis. 2004;44:950–62.
143. Pitts R. The effects of infusing glycin and of varying the dietary protein intake on renal hemodynamics in the dog. Am J Physiol. 1944;142:355–65.
144. Premen AJ. Nature of the renal hemodynamic action of amino acids in dogs. Am J Physiol. 1989;256:F516–23.
145. Bilo HJ, Schaap GH, Blaak E, Gans RO, Oe PL, Donker AJ. Effects of chronic and acute protein administration on renal function in patients with chronic renal insufficiency. Nephron. 1989;53:181–7.
146. Viberti G, Bognetti E, Wiseman MJ, Dodds R, Gross JL, Keen H. Effect of protein-restricted diet on renal response to a meat meal in humans. Am J Physiol. 1987;253:F388–93.
147. Wiseman MJ, Hunt R, Goodwin A, Gross JL, Keen H, Viberti GC. Dietary composition and renal function in healthy subjects. Nephron. 1987;46:37–42.
148. Coppo R, Amore A, Roccatello D, et al. Microalbuminuria in single kidney patients: relationship with protein intake. Clin Nephrol. 1988;29:219–28.
149. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med. 1982;307:652–9.

150. Gonzalez E, Gutierrez E, Morales E, et al. Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. Kidney Int. 2005;68:263–70.
151. Praga M, Hernandez E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int. 2000;58:2111–8.
152. Friedman AN, Yu Z, Juliar BE, et al. Independent influence of dietary protein on markers of kidney function and disease in obesity. Kidney Int. 2010;78:693–7.
153. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int. 2006;69:2131–47.
154. Wiggins JE, Goyal M, Sanden SK, et al. Podocyte hypertrophy, "adaptation," and "decompensation" associated with glomerular enlargement and glomerulosclerosis in the aging rat: prevention by calorie restriction. J Am Soc Nephrol. 2005;16:2953–66.
155. Nagase M, Shibata S, Yoshida S, Nagase T, Gotoda T, Fujita T. Podocyte injury underlies the glomerulopathy of Dahl salt-hypertensive rats and is reversed by aldosterone blocker. Hypertension. 2006;47:1084–93.
156. Liang X, Kanjanabuch T, Mao SL, et al. Plasminogen activator inhibitor-1 modulates adipocyte differentiation. Am J Physiol Endocrinol Metab. 2006;290:E103–13.
157. Deji N, Kume S, Araki S, et al. Structural and functional changes in the kidneys of high-fat diet-induced obese mice. Am J Physiol Renal Physiol. 2009;296:F118–26.
158. Gloy J, Henger A, Fischer KG, et al. Angiotensin II depolarizes podocytes in the intact glomerulus of the Rat. J Clin Invest. 1997;99:2772–81.
159. Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest. 2008;118:1645–56.
160. Fu Y, Hall JE, Lu D, et al. Aldosterone blunts tubuloglomerular feedback by activating macula densa mineralocorticoid receptors. Hypertension. 2012;59(3):599–606.
161. Griffin KA, Kramer H, Bidani AK. Adverse renal consequences of obesity. Am J Physiol Renal Physiol. 2008;294:F685–96.
162. Chagnac A, Herman M, Zingerman B, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transplant. 2008;23:3946–52.
163. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med. 1981;304:930–3.
164. Praga M, Hernandez E, Andres A, Leon M, Ruilope LM, Rodicio JL. Effects of body-weight loss and captopril treatment on proteinuria associated with obesity. Nephron. 1995;70:35–41.
165. de Paula RB, da Silva AA, Hall JE. Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. Hypertension. 2004;43:41–7.
166. Ahmed SB, Fisher ND, Stevanovic R, Hollenberg NK. Body mass index and angiotensin-dependent control of the renal circulation in healthy humans. Hypertension. 2005;46:1316–20.
167. Ruster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol. 2006;17:2985–91.
168. Young JB, Landsberg L. Diet-induced changes in sympathetic nervous system activity: possible implications for obesity and hypertension. J Chronic Dis. 1982;35:879–86.
169. Kassab S, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP. Renal denervation attenuates the sodium retention and hypertension associated with obesity. Hypertension. 1995;25:893–7.
170. Sklar AH, Chaudhary BA. Reversible proteinuria in obstructive sleep apnea syndrome. Arch Intern Med. 1988;148:87–9.
171. Hall IE, Kashgarian M, Moeckel GW, Dahl NK. Resolution of proteinuria in a patient with focal segmental glomerulosclerosis following BiPAP initiation for obesity hypoventilation syndrome. Clin Nephrol. 2012;77:62–5.
172. Casserly LF, Chow N, Ali S, Gottlieb DJ, Epstein LJ, Kaufman JS. Proteinuria in obstructive sleep apnea. Kidney Int. 2001;60:1484–9.
173. Kincaid-Smith P. Hypothesis: obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled 'hypertensive nephrosclerosis'. J Hypertens. 2004;22:1051–5.
174. Dengel DR, Goldberg AP, Mayuga RS, Kairis GM, Weir MR. Insulin resistance, elevated glomerular filtration fraction, and renal injury. Hypertension. 1996;28:127–32.
175. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol. 2007;2:550–62.
176. Dwyer TM, Mizelle HL, Cockrell K, Buhner P. Renal sinus lipomatosis and body composition in hypertensive, obese rabbits. Int J Obes Relat Metab Disord. 1995;19:869–74.
177. Foster MC, Hwang SJ, Porter SA, Massaro JM, Hoffmann U, Fox CS. Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. Hypertension. 2011;58:784–90.
178. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. Am J Kidney Dis. 2002;39:1–11.
179. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab. 2004;89:2563–8.

180. Tsioufis C, Dimitriadis K, Chatzis D, et al. Relation of microalbuminuria to adiponectin and augmented C-reactive protein levels in men with essential hypertension. Am J Cardiol. 2005;96:946–51.
181. Ix J, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. J Am Soc Nephrol. 2010;21:406–12.
182. Abitbol CL, Ingelfinger JR. Nephron mass and cardiovascular and renal disease risks. Semin Nephrol. 2009;29:445–54.
183. Praga M. Synergy of low nephron number and obesity: a new focus on hyperfiltration nephropathy. Nephrol Dial Transplant. 2005;20:2594–7.
184. Abitbol CL, Chandar J, Rodriguez MM, et al. Obesity and preterm birth: additive risks in the progression of kidney disease in children. Pediatr Nephrol. 2009;24:1363–70.
185. Navaneethan S, Kirwan J, Arrigain S, Schreiber M, Sehgal A, Schold S. Overweight, obesity and intentional weight loss in chronic kidney disease: NHANES 1999–2006. Int J Obes (Lond). 2012;36(12):1585–90.
186. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4:1565–74.
187. MacLaughlin HL, Cook SA, Kariyawasam D, Roseke M, van Niekerk M, Macdougall IC. Nonrandomized trial of weight loss with orlistat, nutrition education, diet, and exercise in obese patients with CKD: 2-year follow-up. Am J Kidney Dis. 2010;55:69–76.
188. Navaneethan SD, Yehnert H. Bariatric surgery and progression of chronic kidney disease. Surg Obes Relat Dis. 2009;5(6):662–5.
189. Alexander JW, Goodman HR, Hawver LR, Cardi MA. Improvement and stabilization of chronic kidney disease after gastric bypass. Surg Obes Relat Dis. 2009;5:237–41.
190. Agnani S, Vachharajani VT, Gupta R, Atray NK, Vachharajani TJ. Does treating obesity stabilize chronic kidney disease? BMC Nephrol. 2005;6:7.
191. Currie A, Chetwood A, Ahmed AR. Bariatric surgery and renal function. Obes Surg. 2011;21:528–39.
192. Nasr SH, D'Agati VD, Said SM, et al. Oxalate nephropathy complicating Roux-en-Y Gastric Bypass: an under-recognized cause of irreversible renal failure. Clin J Am Soc Nephrol. 2008;3:1676–83.
193. Turgeon NA, Perez S, Mondestin M, et al. The impact of renal function on outcomes of bariatric surgery. J Am Soc Nephrol. 2012;23(5):769–70.
194. Modanlou KA, Muthyala U, Xiao H, et al. Bariatric surgery among kidney transplant candidates and recipients: analysis of the United States renal data system and literature review. Transplantation. 2009;87:1167–73.
195. Koshy AN, Coombes JS, Wilkinson S, Fassett RG. Laparoscopic gastric banding surgery performed in obese dialysis patients prior to kidney transplantation. Am J Kidney Dis. 2008;52:e15–7.
196. Takata MC, Campos GM, Ciovica R, et al. Laparoscopic bariatric surgery improves candidacy in morbidly obese patients awaiting transplantation. Surg Obes Relat Dis. 2008;4:159–64. discussion 64–5.
197. Jezior D, Krajewska M, Madziarska K, et al. Weight reduction in renal transplant recipients program: the first successes. Transplant Proc. 2007;39:2769–71.
198. Patel MG. The effect of dietary intervention on weight gains after renal transplantation. J Ren Nutr. 1998;8:137–41.
199. Rogers CC, Alloway RR, Alexander JW, Cardi M, Trofe J, Vinks AA. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant. 2008;22:281–91.
200. Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med. 2011;171:703–4.

Part III
Kidney Disease in Adults Treated by Renal Replacement Therapies

Chapter 11
Dialysis

Karen Wiesen

Key Points

- Describe the goals of medical nutrition therapy for patients receiving hemodialysis, peritoneal dialysis, nocturnal home dialysis, and short daily dialysis.
- Describe the differences in nutrition therapy between the different types of renal replacement therapies.
- Identify factors that may impact the nutritional status of patients receiving maintenance dialysis.

Keywords Protein energy wasting • Medical nutrition therapy • Hemodialysis • Peritoneal dialysis • Nocturnal home hemodialysis • Short daily hemodialysis

Introduction

Medical nutrition therapy (MNT) plays an integral role in the health of the patient with Stage 5 chronic kidney disease (CKD) receiving maintenance dialysis. The health professional must understand the role of nutrition in Stage 5 CKD, the factors affecting assessment and maintenance of adequate nutritional status, and the nutritional implications associated with the different types of renal replacement therapies (RRT). Currently there are almost 400,000 patients receiving RRT in the United States with those numbers expected to steadily increase [1, 2]. The average age of the patient starting dialysis is increasing with a significant number of patients presenting to dialysis with numerous comorbid conditions that may have already negatively impacted their nutritional status. The nutritional status of the patient at the initiation of RRT is an important risk factor for future outcomes, and malnutrition is associated with increased mortality in patients receiving maintenance dialysis [3]. Nutritional management should include ongoing diet education, nutrition assessment, individualized interventions, and monitoring of nutritional status. The goals of MNT in Stage 5 CKD are (a) to achieve and maintain neutral or positive nitrogen balance, (b) to achieve and maintain good nutritional status, (c) to prevent the accumulation of electrolytes and minimize fluid imbalance, and (d) to minimize the effect of metabolic disorders associated with Stage 5 CKD.

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Box 11.1 Types of dialysis modalities

Type of dialysis	Location	Duration	Frequency
Conventional hemodialysis	In-center	3–5 h	3×/week
Peritoneal dialysis	Home	Varies with type of PD	Daily
CAPD			
CCPD			
Home hemodialysis	Home	3–5 h	3×/week
Home nocturnal hemodialysis	Home	7–10 h	5–7×/week
In-center nocturnal hemodialysis	In-center	7–8 h	3×/week
Home short daily hemodialysis	Home	2–3 h	5–7×/week
In-center short daily hemodialysis	In-center	2–3 h	5–6×/week

Patients beginning RRT now have a choice of modalities that include hemodialysis (HD), peritoneal dialysis (PD), nocturnal home hemodialysis (NHD), short daily hemodialysis (SDHD), and renal transplantation (Box 11.1). This chapter will review the MNT for each dialysis modality and discuss factors that may impact nutrition assessment and overall nutritional status. Renal transplantation is another treatment option and is discussed in Chap. 12.

Factors Influencing Nutritional Status

Malnutrition in the maintenance dialysis population is associated with increased morbidity and mortality [4–7]. Between 10 and 50 % of HD patients and 18–56 % of PD patients have some degree of malnutrition [8, 9]. Routine monitoring of the patients' nutritional status through the use of anthropometric measures, biochemical parameters, and diet histories and interviews is important in the early detection and prevention of malnutrition. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Nutrition recommends that a panel of measures be used to routinely assess nutritional status [10]. Refer to Chaps. 3–6 for more information on individual parameters used in nutrition assessment. The use of a variety of assessment tools is important since some of the traditional anthropometric and biochemical measures employed to assess nutritional status can be influenced by multiple catabolic factors such as anorexia, inflammation, acidosis, and dialysis-related losses. This section will provide a brief overview of some of these factors.

Serum albumin has long been used as a marker of nutritional status in the maintenance dialysis population and has been shown to independently correlate with an increased risk of mortality [5–7]. Serum albumin between 3.5 and 4.0 g/dL is associated with a twofold increased risk of death, and a low albumin at the initiation of dialysis increases the risk of hospitalization as well as length of stay in the first year of dialysis [3, 5]. The terminology defining malnutrition in the dialysis patient has evolved. Historically it was divided into two types. Classic or type 1 malnutrition was defined by loss of lean body mass, inadequate oral intake, normal to mildly depleted albumin and normal C-reactive protein (CRP) levels, and responsive to nutrition intervention [8, 11]. Type 2 malnutrition was defined as caused by inflammation and characterized by markedly low albumin despite adequate oral intake, increased oxidative stress, elevated CRP and other pro-inflammatory markers, and not reversible with nutrition intervention alone [11]. Type 2 was also referred to as malnutrition-inflammation complex syndrome (MICS) because of the interrelationship between malnutrition and inflammation in the dialysis patient. The challenge for the clinician trying to assess the type of malnutrition present was difficult and emerging evidence has indicated that these definitions were not necessarily accurate for the CKD patient. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM)

proposed the definition and specific diagnostic criteria for protein energy wasting (PEW) which better reflects the type of wasting that occurs in CKD. PEW is defined as the "state of decreased body stores of protein and energy fuels (body protein and fat masses)" [12]. PEW is characterized by very low albumin levels, the presence of inflammation and oxidative stress, and higher levels of protein breakdown versus protein synthesis [12, 13]. Effective therapeutic interventions to treat PEW are still being explored.

Anorexia or poor appetite is a subjective factor in nutrition assessment; however, recent studies have shown it to be predictive of poor clinical outcomes as well as being associated with inflammation [14]. Anorexia is estimated to be present in one-third of patients receiving maintenance dialysis [13, 15]. The etiology of anorexia is multifactorial and includes uremia, inflammation, infection, delayed gastric emptying, comorbid conditions, medications, psychosocial and socioeconomic factors, absorption of glucose in PD, early satiety and age [15–17]. See Chap. 9 for further information on PEW in CKD.

Metabolic acidosis impacts nutritional status by increasing protein catabolism and possibly decreasing protein synthesis leading to negative nitrogen balance and loss of lean body mass [18]. Correction of acidosis with sodium bicarbonate has been shown to correct the protein catabolism [19]. Metabolic acidosis may induce insulin resistance and chronic inflammation, both of which may also increase protein catabolism but more research is needed [18, 20, 21]. KDOQI recommends that predialysis bicarbonate levels be ≥22 mEq/L and that levels be monitored monthly [10].

HD has long been considered a catabolic procedure. Approximately 4–9 g net amino acids and 1–2 g protein are lost during HD and 5–15 g protein during PD [22–25]. The use of high-flux membranes, bio-incompatible membranes, and reuse of high-flux dialyzers have been shown to increase amino acid loss [26–28]. Dialysate protein losses are also higher with polysulfone dialyzers processed with bleach and losses significantly increase after the 16th use [29]. HD has been shown to induce a protein catabolic state that can stimulate muscle and whole-body protein loss, decrease protein synthesis, and increase energy expenditure with the effects lasting up to 2 h post-dialysis [29–31]. PD is not as catabolic unless the patient has peritonitis. A mild inflammatory response may be triggered by peritoneal dialysate bioincompatability, endotoxin transfer from the dialysate, or the PD catheter itself that can lead to protein catabolism [25, 32]. Patients receiving PD who are classified as high transporters by their peritoneal equilibration test (PET) have a higher incidence of poor nutrition due to the loss of larger amounts of protein into the dialysate. Serum albumin levels are usually low in these patients and they may require nutritional supplementation.

Assessment of dialysis adequacy should be part of the routine evaluation of nutrition in patients receiving maintenance dialysis. The relationship between Kt/V (a marker for dialysis adequacy where K = clearance, t = time, and V = volume) and the protein equivalent of nitrogen appearance (PNA), may be confounded by mathematical coupling. Using Kt alone, the non-normalized dose of dialysis may be more closely associated with serum albumin levels [33]. The Hemodialysis (HEMO) Study looked at the optimal dose of dialysis for patients receiving maintenance HD in order to determine the best parameters needed for achieving dialysis adequacy. Patients were randomly assigned to standard-dose dialysis (single pool Kt/V 1.25) or high-dose dialysis (single pool Kt/V 1.65) and to low- or high-flux dialyzers. When the study group looked at the effect of dialysis dose and membrane flux on various nutritional parameters, they found no significant differences between the various groups [34].

The relationship between nutritional intake and dose of dialysis in patients receiving continuous PD was evaluated as part of the CANUSA (Canada-USA) peritoneal dialysis study. A number of different nutritional markers were evaluated, and in the first 6 months, there was a positive correlation between the PD dose and all of the nutritional markers except for serum albumin levels. After 6 months, reduction in overall clearance because of loss of residual renal function was associated with a trend towards declining nutritional parameters [35]. Current minimum recommendations are a Kt/V of 1.3–1.4 for maintenance HD and a weekly total Kt/V of 1.7 for continuous PD [36].

In numerous observational studies, the use of short daily and NHD has been shown to reduce anorexia, improve protein intake, and have a positive impact on a number of nutritional markers [23, 27, 37, 38]. Recent results from the Frequent HD Study, however, did not show any significant effect on nutritional parameters with either NHD or SDHD [39]. Both of these treatment modalities are not available to all dialysis patients because of reimbursement obstacles and limited experience by dialysis providers. Research is ongoing.

Nutrient Recommendations in Dialysis

Energy

KDOQI recommends a daily energy intake of 35 kcal/kg standard or adjusted body weight/day for stable maintenance dialysis patients who are less than 60 years old and 30–35 kcal/kg standard or adjusted body weight/day for those age 60 and older [10]. These recommendations are based on metabolic studies that showed 35 kcal/kg was necessary to maintain neutral nitrogen balance and stable body composition. Since patients 60 years or older may be more sedentary and have less lean body mass, a lower energy intake of 30–35 kcal/kg body weight is thought to be acceptable. Energy intakes should be adjusted if the patient is involved in heavy physical exercise, underweight, or catabolic [10, 40]. Energy intakes for acutely ill maintenance dialysis patients are the same.

Hemodialysis

Many HD patients are unable to consume the recommended energy intake, resulting in a low body weight and body mass index, both of which are associated with increased mortality in the HD patient [10, 23]. The average energy intake has been reported at 24–27 kcal/kg/day [15, 40]. In the HEMO Study, patients averaged 23 kcal/kg/day, significantly less than the NKF-KDOQI guidelines for calories and less than the HEMO target of 28 kcal/kg/day [41]. Energy intake was less and patient reported appetite was suboptimal on dialysis days when compared to a non-dialysis days. Contributing factors were thought to be fatigue after dialysis or the catabolic, physiologic, and metabolic effects of dialysis on the body [42]. Other factors such as taste disturbances, medications, missed meals on dialysis days, overly restricted diet, delayed gastric emptying, repeated hospitalizations, and psychosocial concerns may also contribute to inadequate energy intake [8, 16, 43]. A standard dialysate solution containing 200 mg/dL glucose contributes only a small amount of calories during thrice weekly dialysis and does not significantly contribute to energy intake [23]. Assessment and counseling by the dietitian is important in helping the patient achieve an adequate intake. The use of nutritional supplements may need to be considered (see Chap. 14).

Peritoneal Dialysis

For patients receiving PD, energy levels should include calories from both diet and the dialysate since calories absorbed during dialysis can be significant and lead to weight gain. Several formulas have been published for determining caloric load from PD and these are found in Table 11.1 [44–47]. The most accurate method is to compare the grams of glucose infused with the grams of glucose in the effluent [48]. Glucose absorption differs between therapies with patients on continuous cyclic peritoneal dialysis (CCPD) absorbing approximately 40 % of calories due to shorter dwell times while

Table 11.1 Suggested methods to estimate calories absorbed from peritoneal dialysis

Formula	Comment
$(11.3X - 10.0) \times$ L inflow $\times 3.4 =$ kcal absorbed from glucose $X =$ average glucose concentration infused [44]	Does not account for differences in membranes
Glucose absorbed (kcal) $= (1 - D/Do)x_1$ D/Do is the fraction of glucose remaining and the x_1 is the initial glucose infused [45]	Considers dialysis modality and membrane transport type
Simple estimate: G glucose infused (based on total vol of exchanges) $\times$ % absorption (per modality) = G glucose absorbed G glucose absorbed $\times 3.4 =$ glucose kcal absorbed *% Absorption*: APD: 40 % CAPD: 60 % Icodextrin: 20–35 % *G glucose/L*: 1.5 % = 15 g 2.5 % = 25 g 4.25 % = 42.5 g 7.5 % icodextrin = 75 g	Does not consider membrane transport type or type of PD modality Provides a rough estimate

From refs. [44–48]

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APD automated peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *PD* peritoneal dialysis, *vol* volume

patients on continuous ambulatory peritoneal dialysis (CAPD) absorb approximately 60 % of calories [46, 48]. The clinician needs to remember that patients are taught to adjust their usual dextrose prescription for incidences of fluid overload or dehydration and low blood pressure so caloric contribution from dextrose may vary. It may be difficult to restrict calories for weight reduction in PD patients without compromising protein intake and nutritional status. To help with weight control, patients should be encouraged to limit excessive sugars and fats and to exercise if possible.

Icodextrin is an alternative polyglucose PD solution produced from the hydrolysis of cornstarch. Because it is a macromolecule, it is absorbed more slowly by the peritoneal membrane resulting in a sustained ultrafiltration (UF) and lower glucose absorption [46–49]. Icodextrin provides a caloric load similar to a 2.5 % dextrose dialysate solution over the longer dwell. One of the metabolites of icodextrin is maltose which can interfere with certain blood glucose monitors and strips causing a falsely elevated reading [47–50]. Individuals with diabetes who use icodextrin need to check with the manufacturer of their glucose meter and strips to assure they are using a system not affected by the maltose.

Nocturnal Hemodialysis/Short Daily Hemodialysis

There have been limited studies examining the nutritional needs of patients receiving NHD and SDHD. The current recommendations are extrapolated from the needs of the conventional HD patient (i.e., thrice weekly dialysis). The diet should be individualized to the patient based on lab data, interdialytic fluid weight gains, and duration of dialysis. Because of the frequency and duration of dialysis,

Table 11.2 Daily nutrient recommendations for adult dialysis patients

Nutrient	Hemodialysis	Peritoneal dialysis	Nocturnal/short daily hemodialysis
Energy (kcal/kg SBW or adj IBW)	30–35 ≥ 60 years 35 < 60 years	Same and include dialysate kcal	None established. Use KDOQI for HD
Protein (g/kg SBW or adj IBW)	1.2 (≥50 % HBV)	1.2–1.3 (≥50 % HBV)	Use KDOQI for HD and individualize
Sodium	2 g/day	2–3 g/day. Monitor BP control, fluid balance	NHD: 2.4–4 g/day SDHD: 2–3 g Monitor BP control, fluid balance
Potassium	2–3 g/day	3–4 g/day-unrestricted. Monitor serum levels	Dependent on serum levels
Calcium	≤2,000 mg total elemental	Same	Same
Phosphorus	800–1,000 mg or 10–12 mg/g protein	Same. Adjust to meet protein needs	NHD: mild to unrestricted SDHD: suggest HD restriction; adjust to control serum levels
Fluid	750–1,000 mL + UO	Individualize for fluid balance	Individualize for BP, UO, and fluid balance
Thiamine	1.2–1.5 mg/day	Same	Same
Riboflavin	1.1–1.3 mg/day	Same	Same
Niacin	20 mg/day	Same	Same
Biotin	30 μ/day	Same	Same
Pantothenic acid	5–10 mg/day	Same	Same
Cobalamin	2–3 μ/day	Same	Same
Pyridoxine	10 mg/day	Same	Same
Folate	1–10 mg/day[a]	Same[a]	Same[a]
Vitamin C	60–100 mg/day	Same	Same
Vitamin A	None	None	None
Vitamin D	Individualize	Individualize	Individualize
Vitamin E	Optional[b]	Optional[b]	Optional[b]
Vitamin K	None[c]	None[c]	None[c]
Zinc	If needed[d]	If needed[d]	If needed[d]
Copper	None	None	None
Iron	Individualize[e]	Individualize[e]	Individualize[e]
Selenium	None	None	None
Magnesium	None	None	None
Aluminum	None	None	None

Source: Data from [23, 51, 68, 98, 102, 104]
SBW standard body weight, *adj IBW* adjusted ideal body weight, *HD* hemodialysis, *BP* blood pressure, *Ca* calcium, *UO* urine output, *EPO* erythropoietin
[a]1 mg is standard recommendation but higher amounts may be needed. See text
[b]400 IU may be indicated. See text
[c]May need supplement if on antibiotics and have poor oral intake
[d]May be supplemented up to 15 mg elemental zinc
[e]Varies based on EPO dose

the diet for NHD tends to be more liberal than conventional HD. There are no established energy guidelines for NHD or SDHD so current recommendations follow the KDOQI Nutrition Guidelines for conventional HD and energy needs can be adjusted as needed to maintain weight (Table 11.2). With both NHD and SDHD, appetite has been reported to improve leading to an increase in both protein and calorie intake [23, 37, 51]. Weight gain may occur so energy needs should be adjusted and exercise encouraged if the patient is physically able to participate [23, 51].

Protein

Hemodialysis

Adequate protein intake is important to ensure that the patient maintains positive or neutral nitrogen balance. The KDOQI Nutrition Guidelines recommend 1.2 g/kg standard or adjusted body weight for the clinically stable HD patient with at least 50 % from high biological value (HBV) sources. HBV protein or animal protein is used more efficiently and provides the required essential amino acids [10]. Vegetarian patients will require ongoing counseling by the dietitian to help ensure they consume adequate protein from legumes or soy products without excess mineral load. Protein recommendations are based on a small number of nitrogen balance studies and do not differentiate for age. While it is possible that protein needs of the elderly patient receiving maintenance HD may be slightly reduced, the catabolic effects of dialysis along with other comorbid conditions may outweigh this reduction. A small number of studies have shown that the risk level for malnutrition in elderly HD patients is higher than in younger patients [52–55].

Protein intake is often inadequate in HD patients and contributes to PEW. In the HEMO Study, less than 20 % of the patients at baseline met the current KDOQI Nutrition Guidelines for protein with the average intake being 0.93 g/kg/day [41]. Protein needs are also influenced by metabolic acidosis, infection, inflammation, or surgical procedures associated with increased catabolism. Current protein recommendations are based on older metabolic studies and do not take into account the newer, highly permeable dialyzer membranes that have been shown to increase amino acid loss and lower serum albumin levels [28]. Further research on the effect of new dialyzer membranes and techniques on nutritional requirements is needed. There is limited data on the protein needs of the acutely ill maintenance HD patient and KDOQI recommends that these patients receive at least 1.2 g protein/kg/day [10]. Hospitalized HD patients generally consume less than the recommended amount of protein and may need intensive nutrition counseling, monitoring, and possibly nutritional support to provide adequate protein to meet their needs.

Peritoneal Dialysis

Protein requirements in PD are higher than for HD due to increased losses during dialysis. PD patients lose between 5 and 15 g protein/day through the peritoneum with the average being 9 g. Approximately half of that protein loss is in the form of albumin [22]. During episodes of peritonitis this loss can increase by 50 % or more and may remain elevated for 2–3 weeks after resolution of the infection [46, 56, 57]. Metabolic balance studies found that in clinically stable patients, 1.2–1.3 g protein/kg/day was required to maintain neutral or positive nitrogen balance [58, 59]. Based on these studies, KDOQI recommends that PD patients consume no less than 1.2 g protein/kg/day and that 1.3 g/kg/day be prescribed with 50 % from HBV sources [10]. Achieving this intake is sometimes difficult for patients and the dietitian needs to assess protein intake for adequacy.

PNA: Hemodialysis and Peritoneal Dialysis

Protein nitrogen appearance (PNA) is used to estimate protein intake in the clinically stable dialysis patient. Protein is metabolized to nitrogenous products, and in the stable patient, nitrogen waste products removed are equal to protein intake. PNA is calculated from the urea appearance rate. Urea nitrogen appearance rate is calculated from 24-h collections of urea dialysate and urine concentrations in the PD patient or estimated from the interdialytic changes in serum urea nitrogen in the HD patient.

The equations can be found in the KDOQI Nutrition Guidelines [10]. After PNA is calculated, it can be normalized (nPNA) to body size. PNA may also be normalized to actual edema free body weight; however, this method will give a higher nPNA in malnourished patients with low body weights than in the overweight patient in good nutritional status [10, 56]. In these cases, normalizing to ideal body weight may be more appropriate [10]. If the patient is catabolic, the PNA will be high in proportion to the actual dietary protein intake. If the patient is anabolic, then the reverse will occur [25].

Nocturnal Hemodialysis/Short Daily Hemodialysis

There are no established guidelines for protein requirements in NHD or SDHD, so current recommendations are to implement the KDOQI guidelines for protein and adjust to maintain adequate serum albumin levels (see Table 11.2) [51]. Patients receiving NHD usually have good protein intakes possibly due to an increased clearance of middle and larger molecular weight substances during the longer dialysis [51]. Patients on SDHD have been shown to also have increased protein intakes possibly due to the increased frequency of dialysis [60, 61].

Nutrition Support

Patients who are malnourished at the initiation of dialysis, later develop malnutrition, or have peritonitis will have increased dietary protein and energy requirements [56]. Achieving adequate intake may be difficult since oral intake may have spontaneously declined. It may be necessary to liberalize the diet and encourage the use of oral nutritional supplements in the form of modular protein powders or nutritionally complete liquid products. Tube feeding or intradialytic parenteral nutrition (IDPN) may be considered for the HD patient who needs significant nutrition support. The use of intraperitoneal amino acids in intraperitoneal nutrition (IPN) has been shown to improve nutritional status in malnourished PD patients and is as an option in the patient who has failed to achieve/maintain an adequate protein intake [62–64]. Both IDPN and IPN are limited by cost and insurance reimbursement. For more information, refer to Chap. 14.

Sodium and Fluid

Hemodialysis

Sodium and fluid control are very important in patients receiving maintenance HD. When the glomerular filtration rate (GFR) falls below 15 mL/min/1.73 m^2, the kidneys' ability to compensate and excrete sodium declines, leading to sodium retention. Since a patient's GFR declines within the first few months on HD to 1–2 mL/min/1.73 m^2 and the patient becomes oliguric or anuric, diet and dialysis become the two controlling factors in sodium and fluid balance [23]. Excessive fluid and sodium intake between treatments can result in sodium and fluid overload leading to hypertension and cardiac problems such as congestive heart failure (CHF) [65, 66]. In addition, removal of large interdialytic fluid weight gains to achieve a dry weight may not be possible during one treatment and may cause intradialytic hypotension, cramping, angina, arrhythmias, and malaise [23, 67]. The recommended sodium intake for HD patients is 2 g/day while the recommended fluid intake is 750–1,000 mL plus urine output and, in general, should not exceed 1,500 mL/day including that in food [22, 23, 67]. The goal is to minimize interdialytic weight gains and control blood pressure. Ideally, interdialytic weight

gains between treatments should not exceed 2–3 kg or 3–5 % of the patient's dry weight [67, 68]. Some nephrology specialists think that lower sodium intakes of 1–1.5 g/day would be beneficial but this may impact the nutritional status of the patient by limiting intake of important nutrients, especially if poor food choices are made. The accessibility of high sodium convenience and fast foods makes patient adherence difficult. Reduced or low sodium convenience foods in the grocery store may have potassium chloride added to replace sodium making them potentially dangerous for the HD patient. Patients should be counseled on avoiding high sodium foods, label reading, making appropriate choices when eating out, and ways to help control thirst. While high interdialytic weight gains can indicate excessive consumption of sodium and fluid, very low interdialytic weight gains, especially in the elderly, may be an early indicator of poor oral intake [69]. The elderly dialysis patient, already at risk for malnutrition, may over restrict both their food and fluid intake. A thorough diet history, along with a review of other nutritional parameters, should be obtained to assess the nutritional adequacy of the diet.

Peritoneal Dialysis

The recommended sodium restriction for patients receiving PD is 2–3 g/day and should be individualized depending on cardiac status, blood pressure control, and fluid balance. Sodium is usually easily cleared in PD, with the majority of patients clearing 3–4 g of sodium daily depending on their dialysis prescription [70, 71]. Excess dietary sodium intake will affect volume retention and blood pressure control [65, 71–73]. Patients receiving PD who are volume-overloaded, hypertensive, and unresponsive to management by medication may require a stricter sodium and fluid restriction [72]. To correct volume overload it becomes necessary to use a hypertonic dialysate solution. The frequent use of high dextrose concentrations can damage the peritoneum leading to alterations in and possible loss of UF by the peritoneal membrane [50, 74, 75]. Hypertonic dextrose solutions can also aggravate hypertriglyceridemia, hyperglycemia, and hyperinsulinemia and promote weight gain [40]. Patients may initially start out with a liberal sodium intake (3 g) but it may become necessary to reassess the patient for declining residual renal function and uncontrolled blood pressure to determine whether a reduction in sodium intake is indicated.

Fluid removal in PD is regulated by the strength of the dialysate concentration used, i.e., the higher the concentration, the more fluid removed [46, 50]. Patients are taught to monitor their blood pressure, weight, and drain volumes to identify if and when any change in their normal dialysis prescription may be needed. Ultrafiltration (UF) using glucose occurs quickly and early in the PD exchange, which can present a problem for the volume overloaded patient who requires a higher UF during the long overnight CAPD dwell or the daytime CCPD dwell [50]. In these circumstances, icodextrin can be used as an alternative dialysate. The recommended fluid allowance for patients receiving PD should be individualized for each patient with the goal of minimizing the use of hypertonic exchanges. The typical daily fluid allowance should not exceed 2 L; however, patients with a high urine output may need to have additional fluid [25, 48]. Fluid allowance may be less depending on cardiac status, blood pressure control, rate of UF, and amount of remaining residual renal function.

Nocturnal Hemodialysis/Short Daily Hemodialysis

Sodium and fluid restriction in the NHD and SDHD patient is dependent on fluid balance, blood pressure control, and the type of dialysis machine used. The current Dietary Reference Intake (DRI) for sodium is 2,400 mg/day and is a good starting point for the stable patient, but no formal guidelines for this cohort have been published. The hypotensive NHD patient may require a more liberal sodium

prescription. Fluid intake should be individualized based on interdialytic weight gain. A fluid restriction may not be required for the NHD patient as long as the patient does not gain more than he/she can safely remove while maintaining hemodynamic stability. This may vary slightly from patient to patient based on the dialysis prescription, but it is approximately 2–4 L/night [51].

Patients on SDHD dialyze 2–3 h/day so they are limited in the amount of fluid they can safely remove in one treatment. Patients may dialyze on a conventional HD machine or the NxStage System One machine. There are no formal guidelines, but clinical experience suggests that 1–1.5 L/h can be removed safely depending on the type of dialysis machine used for treatment.

Potassium

Hemodialysis

As the GFR falls, the kidneys lose their ability to filter potassium, and fecal potassium excretion increases [23, 76]. Potassium removal during HD averages between 70 and 150 mEq per treatment [77]. This will vary depending on the dialyzer clearance and the potassium concentration of the dialysate, i.e., the higher the dialysate concentration, the less potassium is cleared. Most patients receiving maintenance HD are placed on a dialysate bath of 2–3 mEq/L, with the standard being 2 mEq/L [23, 77]. Use of low-potassium dialysate (0–1 mEq/L) is rarely used in the outpatient dialysis setting because of the increased risk of cardiac arrest due to hypokalemia [23]. Patients with a low pre-dialysis serum potassium (<3.5 mEq/L) will generally require the upper range of the dialysate bath (3–4 mEq/L) especially if oral intake is poor. Hyperkalemia may be categorized as either mild (serum potassium 5.5–6.5 mEq/L) or moderate (>6.5 mEq/L) and may result in cardiac arrhythmias and cardiac arrest [23].

The recommended dietary potassium restriction is 2–3 g/day and should be individualized based on serum lab values [22, 23, 40]. Nutritional counseling regarding food sources of potassium and patient education about the complications of hyperkalemia are important to help the patient avoid elevated potassium levels during the interdialytic period. The primary sources of potassium are fruits, vegetables, and dairy along with nuts, seeds, nut butters, and dried beans and peas. Patients should also avoid salt substitutes, which contain potassium chloride, and check with their doctor or dietitian before using any herbal products or dietary supplements. Patients should also be counseled to check food labels on reduced or low sodium products for the addition of potassium chloride. For patients who are chronically nonadherent and whose dialysate bath cannot be lowered, a short-term dose of an oral sodium polystyrene sulfonate resin such as Kayexalate may be given [23, 40]. While the primary cause of hyperkalemia may be dietary intake, non-dietary factors such as medications, hyperglycemia, metabolic acidosis, pica behaviors, and inadequate dialysis can also lead to elevated serum levels and should be investigated if dietary causes can be ruled out (Table 11.3) [76–79].

Peritoneal Dialysis

Hyperkalemia is less common in patients receiving PD due to the continuous nature of the dialysis and some patients may not require a potassium restriction [48, 77]. A 3–4 g/day dietary potassium restriction is recommended and should be adjusted based on laboratory values to maintain serum potassium within normal ranges [48]. It is advisable to have patients spread their high-potassium food choices throughout the day. Patients with diabetes should be cautioned not to treat frequent low blood glucose levels with only high-potassium fruit juices, such as orange juice, as this may cause hyperkalemia. Some patients may become hypokalemic due to nausea, vomiting, diarrhea, or inadequate dietary intake and may require liberalization of the diet and oral potassium supplementation [77, 80].

Table 11.3 Dietary and non-dietary causes of hyperkalemia in hemodialysis patients

Dietary causes
Use of salt substitutes
Pica behavior
Use of herbal or over-the-counter vitamin/mineral supplements
Excessive consumption of high-potassium foods
Excessive consumption of liquid nutritional supplements
Non-dietary causes
Severe, chronic constipation
Loss of remaining residual renal function
High dialysate potassium concentration
Frequent use of chewing tobacco
Metabolic acidosis
Inadequate dialysis
Blood transfusions
Hemolysis of blood sample due to error in blood draw or specimen handling
Hyperglycemia: potassium shifts from cell into serum
Conditions causing release of potassium through tissue destruction such as catabolism, starvation, infection, burns, surgical stress, chemotherapy
Drug interactions: beta blocking agents, spironolactone, angiotensin-converting enzyme inhibitors, cyclosporine, digoxin
Comorbid conditions such as Addison's disease, sickle-cell anemia, hypoaldosteronism

Data from refs. [23, 68, 76, 77]
Adapted from Beto J. Hyperkalemia: Evaluation of dietary and non-dietary etiology. J Ren Nutr. 1992;2:28–29

Nocturnal Hemodialysis/Short Daily Hemodialysis

A potassium restriction in NHD is normally not required unless mid-week serum levels are high [51, 81]. If a patient skips one night of treatment and has a high interdialytic potassium level, then that patient should be placed on a potassium restriction over their longest skip period [51]. Although no specific recommendations are available, clinical experience suggests that a 2.5–3 g potassium diet may be appropriate depending on the degree of hyperkalemia. Patients who are hypokalemic will need to increase their dietary potassium intake, be given a potassium supplement, or have the potassium concentrate of the dialysate adjusted if unable to maintain normal levels by diet alone [51].

There have been limited studies on potassium removal in SDHD. One study using the NxStage System showed an average of 73 mmol of potassium cleared per treatment [82]. Kohn demonstrated an average of 55 mEq removed with a range of 35–80 mEq [83]. Potassium clearance on SDHD is not as good as on PD but slightly better than conventional HD when one compares weekly potassium removal. There are no formal guidelines and more research is needed. Since most patients transition from conventional HD to SDHD, clinical experience suggests patients continue with their conventional HD dietary recommendations and then adjust the diet during the initial training period to control serum levels.

Calcium/Phosphorus/Vitamin D

Hemodialysis and Peritoneal Dialysis

Calcium and phosphorus balance in healthy individuals is maintained through interactions between the kidneys, parathyroid glands, bones, and intestines. In CKD, the decline in GFR results in increased phosphorus retention and the decreased production of 1-25-dihydroxycholecalciferol

($1,25(OH)_2$ Vit D) or calcitriol, the active form of vitamin D. Decreases in calcitriol can result in reduced intestinal calcium absorption, decreased mineral reabsorption/excretion by the kidneys, increased bone turnover, and increased parathyroid hormone (PTH) production [84]. These metabolic changes, along with hyperphosphatemia, can lead to secondary hyperparathyroidism, renal osteodystrophy, and elevated PTH levels. Active vitamin D can be given orally or intravenously during dialysis to correct vitamin D deficiency and suppress PTH production and secretion; however, calcitriol supplementation can also increase intestinal absorption of calcium and phosphorus and increase calcium mobilization from the bone leading to further mineral imbalance [84]. Newer analogs are available to suppress PTH with less impact on calcium and phosphorus. Regardless of therapy, all patients should be closely monitored to keep calcium, phosphorus, and PTH levels within recommended guidelines.

Both excessive calcium load and hyperphosphatemia are associated with bone disease, vascular and soft tissue calcification, and increased cardiovascular mortality because they contribute to an elevated Ca × P product [85–87]. Research indicates that a Ca × P product >55 is related to an increase in mortality in CKD patients [88]. Calcium load is affected by the amount of dialysate calcium, dietary calcium intake, and use of calcium-based medications, specifically phosphorus binders, while serum phosphorus is controlled by adequate dialysate, diet restrictions, and use of phosphorus binders [23, 89]. Dietary calcium intake in dialysis patients is generally about 500 mg/day when high-phosphorus foods are limited, the patient is compliant with restrictions, and no calcium-fortified foods are used. The increasing amount of calcium-fortified foods in the supermarket means that patients must be counseled to carefully read food labels to avoid these items. KDOQI recommends no more than 800–1,000 mg phosphorus per day; however, in some cases this may be difficult to achieve since many high-phosphorus foods are also high in protein. The phosphorus restriction needs to be adjusted to dietary protein requirements to prevent protein malnutrition. For PD and HD patients with higher protein needs, calculating phosphorus based on protein requirements (using 10–12 mg phosphorus/gram protein) should provide a reasonable phosphorus restriction [90]. Phosphorus is not currently required to be listed on food labels, and the use of phosphate-based food additives has contributed to hidden sources of phosphorus outside the traditionally known high-phosphorus foods. The inorganic phosphates used as food additives are also 100 % absorbable as compared to the 50–60 % absorption rate from naturally occurring phosphorus [91]. Refer to Chap. 15 for a review of bone disease management in CKD.

Nocturnal Hemodialysis/Short Daily Hemodialysis

With NHD, weekly phosphate removal is twice that of conventional HD so phosphate levels are generally normal or low and calcium-phosphorus balance is normal [81, 92, 93]. Phosphorus restriction is not needed in the majority of patients, but it is dependent on the patients' appetite, oral intake, and serum phosphorus levels. A large percentage of patients may be able to decrease or discontinue use of phosphate binders. Phosphorus levels should be monitored and the diet individualized. In patients who are hypophosphatemic and unable to increase dietary phosphorus intake, phosphate may be added to the bicarbonate bath [92].

Phosphorus control is not as good on SDHD compared to NHD. Weekly phosphorus removal has been shown to be 606–694 mg per treatment and is dependent on pre-dialysis levels of phosphorus as well as time on dialysis [82, 83]. Phosphorus removal is increased when levels are greater than 5 mg/dL [82, 83]. Phosphorus binder dose has been shown to either increase or decrease slightly depending on HD duration and frequency and dietary protein and phosphorus intake [61, 82, 83]. Phosphorus intake may be higher due to improved appetite and higher protein intakes. There are no formal

evidence-based guidelines for dietary phosphorus restrictions in SDHD. However, based on current studies, it is prudent to restrict phosphorus intake to control serum levels.

Lipids

Hemodialysis

There is a high prevalence of lipid abnormalities in the dialysis population, which is a contributing risk factor to cardiovascular disease (CVD). The mortality rate from CVD in patients undergoing maintenance HD is almost 50 % [23]. HD patients generally have normal or high total cholesterol, low-density lipoproteins (LDL), and triglycerides (TG) and normal or low high-density lipoproteins (HDL) [23, 94]. According to the Dialysis Morbidity and Mortality Study, only 20 % of patients receiving maintenance HD meet the recommended normal lipid parameters outlined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) [95]. The KDOQI recommended therapeutic lifestyle changes (TLC) are covered in detail in Chap. 9. Briefly, it recommends: (a) a reduction in saturated fat to <7 % of total calories; (b) a reduction in total fat to 25–35 % of total calories with monounsaturated fat providing up to 20 % of calories and polyunsaturated fat up to 10 %; (c) total dietary cholesterol <200 mg/day; (d) increased dietary fiber; and (e) modifications in calories to attain or maintain a desired weight along with exercise and smoking cessation [95].

Before beginning any dietary modifications, the dietitian should assess the patient for any signs of PEW, as addition of a fat restricted diet can compromise caloric intake which can further compromise nutritional status [96]. Patients also encounter difficulty trying to comply with the fat recommendations in addition to a complex renal diet. Dietary modification may be undertaken if the patient is well-nourished; however, pharmacological intervention with lipid-lowering medication may be the only intervention used if the patient is unable or unwilling to further modify their diet. Encouraging general recommendations for modifying saturated fat along with smoking cessation and promoting exercise should be encouraged.

Peritoneal Dialysis

Patients receiving PD often have elevated LDL, total cholesterol, and TG levels along with abnormalities in serum apoproteins thought to be related to the glucose uptake from the dialysate and increased protein losses during dialysis [25, 50, 97]. There is little data as to the effectiveness of diet modification on lipid levels in PD patients with the exception of maintaining good glycemic control in those with diabetes [96, 97]. Strict fat restricted diets may also compromise protein and calorie intake and lipid-lowering medications are generally the first line of treatment along with encouraging general TLC such as smoking cessation and exercise. Maintaining adequate protein intake is the primary goal. Minimizing saturated fat and sugar intake should be recommended when possible, but strict dyslipidemia diets may not be appropriate for patients receiving PD if nutritional status is compromised [94–96].

Nocturnal Hemodialysis/Short Daily Dialysis

While there are no specific recommendations for NHD and SDHD, it would be prudent to encourage patients to follow general therapeutic lifestyle recommendations suggested by the KDOQI guidelines for dyslipidemias due to the high risk of CVD in the dialysis population.

Vitamins, Minerals, and Trace Elements

Vitamins, minerals, and trace elements are micronutrients required by the body to help with normal metabolism, energy production, cell function, and growth and recently have been shown to help lower the risk for CVD and cancer in the general population [98, 99]. The Food and Nutrition Board of the Institute of Medicine has developed DRIs for most of the micronutrients for the general healthy population. The DRIs for the patient receiving maintenance dialysis have not been established and the vitamin and mineral recommendations are the same for HD and PD. Kidney failure can cause impaired or excessive excretion of micronutrients due to the loss of glomerular filtration or impaired tubular function leading to either a deficiency or toxicity [98].

The current recommendations for vitamins and minerals in NHD and SDHD are the same as those for conventional HD. There is some concern that there may be an increased loss of water-soluble vitamins, especially vitamin C, because patients are dialyzing twice as many days. In the few studies that have been done, lower levels of vitamin C and thiamine have been found [51, 81, 100, 101]. Further research is needed in this area.

Water-Soluble Vitamins

There are numerous causes of water-soluble vitamin deficiency in dialysis patients and these include patient anorexia, alterations in metabolism caused by renal failure, the dialysis process, drugs which may affect absorption, and the renal diet restrictions [23, 25, 102]. Water-soluble vitamins are small, nonprotein bound substances which are removed by dialysis and may be lost at a rate greater than normal urinary excretion [102]. Dialysis membrane pore size, surface area, and increased flow rates can adversely affect water-soluble vitamin retention [98, 103]. Some drugs such as immunosuppressants, anticonvulsants, and chemotherapy drugs used to treat comorbid conditions can also interfere with vitamin absorption [104]. See Chap. 24 for an in-depth review of vitamins in CKD.

Little research has been done to determine the exact requirements for biotin, riboflavin, pantothenic acid, niacin, cobalamin, and thiamine in kidney failure and serum levels are usually normal [98]. Thiamine deficiency has been reported in dialysis patients and several symptoms of thiamine deficiency, such as CHF with fluid overload (wet beriberi), lactic acidosis, and unexplained encephalopathy, can mimic uremic complications making an early diagnosis difficult [98, 105, 106]. Biotin levels have been shown to be normal, but supplementation may help with dialysis-related intractable hiccups [107, 108].

The water-soluble vitamins most likely to be deficient are pyridoxine (B-6), folic acid, and vitamin C [22, 98, 102, 103]. Adequate stores of B-6 are necessary for erythropoietin (EPO) to be effective in promoting red blood cell (RBC) formation, and deficiency symptoms include peripheral neuropathy and burning [98, 104]. Levels of B-6 are low to normal in patients receiving conventional dialysis with higher losses for patients on high-flux/high-efficiency dialyzers or those receiving EPO therapy [40, 98, 103]. B-6, along with folic acid and vitamin B-12, is a cofactor in homocysteine metabolism, and low levels may result in hyperhomocysteinemia, which can contribute to increased cardiovascular risk in patients receiving maintenance dialysis [109–112]. Therefore, more than the DRI for pyridoxine is required with the recommended amount being 10 mg/day [99]. Although the risk for pyridoxine toxicity is low, an upper limit (UL) has been established at 100 mg/day. Doses higher than this can cause a sensory neuropathy [98, 102].

Adequate serum levels and body stores of folic acid are important for RBC [98, 113]. Levels are generally normal, but losses may be higher in hemodialysis especially with high-flux dialysis. Folic acid supplementation may be indicated for the management of hyperhomocysteinemia as it enhances

homocysteine removal [112, 113]. Hyperhomocysteinemia can damage vascular endothelial cells, cause lesion formation, and promote platelet aggregation leading to CVD [112]. High-dose folic acid therapy (5–15 mg daily) has been shown to reduce homocysteine levels by 25–30 %, but does not normalize the levels. Further research on CVD outcomes are needed before conclusive recommendations on routine supplementation can be made [98, 113].

Vitamin B-12 plays a role in folic acid metabolism and the formation of RBC. Levels may be normal as vitamin B-12 may not be removed as much as other water-soluble vitamins [23, 104]. There have been reports of B-12 deficiency in patients on high-flux dialyzers and EPO and high-dose folic acid supplementation may increase requirements [103, 104, 109]. Vitamin B-12 levels may decrease as the length of time on dialysis increases [23]. Since vitamin B-12 relies on intrinsic factor for absorption, it may also be deficient in patients with malabsorption, partial or total gastrectomy, and intestinal resection [23]. A water-soluble renal vitamin supplement containing thiamine, niacin, biotin, riboflavin, pantothenic acid, and cobalamin is generally recommended at levels to meet the DRIs for the general healthy population to help maintain normal levels (see Table 11.2).

Vitamin C has antioxidant properties, it regulates iron distribution and storage, and it may help to promote intestinal iron absorption [40, 98, 114]. Vitamin C levels can be low if not supplemented, since it is removed during dialysis and the patient's dietary intake of vitamin C may be marginal [99, 102]. The recommended daily dose of vitamin C is 60–100 mg. Higher doses can lead to oxalosis resulting in increased oxalate deposition in soft tissue, which can increase the risk of kidney stones, myocardial infarction, bone disease, and shunt failure [22, 98, 102, 104, 114]. Whether or not vitamin C supplementation can help reduce inflammation and oxidative stress is still unclear and research is ongoing [22, 98]. Vitamin C has been shown to reduce leg cramps when given with vitamin E; however, the long-term safety has not been established [40, 115].

Fat-Soluble Vitamins

Vitamin A is not removed by dialysis and can accumulate in kidney failure. Vitamin A levels increase with duration of time on dialysis but not frequency, and levels are generally two to five times higher in dialysis after patients in the general population [23, 98, 116]. Elevated vitamin A levels are thought to be due to the lack of removal of retinol-binding protein (RBP) by the kidney. Toxicity occurs when the amount of retinol exceeds the binding capability of RBP. Symptoms include hypercalcemia, anemia, hypertriglyceridemia, and increased alkaline phosphate levels. These symptoms may mimic uremia and a diagnosis of toxicity cannot be made without assessing serum vitamin levels [23, 98, 116, 117]. Vitamin A supplementation is not recommended and intake from food and/or supplements should not exceed the DRI. Patients with malabsorption syndromes may require supplemental vitamin A, but retinol levels should be checked before initiating therapy and then monitored regularly to avoid toxicity [98, 102, 104, 117].

Vitamin E is not removed by dialysis and levels have been reported to be low, normal, or high [23, 102, 117]. Low serum levels of vitamin E are thought to be associated with the development of atherosclerosis and cardiovascular events in the dialysis population, but research into the role of vitamin E in decreasing oxidative stress, inflammation, and mortality has not demonstrated any appreciable benefit [106, 117]. Vitamin E (400 μg), given with 250 mg vitamin C, has been shown to reduce leg cramps in patients receiving maintenance HD [115]. Vitamin E can cause an increased risk of deep vein thrombosis and a vitamin K-like responsive hemorrhagic condition in patients taking an anticoagulant [23, 98]. Research indicates that supplementation ≥400 IU may increase all-cause mortality in the general population so amounts greater than the DRI are not recommended [118]. Vitamin K was thought not to be deficient in patients receiving maintenance dialysis; however, recent research

indicates that close to 30 % of maintenance HD and PD patients demonstrate subclinical vitamin K deficiency [23, 104, 117]. Adequate levels of Vitamin K may play a role in bone health by decreasing the frequency of bone fractures [119]. Further clinical trials are needed to look at the benefits or potential side effects of vitamin K supplementation; therefore, at this time there is still not enough evidence to recommend routine supplementation. Patients at possible risk for vitamin K deficiency are those receiving long-term antibiotic therapy, those eating poorly over an extended period of time, or those patients on unsupplemented total parenteral nutrition [23, 109]. Excessive vitamin K can interfere with anticoagulant therapy; therefore, patients receiving vitamin K supplements should be closely monitored [23, 102, 104].

Minerals and Trace Elements

Minerals and trace elements are mainly supplied by diet; however, serum levels can also be affected by environmental exposure, length of dialysis, concentrations of the dialysate, poor nutrition, impaired absorption, or age [98, 109, 120]. Many minerals and trace elements are protein bound so uremia itself may alter levels; however, losses during dialysis are probably minimal [98, 120]. Levels of some minerals and trace elements will be affected by the concentration gradient between the dialysate fluid and the serum. This section will provide an overview of select minerals in MHD. See Chap. 24 for further information.

Zinc deficiency can lead to taste and smell dysfunction, impaired wound healing, decreased resistance to infection, and sexual dysfunction [98, 121]. The prevalence of zinc deficiency in patients receiving maintenance dialysis is not known but can occur, and toxicity is rare [23, 98, 121]. Zinc is protein bound so levels may be falsely low when albumin levels are low. Calcium and iron supplements as well as fiber and alcohol intake can interfere with zinc absorption [98, 109]. These factors decrease the reliability of using serum zinc alone as a diagnostic tool for zinc deficiency or for monitoring patients receiving zinc supplements [98, 109]. Assessment of patient response to supplementation should use a combination of laboratory levels and changes in clinical symptoms. Chronic uremia can impair taste acuity; however, controversy exists as to whether or not zinc supplementation will improve taste perception [122, 123]. Short-term zinc supplementation may be beneficial for wound healing; however, optimal dose levels have not been determined [109]. Therefore, until more definitive outcomes are determined, the recommended amount of zinc should not exceed the DRI of 15 mg/ day.

Selenium levels have been found to be low in patients receiving maintenance dialysis and may be associated with low protein intakes [98, 124]. Selenium supplementation may help improve immune function by decreasing oxidative stress [22, 120]. Toxicity is rare but until more clinical evidence is established, regular supplementation is not recommended.

Copper levels have been shown to be normal and deficiency is rarely seen unless the patient is receiving long-term parenteral nutrition with inadequate supplementation [98]. Serum copper levels can be affected by excessive intake or high zinc intakes can interfere with copper absorption [109]. Copper supplementation is not recommended for the dialysis patient.

Aluminum does not appear to have any essential function in the human body but it is important because of its potential toxicity in patients receiving maintenance dialysis [98]. Age, PTH, citrate, vitamin D, and fluorine may increase aluminum absorption in the gut, and the length of time on dialysis may increase aluminum levels in bone [23]. Aluminum toxicity in dialysis patients is due to increased uptake and storage and is associated with dialysis encephalopathy syndrome, refractory anemia, and a reduction in bone formation leading to aluminum-induced adynamic bone disease (ABD) or osteomalacia [23, 98]. A primary source of aluminum is aluminum-containing antacids and patients should avoid long-term use of these medications. However, as stated in the KDOQI Guidelines for Bone Disease, aluminum-based binders may be used on a short-term basis for patients with chronic hyperphosphatemia (refer to Chap. 15).

Magnesium levels in patients receiving maintenance dialysis are generally normal to mildly elevated due to a decrease in gastrointestinal absorption and the fact that high magnesium containing foods, such as green leafy vegetables and legumes, are generally restricted [23, 40]. Hypermagnesemia occurs primarily from excessive intake from drinking water, over-the-counter medications such as antacids or laxatives, alcoholism, or some phosphorus binders. Magnesium can be removed using a lower magnesium dialysate (0.75–1.5 mEq/L) [23]. Hypermagnesemia can cause hypertension, weakness, and arrhythmias. Long-term hypermagnesemia may cause ABD by suppressing PTH secretion [40, 125]. Deficiency can result in muscle weakness, seizures, and arrhythmias and may interfere with the release of PTH leading to hypocalcemia [23, 125]. Dietary restrictions are not instituted unless a patient develops hypermagnesemia and non-dietary sources are ruled out. Supplementation is not routinely prescribed unless the patient develops a magnesium deficiency.

Iron is essential in many metabolic processes including oxygen transport by hemoglobin and myoglobin. Iron is stored in the liver as ferritin and transported to cells as transferrin. Iron deficiency is common in patients receiving maintenance dialysis because of frequent blood sampling, dialysis associated losses, decreased availability of ferritin, losses during surgery, and gastrointestinal losses [98]. EPO therapy increases RBC production thereby increasing iron utilization [98, 126]. Monitoring iron balance using transferrin saturation and ferritin is important to correct deficiency and prevent iron overload. Patients with CKD are unable to obtain adequate iron from diet alone and oral iron supplementation may not be effective since absorption can be decreased by the presence of an inflammatory state, iron stores, age, sex, timing of supplement administration, and simultaneous use of iron inhibiting medications such as calcium [127, 128].

Intravenous (IV) iron is usually administered during HD and when oral therapy in PD has failed. IV iron therapy has less gastrointestinal side effects and is more efficient. Iron management in PD is similar to recommendations for HD except that patients are brought in-center for an IV iron infusion [48, 98]. See Chap. 13 for an in-depth review of anemia management.

Summary

Diet is an essential component in the treatment of patients receiving maintenance dialysis. The diet for Stage 5 CKD presents many challenges for the patient receiving maintenance dialysis that include lifestyle changes in food choices and preparation, adjusting to taking new medications, such as phosphorus binders with meals, and possibly having to combine the renal diet with other dietary modifications such as diabetes. The diet must be individualized for each patient to help promote adherence and maintain an optimal intake while balancing protein, sodium, potassium, phosphorus, and fluid requirements. There are a variety of educational materials available to help educate both the patient and the professional. The National Kidney Foundation and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) provide both patient and professional educational material in the area of kidney disease that can be accessed online or by contacting the organizations. Understanding the different types of RRT and their nutritional implications are important in maintaining nutritional status and improving outcomes. Nutrition therapy should involve routine nutrition assessment, ongoing monitoring of biochemical parameters, and individualized patient nutrition education.

Case Study

CT is a 34-year-old male, self-employed graphic designer who presents for training on CAPD after transferring from HD at another unit following failure of his 13-year-old kidney transplant. He has a history of esophageal reflux and hypertension. CT lives alone and his reported appetite is fair. He

notes an 8-lb weight loss prior to starting HD and now complains of occasional indigestion stating food occasionally feels like it is lodged in his throat producing a feeling of choking. Height 6′2″, weight 182 lb (82.7 kg), estimated dry weight 182 lb (82.7 kg), usual weight 190 lb (86.4 kg). Medications: prenatal vitamin, Tums as needed, 10 mg prednisone, 1 (800 mg) sevelamer carbonate (Renvela) as phosphorus binder three times a day with meals. Initial labs: Ca 9.0 mg/dL, P 6.3 mg/dL, Na 141 mEq/L, K^+ 4.7 mEq/L, Chol 102 mg/dL, BUN 39 mg/dL, Cr 7.8 mg/dL, Alb 3.4 g/dL, CO_2 22 mEq/L, *Kt*/*V* 2.0, urine output = 1,500 mL. CAPD prescription: 3 (2.5 L) 1.5 % dextrose plus 1 (2.5 L) 2.5 % dextrose. Twenty-four-hour diet recall indicates patient consumes an estimated 1,800–2,000 kcal and 70–80 g protein over three meals with an occasional snack. CT does not use the salt shaker at the table and has had difficulty decreasing his dairy intake. Estimated sodium intake is 2,000–2,500 mg, potassium 3,000 mg, and phosphorus 1,800 mg.

After 3 months on PD, patient complains of increased dysphagia and decreased oral intake. There has been no change in the CAPD prescription. Weight 180 lb (81.8 kg). Lab: Ca 8.6 mg/dL, P 3.0 mg/dL, Na 142 mEq/L, K^+ 2.8 mEq/L, BUN 28 mg/dL, Alb 3.1 g/dL, TP 6.1 g/dL, Chol 110 mg/dL, *Kt*/*V* 2.1, urine output 1,400 mL. The patient is referred for a barium swallow that indicates a severe hiatal hernia and Schatzki's ring. CT had an esophageal dilation and dysphagia resolved. After 1 year on PD, CT's UF declines leading to poor clearance and fluid retention. He complains of early satiety, nausea, and severe anorexia and develops 3+ edema to the knee. Use of diuretics and 4.25 % dextrose is unsuccessful. A repeat *Kt*/*V* has dropped to 1.4. CT is switched to conventional HD on a 3.5 mEq calcium and 2.0 mEq potassium bath. After 1 week of HD, his appetite begins to improve and his labs are Ca 9.5 mg/dL, P 6.0 mg/dL, Na 128 mEq/L, K^+ 5.8 mEq/L, BUN 44 mg/dL, Cr 8.0 mg/dL, Alb 3.0 g/dL, CO_2 24 mEqQ/L, Chol 150 mg/dL, urine output 500 mL, 1+ edema, weight 184 lb (83.6 kg), and estimated dry weight 182 lb (82.7 kg).

Case Questions and Answers

1. What are CTs' estimated calorie and protein needs for CAPD? Using the simple formula for estimating glucose, how many calories is CT getting from his dialysate?

   Answer: CT has no edema so using 35 kcal/kg of his current body weight puts estimated kcal needs at 2,894 kcal. Based on 1.3 g/kg body weight, his protein needs are 107.5 g. Based on a 60 % absorption rate for CAPD, CT receives approximately 357 kcal from his dialysate.
2. What are the diet recommendations for CT for CAPD based on his weight and initial labs?

   Answer: The recommended diet is 107 g protein, 3 g sodium (since he has no overt cardiac issues or problems with fluid retention), 3–4 g potassium, 1,070–1,284 mg phosphorus (using 10–12 mg/g protein). Fluid intake should be kept to 2,000–2,500 mL (urine output plus 1,000 mL) and adjusted based on UF. Based on CT's initial intake of 1,800–2,000 kcal and 70–80 g protein and allowing for the 357 kcal absorbed from dialysate, he will have to add a minimum 500–700 kcal and 27–37 g of protein to his diet. Sodium and potassium intake is acceptable but he will need to decrease his intake of dairy foods to bring the phosphorus content of the diet within guidelines.
3. Are CTs' medications at the start of CAPD appropriate? Any recommendations for changes?

   Answer: The prenatal vitamin should be changed to a renal B- and C-complex with folic acid. His corrected calcium = 9.5 and to avoid any elevation in calcium his Tums should be discontinued and another calcium-free medication prescribed for his indigestion. He is currently on a small dose of phosphorus binders (sevelamer) and with the increased protein in the diet and elevated phosphorus, an increase in binders will be needed. Sevelamer (Renvela) was increased to 1,600 mg at each meal and patient was also instructed to take 800 mg with snacks which he had not been doing.

4. At 3 months what diet and or medication changes are indicated for CT?

   Answer: At 3 months CT presents with a low potassium, low phosphorus, declining albumin and BUN secondary to poor oral intake due to dysphagia. His binders should be decreased by one-third and potassium intake liberalized along with being given an oral potassium supplement until his labs indicate normal levels and oral intake has improved. It should be suggested that he use a liquid nutritional calorie and protein supplement until after his dilation since his oral intake is limited.
5. When CT changes his treatment modality to HD, what dietary modifications are necessary based on weight and laboratory data?

   Answer: Due to edema, his dry weight should be used to calculate his protein needs at 1.2 g/kg body weight. His protein needs will now change to 99 g. Because of edema his sodium intake should be decreased to 2–2.5 g. His potassium supplement should be stopped and dietary potassium limited to 2–2.5 g/day. His phosphorus is elevated so his binders should be increased to at least 1,600 mg with each meal and 800 mg with snacks and a dietary phosphorus restriction restarted. Corrected calcium is high so his dialysate Ca bath should be lowered. Fluid restriction should be limited to 1,500 mL or less (urine output plus 1,000 mL) and interdialytic weight gains monitored. His albumin level should be monitored for changes with improved appetite and loss of edema.

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References

1. US Renal Data System: USRDS 2012 annual data report. www.usrds.org. Accessed 6 Oct 2012.
2. Gilbertson DT, Liu J, Xue JF, Louis TA, et al. Projecting the number of patients with end-stage renal disease in the United States to the year 2015. J Am Soc Nephrol. 2005;10:3736–41.
3. Pupim LB, Evanson JA, Hakim RM, Ikizler TA. The extent of uremic malnutrition at the time of initiation of maintenance dialysis is associated with the subsequent hospitalization. J Ren Nutr. 2003;13:259–66.
4. Hakim RM, Levin N. Malnutrition in hemodialysis patients. Am J Kidney Dis. 1993;21:125–37.
5. Zeir M. Risk of mortality in patients with end-state renal disease: the role of malnutrition and possible therapeutic implications. Horm Res. 2002;56:30–4.
6. Pupim LB, Caglar K, Hakim RM, Shyr Y, et al. Uremic malnutrition is a predictor of death independent of inflammatory status. Kidney Int. 2004;66:2054–60.
7. Kopple JD. Effect of nutrition on morbidity and mortality in maintenance dialysis patients. Am J Kidney Dis. 1994;24:1002–9.
8. Boxall MC, Goodship THJ. Nutritional requirements in hemodialysis. In: Mitch WE, Klahr S, editors. Handbook of nutrition and the kidney. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 218–27.
9. Dombros NV, Digenis GE, Oreopoulos DG. Nutritional markers as predictors of survival in patients on CAPD. Perit Dial Int. 1995;15:S10–9.
10. National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35:S17–103.
11. Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, et al. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15:953–60.
12. Fouqe D, Kalantar-Zadeh K, Kopple J, Cano N, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
13. Mak RH, Ikizler TA, Kovesdy CP, et al. Wasting in chronic kidney disease. J Cachexia Sarcopenia Muscle. 2011;2:9–25.
14. Kalantar-Zadeh K, Block G, McAllister J, Humphreys MH, et al. Appetite and inflammation, nutrition, anemia and clinical outcomes in hemodialysis patients. Am J Clin Nutr. 2004;80:299–307.
15. Bossola M, Muscaritoli M, Tazza L, Panocchia N, et al. Variables associated with reduced dietary intake in hemodialysis patients. J Ren Nutr. 2005;15:244–52.
16. Mehrotra R, Kopple JD. Nutritional management of maintenance dialysis patients: why aren't we doing better? Ann Rev Nutrition. 2001;21:343–79.

17. Bergstrom J. Appetite in CAPD patients. Perit Dial Int. 1995;16:8–21.
18. Kopple JD, Kalantar-Zadeh K, Mehrotra R. Risks of chronic metabolic acidosis in patients with chronic kidney disease. Kidney Int. 2005;67:S21–7.
19. Papadoyannakis NJ, Stefanidis CJ, McGeown M. The effect of the correction of metabolic acidosis on nitrogen and potassium balance of patients with chronic renal failure. Am J Clin Nutr. 1984;40:623–7.
20. Walls J. Effect of correction of acidosis on nutritional status in dialysis patients. Miner Electrolyte Metab. 1997;23:234–6.
21. Kalantar-Zadeh K, Mehrotra R, Fouque T, Kopple JD. Metabolic acidosis and malnutrition inflammation complex syndrome in chronic renal failure. Semin Dial. 2004;17:455–65.
22. Kopple JD, Kalantar-Zadeh K. Malnutrition and IDPN in patients with ESRD. In: Principles and practices of dialysis. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 473–88.
23. Kalantar-Zadeh K, Kopple JD. Nutritional management of patients undergoing maintenance hemodialysis. In: Kopple JD, Massry SG, editors. Kopple and Massry's nutritional management of renal disease. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 433–58.
24. Bossola M, Muscaritoli M, Tazza L, Giungi S, et al. Malnutrition in hemodialysis patients: what therapy? Am J Kidney Dis. 2005;46:371–86.
25. Ikizler TA. Nutrition and peritoneal dialysis. In: Handbook of nutrition and the kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 228–44.
26. Gutierrez A, Bergstrom J, Alvestrand A. Protein catabolism in sham-hemodialysis: the effect of different membranes. Clin Nephrol. 1992;38:20–9.
27. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. Kidney Int. 1994;46:830–7.
28. Fouque D, Pelletier S, Guebre-Egziabher F. Have recommended protein and phosphate intake recently changed in maintenance hemodialysis? J Ren Nutr. 2011;1:35–8.
29. Kaplan AA, Halley SE, Lapkin RA, Graeber CW. Dialysate protein losses with bleach processed polysulphone dialyzers. Kidney Int. 1995;47:573–8.
30. Ikizler TA, Pupim LA, Brouillette JR, Levenhagen DK, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. Am J Physiol Endocrinol Metab. 2002;282:E107–16.
31. Pupim LB, Flakoll PJ, Ikizler TA. Protein homeostasis in chronic hemodialysis patients. Curr Opin Clin Nutr Metab Care. 2004;7:890–5.
32. Bergstrom J. Why are dialysis patients malnourished? Am J Kidney Dis. 1995;26:229–41.
33. Jager KJ, Merkus MP, Husiman RM, Boeschoten EW, et al. Nutritional status over time in hemodialysis and peritoneal dialysis. J Am Soc Nephrol. 2001;12:1272–9.
34. Rocco MV, Dwyer JT, Larive B, Greene T, et al. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: results of the HEMO study. Kidney Int. 2004;65:2321–34.
35. McCusker FX, Teehan BP, Thorpe KE, Keshaviah PR, et al. How much peritoneal dialysis is required for the maintenance of a good nutritional state? Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Kidney Int Suppl. 1996;56:S56–61.
36. National Kidney Foundation. Clinical practice guidelines for peritoneal dialysis adequacy. Am J Kidney Dis. 2006;48:S98–129.
37. Punal J, Lema LV, Sanhez-Guisande D, Ruano-Ravina A. Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: a systematic review. Nephrol Dial Transplant 2008; 10: 1–13.
38. Ipema KJR, Health B, van der Schans CP, et al. A difference between day and night: protein intake improves after the transition from conventional to frequent nocturnal home hemodialysis. J Ren Nutr. 2012;22:365–72.
39. Kaysen GA, Greene T, Larive B, Mehta RL, et al. The effect of frequent hemodialysis on nutrition and body composition: frequent Hemodialysis Network Trial. Kidney Int. 2012;82:90–9.
40. Hutson B, Stuart N. Nutrition management of the adult hemodialysis patient. In: A clinical guide to nutrition care in kidney disease. 2nd ed. Chicago: American Dietetic Association; 2013.
41. Rocco MV, Paranandi L, Burrowes JD, Cockram DB, et al. Nutritional status in the HEMO study cohort at baseline. Am J Kidney Dis. 2002;39:245–56.
42. Burrowes JD, Larive B, Cockram DB, Dwyer J, et al. Effects of dietary intake, appetite and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross sectional results from the HEMO study. J Ren Nutr. 2003;13:191–8.
43. Laville M, Fouque D. Nutritional aspects of hemodialysis. Kidney Int. 2000;58:133–9.
44. Grodstein GP, Blumenkrantz MJ, Kopple JD, Moran JK, et al. Glucose absorption during continuous ambulatory peritoneal dialysis. Kidney Int. 1981;19:564–7.
45. Bodnar DM, Busch S, Fuchs J, Piedmonte M, et al. Estimating glucose absorption in peritoneal equilibration tests. Adv Perit Dial. 1993;9:114–8.
46. Burkart J. Metabolic consequence of peritoneal dialysis. Semin Dial. 2004;17:498–504.

47. Chhabra D, Nash K. Icodextrin: an alternative peritoneal dialysis fluid. Expert Opin Drug Metab Toxicol. 2008;4:1455–64.
48. McCann L. Nutrition management of the adult peritoneal dialysis patient. In: A clinical guide to nutrition care in kidney disease. 2nd ed. Chicago: American Dietetic Association; 2013.
49. Hamburger RJ, Iknaus MA. Icodextrin fulfills unmet clinical need of PD patients: improved ultrafiltration. Dial Transplant. 2003;32:675–84.
50. Teitelbaum I, Burkart J. Peritoneal dialysis. Am J Kidney Dis. 2003;42:1082–96.
51. McPhatter LL. Nocturnal home hemodialysis. In: A clinical guide to nutrition care in kidney disease. 2nd ed. Chicago: American Dietetic Association; 2013.
52. Cianciaruso B, Brunori G, Traverso G, Paanarello G, et al. Nutritional status in the elderly patient with uraemia. Nephrol Dial Transplant. 1995;10:65–8.
53. Chauveau P, Combe C, Laville M, Fouque D, et al. Factors influencing survival in hemodialysis patients aged older than 75 years: 2.5 year outcome study. Am J Kidney Dis. 2001;37:997–1003.
54. Wolfson M. Nutrition in elderly dialysis patients. Semin Dial. 2002;15:113–5.
55. Burrowes JD, Dalton S, Backstrand J, Levin NW. Patients receiving maintenance hemodialysis with low vs high levels of nutritional risk have decreased morbidity. J Am Diet Assoc. 2005;105:563–71.
56. Heimburger O, Stenvinkel P, Lindholm B. Nutritional effects and nutritional management of chronic peritoneal dialysis. In: Kopple JD, Massry SG, editors. Kopple and Massry's nutritional management of renal disease. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 477–510.
57. Lindholm B, Bergstrom J. Protein and amino acid metabolism in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Clin Nephrol. 1988;30:S59–63.
58. Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW. Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. Kidney Int. 1982;21:849–61.
59. Kopple JD, Blumenkrantz MJ. Nutritional requirements for patients undergoing continuous ambulatory peritoneal dialysis. Kidney Int. 1983;16:S295–302.
60. Galland R, Traeger J. Short daily hemodialysis and nutritional status in patients with chronic renal failure. Semin Dial. 2004;2:104–8.
61. Ayus JC, Achinger SG, Mizani MR, Chertow GM, et al. Phosphorus balance and mineral metabolism with 3 h daily dialysis. Kidney Int. 2007;71:336–42.
62. Hagen JM, Boyle CA, Hamburger VE, Sandroni CC, et al. Treatment of malnutrition with 1.1% amino acid peritoneal dialysis solution: results of a multicenter outpatient study. Am J Kidney Dis. 1998;32:761–9.
63. Lindholm B, Bergstrom J. Nutritional aspects on peritoneal dialysis. Kidney Int. 1992;42:S165–71.
64. Tjiong HL, van den Berg JW, Wattimena JL, Rietveld T, et al. Dialysate as food: combined amino acid and glucose dialysate improves protein anabolism in renal failure patients on automated peritoneal dialysis. J Am Soc Nephrol. 2005;16:1486–93.
65. Ahmad S. Dietary sodium restriction for hypertension in dialysis patients. Semin Dial. 2004;17:284–7.
66. Wilson J, Shah T, Nissenson AR. Role of sodium and volume in the pathogenesis of hypertension in hemodialysis. Semin Dial. 2004;17:260–4.
67. Goldstein-Fuchs J. Nutrition intervention for chronic renal diseases. In: Mitch WE, Klahr S, editors. Handbook of nutrition and the kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 267–301.
68. McCann L. Pocket guide to nutrition assessment of the patient with chronic kidney disease. 4th ed. New York: National Kidney Foundation; 2009.
69. Testa A, Plou A. Clinical determinants of interdialytic weight gain. J Ren Nutr. 2001;11:155–60.
70. Moncrief JW. Continuous ambulatory peritoneal dialysis. Contrib Nephrol. 1979;17:139–45.
71. Nolph KD, Sorkin MI, Moore H. Autoregulation of sodium and potassium removal during continuous ambulatory peritoneal dialysis. Trans Am Soc Artif Intern Organs. 1980;26:334–8.
72. Lameire N, Van Biesen W. Hypervolemia in peritoneal dialysis patients. J Nephrol. 2004;17:58–66.
73. Wang X, Axelesson J, Lindholm B, Wang T. Volume status and blood pressure in continuous ambulatory peritoneal dialysis patients. Blood Purif. 2005;23:373–8.
74. Krediet RT, van Westrhenen R, Zweers MM, Struijk DG. Clinical advantages of new peritoneal dialysis solutions. Nephrol Dial Transplant. 2002;17:16–8.
75. Davies SJ, Phillips L, Naish PF, Russel GI. Peritoneal glucose exposure and changes in membrane transport with time on peritoneal dialysis. J Am Soc Nephrol. 2001;12:1046–51.
76. Beto J, Bansai VK. Hyperkalemia: evaluating dietary and non-dietary etiology. J Ren Nutr. 1992;2:28–9.
77. Musso CG. Potassium metabolism in patients with chronic kidney disease. Part II: patients on dialysis (stage 5). Int Urol Nephrol. 2004;36:469–72.
78. Constantino J, Roberts C. Life-threatening hyperkalemia from chewing tobacco in a hemodialysis patient. J Ren Nutr. 1997;7:106–8.
79. Ifudu O, Reydel K, Vlacich V, Delosreyes G, et al. Dietary potassium is not the sole determinant of serum potassium concentration in hemodialysis patients. Dial Transplant. 2004;33:684–8.

80. Rostand SG. Profound hypokalemia in continuous ambulatory peritoneal dialysis. Arch Intern Med. 1983;143:377–8.
81. Pierratos A, Ouwendyk M, Francoeur R, Vas S, et al. Nocturnal hemodialysis: three year experience. J Am Soc Nephrol 1998;9:859–868.
82. Argoudelis A, McCarty C, Re R, et al. Phosphorus and potassium removal with short daily hemodialysis. In: Poster presentation. Annual dialysis conference 2009.
83. Kohn OF, Coe FL, Ing TS. Solute kinetics with short-daily home hemodialysis using slow dialysate rate flow. Hemodial Int. 2010;14:39–46.
84. Goodman WG. Calcium, phosphorus and vitamin D. In: Handbook of nutrition & the kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 47–69.
85. Qunibi WY. Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). Kidney Int. 2004;66:S8–12.
86. Coladonato JA. Control of hyperphosphatemia among patients with ESRD. J Am Soc Nephrol. 2005;16:S107–14.
87. Rodrigues-Benot A, Martin-Malo A, Alvarez-Lara A, Rodriguez M, et al. Mild hyperphosphatemia and mortality in hemodialysis patients. Am J Kidney Dis. 2005;46:68–77.
88. Block GA, Klassen PS, Lazarus M, Ofsthun N, et al. Mineral metabolism, mortality and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208–18.
89. McCann L. Total calcium load in dialysis patients: an issue of concern for dietitians. Dial Transplant. 2004;33:282–9.
90. National Kidney Foundation. Clinical practice guidelines: bone metabolism and disease in chronic renal failure. Am J Kidney Dis. 2003;42:S12–143.
91. Murphy-Gutekunst L. Hidden phosphorus in popular beverages: Part I. J Ren Nutr. 2005;15:e1–6.
92. Lockridge RS, Spencer M, Craft V, Pipkin M, et al. Nightly home hemodialysis: five and one-half years of experience in Lynchburg, Virginia. Hemodial Int. 2004;8:61–9.
93. Schulman G. Nutrition in daily dialysis. Am J Kidney Dis. 2003;41:S112–5.
94. Goldstein-Fuchs J. Dyslipidemias in chronic kidney disease. In: A clinical guide to nutrition care in kidney disease. 2nd ed. Chicago: American Dietetic Association; 2013.
95. National Kidney Foundation. KDOQI clinical practice guidelines for managing dyslipidemia in chronic kidney disease patients. Am J Kidney Dis. 2003;41:S1–91.
96. Saltissi D, Morgan C, Knight B, Chang W, et al. Effect of lipid-lowering dietary recommendations on the nutritional intake and lipid profiles of chronic peritoneal dialysis patients and hemodialysis patients. Am J Kidney Dis. 2001;37:1209–15.
97. Fried L, Hutchison A, Stegmayr B, Prichard S, et al. Recommendations for the treatment of disorders in patients on peritoneal dialysis. Perit Dial Int. 1999;19:7–21.
98. Masud T. Trace elements and vitamins in renal disease. In: Handbook of nutrition & the kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 196–217.
99. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults. JAMA. 2002;287:3127–9.
100. Coveney N, Polkinghorne KR, Linehan L, et al. Water-soluble vitamin levels in extended hours hemodialysis. Hemodial Int. 2010;15:30–8.
101. Kannampuzha J, Donnelly SM, McFarlane PA, et al. Glutathione and riboflavin status in supplemented patients undergoing home nocturnal hemodialysis versus standard hemodialysis. J Ren Nutr. 2010;20:199–208.
102. Makoff R, Gonick H. Renal failure and the concomitant derangement of micronutrient metabolism. Nutr Clin Pract. 1999;14:238–46.
103. Kasama R, Koch T, Canals-Navas C, Pitone JM. Vitamin b6 and hemodialysis: the impact of high-flux/high efficiency dialysis and review of the literature. Am J Kidney Dis. 1996;27:680–6.
104. Rocco MV, Makoff R. Appropriate vitamin therapy for dialysis patients. Semin Dial. 1997;10:272–7.
105. Hung SC, Hung SH, Tarng DC, Yang WC, et al. Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis. 2001;38:941–7.
106. Handleman GJ, Levin NW. Guidelines for vitamin supplements in chronic kidney disease patients: what is the evidence? J Ren Nutr. 2011;21:117–9.
107. Jung U, Helbich-Endermann M, Bitsch R, Schenider BR, et al. Are patients with chronic renal failure (CRF) deficient in biotin and is regular biotin supplementation required? Z Ernahrungswiss. 1998;37:363–7.
108. Jones WO, Nidus BD. Biotin and hiccups in chronic dialysis patients. J Ren Nutr. 1991;1:80–3.
109. Wiggins KL. Renal care: resources and practical applications. Chicago: American Dietetic Association; 2004. p. 39–60.
110. Shemin D, Bostom AG, Selhub J. Treatment of hyperhomocysteinemia in end-stage renal disease. Am J Kidney Dis. 2001;38:S91–4.
111. Obeid R, Kuhlmann MK, Kohler H, Herrmann W. Response of homocysteine cystathionine, and methylmalonic acid to vitamin treatment in dialysis patients. Clin Chem. 2005;51:196–201.

112. Clement L. Homocysteine: the newest uremic toxin? Renal Nutr Forum. 2003;23:1–4.
113. Schaefer RM, Tschner M, Kosch M. Folate metabolism in renal failure. Nephrol Dial Transplant. 2002;17:24–7.
114. Handelman GJ. New insight on vitamin C in patients with chronic kidney disease. J Ren Nutr. 2011;21:110–2.
115. Khajehdehi P, Mojerlou M, Behzadi S, Rais-Jalali GA. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. Nephrol Dial Transplant. 2001;16:1448–51.
116. Muth I. Implications of hypervitaminosis A in chronic renal failure. J Ren Nutr. 1991;1:2–8.
117. Holden RM, Ki V, Morton AR, Clase C. Fat-soluble vitamins in advanced CKD/ESRD: a review. Semin Dial. 2012;25:334–43.
118. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, et al. Meta-analysis: high dose vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37–46.
119. Kohlmeier M, Saupe J, Shearer MJ, et al. Bone health of adult hemodialysis patients is related to vitamin K status. Kidney Int. 1997;51:1218–21.
120. Rucker D, Thadhani R, Tonelli M. Trace elements status in hemodialysis patients. Semin Dial. 2010;23:389–95.
121. Erten Y, Kayata M, Sezer S, Ozdemir FN. Zinc deficiency: prevalence and causes in hemodialysis patients and effect on cellular immune response. Transplant Proc. 1998;30:850–1.
122. Matson A, Wright M, Oliver A, Woodrow G, et al. Zinc supplementation at conventional doses does not improve the disturbance of taste perception in hemodialysis patients. J Ren Nutr. 2003;13:224–8.
123. van der Eijk I, Allman Farinelli MA. Taste testing in renal patients. J Ren Nutr. 1997;7:3–9.
124. Smith AM, Temple K. Selenium metabolism and renal disease. J Ren Nutr. 1997;7:69–72.
125. Ng AHM, Hercz G, Kandel R, Grynpas MD. Association between fluoride, magnesium, aluminum and bone quality in renal osteodystrophy. Bone. 2003;34:216–24.
126. Skikine BS, Ahluwalia B, Fergusson B, Chonko A, et al. Effects of erythropoietin therapy on iron absorption in chronic renal failure. J Lab Clin Med. 2000;135:452–8.
127. Cook JD, Dassenko SA, Whittaker P. Calcium supplementation: effect on iron absorption. Am J Clin Nutr. 1991;53:106–11.
128. Hallberg I, Hulten L, Gramatkovski E. Iron absorption from the whole diet in men: how effective is the regulation of iron absorption? Am J Clin Nutr. 1997;66:347–56.

Chapter 12
Transplantation

Maureen P. McCarthy

Key Points

- Apply the nutrition care process (NCP) in the management of individuals before and after kidney transplantation. This includes:
  1. Nutrition input during the process of pre-kidney transplant evaluation.
  2. Nutrition management of patients in the acute post-kidney transplant period (first 8 weeks) to support postsurgical needs and to intervene as needed when immunosuppression is adjusted.
  3. Nutrition care for the long-term post-kidney transplant individual, including management of side effects related to medications used for immunosuppression.
- Review in detail the nutrition-related side effects of immunosuppression post-kidney transplant.

Keywords Kidney transplantation • Nutrition • Diabetes • Cardiovascular disease Immunosuppressants • Medical nutrition therapy

Introduction

Kidney transplantation has become a viable option for patients with chronic kidney disease (CKD). After several years of declining numbers of transplanted kidneys, there was a slight increase in 2010, with 10,977 deceased donor transplants and 5987 living donor transplants. At the end of 2010, there were 75,807 individuals on the United Network for Organ Sharing (UNOS) waiting list [1]. Insufficient organ donation accounts for the discrepancy between the number of recipients and candidates. Advances in surgical technique and immunosuppressive agents have led to significant improvements in morbidity and mortality.

Adequate nutrition is essential for the well-being of kidney transplant patients. To minimize nutrition depletion and optimize nutritional status, a complete and thorough nutrition evaluation by an Registered dietitian (RD) (registered dietitian) should be performed following the steps of the NCP: assessment, diagnosis, intervention, and monitoring, and evaluation [2]. The evaluation should

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integrate the patient's complex medical condition related to CKD and the impact of ongoing therapeutic interventions on the patient's nutritional status. Providing adequate nutrition and reducing the long-term side effects are essential for graft survival in kidney transplant recipients.

There are three treatment phases to consider when providing care to kidney transplant recipients [3]. In the pre-transplant phase, the goal is to identify and treat nutrition problems before transplant, thus optimizing. Clinicians should recognize that some nutrition issues may only be improved after transplant. Nevertheless, the pre-transplant nutrition evaluation provides the opportunity to prescribe nutrition interventions and to complete nutrition education that will assist the patient in establishing pre-transplant and post-transplant nutrition goals [3, 4].

In the acute post-transplant phase (up to 8 weeks after transplantation), the goal is to support the increased metabolic demands of the postoperative period, including high-dose immunosuppressive therapy. During the chronic post-transplant phase, the goal is to manage long-term complications related to immunosuppressive therapy, especially in individuals genetically predisposed to diabetes and cardiovascular disease [3, 4].

At any phase of the transplant continuum, the RD's evaluation should cover the five domains of nutrition assessment described in the NCP [2]. These are:

1. Food/nutrition-related history (food intake; use of medications, herbs, other supplements; physical activity; and nutrition quality of life)
2. Anthropometric measurements (height, weight, weight history, and other measurements)
3. Biochemical data, medical tests, and procedures (laboratory data including urine tests and urine volume, pertinent studies of gastrointestinal function, kidney biopsy, and others)
4. Nutrition-focused physical findings, such as edema and muscle and/or fat wasting
5. Client history (personal data, family history, previous treatment, social history)

Within this framework provided by the NCP, the RD can assess the nutritional needs and develop a nutrition diagnosis and a full care plan for each patient (refer to Chaps. 3–6).

The Pre-transplant Phase

A complete evaluation of the patient by the RD is imperative to identify one or more nutrition diagnoses, plan a nutrition prescription and interventions, and to establish parameters for monitoring and evaluation [2]. This will serve to optimize nutritional status, identify deficits, and, when possible, to correct these deficits before kidney transplant surgery. It is important to remember that the candidates for kidney transplantation have been subjected to the effects of a chronic disease and that not all deficiencies identified can be corrected without organ replacement.

The pre-transplant evaluation also provides an opportunity to create early awareness of issues that are significant in the post-transplant period. These topics include nutrition-related side effects of immunosuppression. Post-transplant adjustments in bone metabolism require close monitoring of phosphorus in the early weeks after transplant and assessment of bone mineral density in the immediate and long-term period after kidney transplantation has implications for nutrition management [5]. In addition, nutrition intervention is important in managing alterations in the lipid profile post-kidney transplant [6].

The effect of obesity at the time of transplant on kidney transplant outcomes continues to be controversial, but there is increasing evidence that obesity is an independent risk factor for CKD and its progression ([7]; also refer to Chap. 10). Increased incidence of obesity in the general population, and in the end-stage renal disease (ESRD) population in particular, means that more obese dialysis patients are presenting for evaluation for kidney transplantation.

The issue is complicated by research which demonstrates a concept that has come to be called "reverse epidemiology." This term describes the observed decrease in morbidity and mortality in maintenance hemodialysis patients at higher body mass index (BMI) [8]. While the concept itself has shown some limitations, it has spurred productive debates about the role of obesity in CKD outcomes.

The pathology of obesity in kidney disease includes anatomical and hemodynamic alterations. Even after adjustments for diabetes and hypertension, there is a relationship between obesity and increased incidence of CKD [9]. In the post-transplant patient, obesity has been linked to increased risk for delayed graft function (DGF) and reduced allograft and patient survival [10]. A BMI >35 kg/m^2 is significant for greater post-transplant complications, especially new-onset diabetes after transplant (NODAT), wound complications, and post-transplant weight gain [10–12].

After kidney transplantation, weight typically increases due to improved appetite, reversal of the uremic state, and immunosuppressant side effects. While there are no evidence-based criteria to identify those at risk for weight gain post-transplant, there are characteristics that are known to increase the risk of NODAT, as described later in this chapter. The pre-transplant nutrition evaluation as part of a kidney transplant evaluation provides an excellent opportunity to educate individuals regarding the risk of NODAT and strategies to reduce modifiable characteristics that are linked with higher risk.

Due to the limited availability of organs, the selection of transplant candidates who are likely to have a positive outcome remains an important issue. Most transplant centers have established BMI criteria for deceased donor transplant and living donor transplant recipients prior to transplantation. These criteria are based on scientific literature which indicates that the transplant candidate should have a BMI greater than 22 but less than 35 [11, 12]. Each transplant center will apply their unique experience to establish a BMI cutoff point somewhere in that broad range.

Unintended weight loss in individuals who are waiting for kidney transplant has been shown to be linked to higher mortality [13]. At the same time, the clinical value of planned weight loss in patients who are awaiting kidney transplant has not been clearly determined [14]. As mentioned earlier, it is not unusual for transplant centers to ask candidates to lose weight in compliance with the center's cutoff points for BMI. Future clinical trials should evaluate if weight modification can favorably impact outcomes in underweight and obese kidney transplant patients and if pharmacologic agents or surgical treatment for obesity are potential options.

The Acute Post-transplant Period

Nutritional Requirements

The nutrition recommendations for adult kidney transplant recipients are shown in Table 12.1. Nutrient requirements are generally greater during the acute post-transplant phase due to increased metabolic demands from surgery and high-dose immunosuppressive therapy.

Protein

Increased nitrogen losses in the immediate postoperative period may be due to surgical stress, administration of large doses of corticosteroids, muscle catabolism, and preexisting malnutrition [15]. During the immediate post-transplant period, daily protein recommendations for patients with

Table 12.1 Nutrient recommendations for adult kidney transplantation during acute and chronic post-transplant phases

Nutrient	Acute phase	Chronic post-transplant phase	Comments
Protein	1.3–2.0 g/kg dry body weight or adjusted body weight [3]	*Without DM*: 0.6–0.8 g/kg body weight	Protein catabolic rate is increased due to surgical stress and high-dose corticosteroids
		With DM: 0.8–0.9 g/kg body weight [32]	Adequate amounts of protein are required for wound healing and to prevent infection
			Additional losses are possible due to surgical drains, wounds, and indication for dialysis
Calories	130–150 % of calculated basal energy expenditure (BEE) [3]	23–35 kcal/kg body weight [32]	The upper range of calories is recommended for underweight patients; the lower range is recommended for overweight patients
	30–35 kcal/kg dry body weight or adjusted body weight [3]	Achieve and maintain a healthy body weight	Caloric needs may further increase in the presence of fever, infections, surgical stress, and high-dose corticosteroid therapy
Carbohydrate	50–70 % of nonprotein calories [3]	45–50 % total calories	Serum glucose levels may be increased because of medications (corticosteroids, cyclosporine, tacrolimus), metabolic stress, or infection
		Emphasize complex carbohydrates [3]	Treat hyperglycemia with insulin dosed on a sliding scale; add other hyperglycemic agents as needed
			Initiate CHO-controlled diet
Fat	30–50 % of nonprotein calories	<30 % total calories	Dyslipidemia is of considerable concern but is not aggressively treated until the chronic post-transplant period
	10 % saturated fat [16]	7–10 % saturated fat [3]	
Sodium	2–4 g/day	2.4 g/day [32]	Sodium should only be restricted in the acute postoperative period in the presence of poor allograft function or post-transplant HTN
	Unrestricted if HTN/edema absent [3]	Or 1.5 g/day [59]	
Fluid	Individualize	Individualize [3]	Fluids should only be restricted in the acute postoperative period in the presence of poor allograft function or post-transplant HTN
	May need to be limited if patient requires dialysis or if edema is present [3]		
Potassium	2–4 g/day [3]	Individualize [3]	Serum levels may increase with administration of tacrolimus, cyclosporine, or potassium-sparing diuretics; renal insufficiency; or metabolic acidosis
			Serum levels may decrease with administration of potassium-wasting diuretics or amphotericin
Phosphorus	Individualize [3]	Individualize [3]	Serum levels may increase with renal insufficiency
			Serum levels may decrease with administration of corticosteroids
Magnesium	Individualize [3]	Individualize [3]	Serum levels may increase with renal insufficiency
			Serum levels may decrease with administration of cyclosporine, tacrolimus, diuretics, diarrhea

functioning grafts or those requiring temporary dialytic support are estimated at 1.3–2.0 g/kg of dry body weight or adjusted weight [3].

Energy

Energy requirements during the post-transplant recovery phase are higher than long-term needs. They may be increased due to fever, infection, surgical stress, or high-dose corticosteroid therapy. Caloric requirements can be estimated as between 30 and 35 kcal/kg dry body weight or weight adjusted for obesity [3]. This recommendation seems adequate for maintaining or achieving neutral nitrogen balance. Estimated energy needs can also be calculated using the Harris–Benedict equation to determine basal energy requirements, multiplied by a stress factor of 1.3–1.5 [3].

Carbohydrate

Glucose intolerance, which may present before and after transplantation, will be discussed in detail later in this chapter as a long-term post-transplant nutrition concern. Evidence-based guidelines have offered recommendations for energy and protein intake, but not specifically for carbohydrate intake. It has been recommended that complex carbohydrates may provide 50–70 % of the nonprotein energy intake in the immediate post-transplant period, with special attention to further modification for glucose tolerance [16].

Fat

During the acute postoperative period, diet modification for fat is not warranted. The amount of fat is only limited by the appropriate energy level and often provides up to 30 % of the total energy, with intake of saturated fat limited to 10 % of energy [17]. Dyslipidemia is usually addressed during the chronic post-transplant period and will be discussed with other topics of that time period later in this chapter. Nutrition education in the acute period should introduce the importance of a “heart-healthy” lifestyle.

Sodium

Sodium intake should be limited in the acute postoperative phase in the presence of poor allograft function or post-transplant hypertension. Some immunosuppressive medications can cause the development of hypertension and fluid retention, which may necessitate a sodium restriction of 2–4 g/day [16].

Potassium

After a successful kidney transplant, serum potassium will normalize, eliminating the need for dietary potassium restriction [16]. However, in cases of DGF it may be necessary to limit dietary potassium [3, 16]. Serum potassium should be closely monitored, with dietary potassium starting at 2 g/day and titrating

upward as renal clearance improves. In addition to initial poor graft function, medications such as potassium-sparing diuretics and calcineurin inhibitors (CNIs) (for example, tacrolimus) may contribute to hyperkalemia in the acute postoperative patient [16]. Hypokalemia may also occur in kidney transplant recipients due to potassium-wasting diuretics.

Vitamins, Minerals, and Trace Elements

Vitamin and mineral supplementation in the acute post-transplant phase should be individualized, depending on preexisting medical conditions and dietary intake. Information about the effect of kidney transplantation on trace elements is scarce, as evidenced by a recent review of vitamin requirements for patients with CKD in which the authors describe the lack of literature in this area ([18]; also refer to Chap. 24). In general, medical nutrition therapy (MNT) in short- and long-term post-transplant individuals should include recommendations for vitamins and minerals that comply with Dietary Reference Intake (DRI) guidelines [19].

Hypomagnesemia is seen in the early post-transplant period due to altered magnesium losses in patients on CNIs such as cyclosporine (CsA) and tacrolimus; and serum levels should be monitored regularly with oral magnesium supplementation as indicated [3].

Herbals

Use of herbal products and botanicals in the United States is believed to have increased by 25 % in the 1990s, reaching as much as 10 % of the population [20]. Some herbal preparations like ginseng are promoted to enhance the immune system, which theoretically may increase the risk of organ rejection. Others, like St. John's wort, can cause drug–drug interactions, requiring higher doses of immunosuppression to maintain trough levels [21]. Due to evidence of nephrotoxicity and due to well-recognized poor control of quality and quantity of ingredients in herbal products in the United States, they are contraindicated in the transplant population ([20]; also refer to Chap. 23).

Common Problems Post-transplant in the Acute Care Setting

Inadequate Intake

Successful kidney transplantation corrects the anorexia and uremia which are typically observed in the patient with CKD. Kidney transplant recipients normally consume an oral diet. There are a few patients whose postsurgical experience may be complicated by slow return of the appetite or by altered gastrointestinal function, such as a post-operative ileus or diabetic gastroparesis. In these cases, nutrition intervention to facilitate surgical recovery is the priority and may include nutritional supplementation and/or nutrition support such as enteral nutrition (tube feeding) or parenteral nutrition [16].

If a patient is unable to meet his/her metabolic demands orally and has a functional gastrointestinal (GI) tract, standard high-nitrogen tube feedings should be initiated. Nutrient-dense enteral formulas may be indicated in the event of poor allograft function with volume overload. If parenteral nutrition (PN) is required, the formula should be tailored to consider allograft function, urine output, electrolytes, and type of renal replacement therapy (RRT) (refer to Chap. 14).

Hyperglycemia

Glucose intolerance is common before and after transplantation. NODAT is often referred to as post-transplant diabetes mellitus (PTDM), but the term NODAT is preferred in keeping with the consensus guidelines of 2003 [23]. The prevalence of diabetes mellitus (DM) is greater among patients with solid organ transplants than in the general population. Insulin resistance is a side effect of corticosteroids and CNIs which are used for immunosuppression [22].

Prior personal history of glucose intolerance, as well as a family history of DM, predisposes a patient to NODAT. Other risk factors include black or Hispanic ethnicity, obesity, age, history of metabolic syndrome, and hepatitis C virus infection [23]. Hyperglycemia may improve as high post-operative corticosteroid doses are tapered to maintenance levels. However NODAT treatment may require exogenous insulin or oral hypoglycemic agents, as well as a carbohydrate-controlled diet, especially in early post-transplant weeks [22].

Gastrointestinal Issues

There is an increased incidence of GI complications in kidney transplant recipients due to infections, mucosal injury, and ulceration, which can manifest anywhere in the GI tract from the mouth to the anus. Oral lesions may be caused by viral and fungal infections or can be a side effect from CsA or sirolimus. The most common esophageal disorder is fungal esophagitis, which is caused by Candida [24]. Transplant programs typically prescribe prophylactic antifungal agents to prevent fungal infections.

Other gastroduodenal disorders are caused by cytomegalovirus (CMV) and herpes simplex infection. Prophylactic antibiotic treatment is recommended when there is a risk of post-transplant CMV infection; herpes simplex infection in the GI tract must be treated with appropriate antibiotic therapy [25, 26]. Bacterial infections of the GI tract are also seen in the transplant recipient and include *Clostridium difficile* colitis. Symptoms include diarrhea and abdominal tenderness and usually respond to appropriate medical treatment [27]. Diarrhea is a frequent disorder, which may be caused by pathogen microorganisms or by immunosuppressive agents. When medications are a causal factor, the dose or frequency may be reduced [28].

The incidence of upper GI ulcers after kidney transplant is particularly low; more ulcers are seen in the gastric and duodenal regions. Contributing factors include the stress of surgery, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunosuppression [28]. One study documented a 70 % incidence of *Helicobacter pylori* and a 65 % incidence of gastritis [29]. The prophylactic use of histamine-2 receptor histamine blockers is common in kidney transplant centers.

Mineral and Bone Disorders

Abnormalities of serum phosphorus levels occur even with stable, functioning allografts. Hypophosphatemia and hypercalcemia can occur when the glomerular filtration rate (GFR) normalizes in transplant recipients with preexisting hyperparathyroidism [25, 26, 30]. In the early weeks after a kidney transplant, serum calcium and phosphorus should be regularly monitored [25, 26].

Other causes of hypophosphatemia include the continued use of phosphate binders or calcium supplements with meals or an inadequate phosphorus intake [3]. If phosphorus levels remain

suboptimal after correcting for obvious causes, intravenous or oral supplementation may be indicated in the acute care setting. Some phosphorus supplements such as Neutra-Phos-K contain appreciable amounts of potassium and require close monitoring of serum potassium levels [3]. With a functioning kidney transplant, oral supplementation of phosphorus may be required to normalize serum levels until dietary intake improves and a new post-transplant equilibrium is achieved.

Hyperkalemia

Hyperkalemia can develop when there is poor graft function. It may also occur secondary to CNI therapy, other medication side effects, or cell lysis related to the catabolic effect of both surgery and corticosteroid therapy. Nutrition interventions should include the control of potassium intake and the provision of adequate calories and protein to minimize catabolism [31]. It is noteworthy that an increased dietary phosphorus intake, which may be prescribed to treat acute post-transplant hypophosphatemia, can also contribute to hyperkalemia since many dietary sources for phosphorus are also high in potassium.

The Chronic Post-transplant Phase

The nutrition goals of the chronic post-transplant phase are to provide adequate nutrition, prevent infection, and manage long-term nutritional complications. During the chronic post-transplant phase, overnutrition may lead to transplant complications, including obesity, dyslipidemias, NODAT, and hypertension [3]. Providing adequate nutrition, supporting acceptable glucose control, and reducing long-term side effects are essential for allograft survival among kidney transplant recipients [16].

Nutritional Requirements

Kidney transplant recipients without complicating factors can enjoy a nutrition regimen defined by the same guidelines suggested for the healthy population, addressing specific issues as needed [3]. In general, the diet should provide a moderate sodium intake, based on the patient's blood pressure and presence of edema. Sodium intake can range from 2 to 4 g. The Evidence-Based Nutrition Practice Guidelines (EBNPG) from the Evidence Analysis Library of the Academy of Nutrition and Dietetics recommend a sodium intake of 2.4 g sodium per day post-kidney transplant. This should be adjusted with consideration of other aspects of the patient's history, including blood pressure, hydration, acid–base balance, and glycemic control [32].

Recommendations for fat intake suggest that it should provide less than 30 % of total calories [3]. A later section in this chapter on long-term challenges will include more detailed recommendations for treating post-transplant dyslipidemias.

A protein intake between 0.8 and 1.0 g/kg of dry body weight or adjusted body weight (ABW)/day is recommended [32]. The EBNPGs also suggest an energy intake of 23–35 kcal/kg/day. Within this broad range, the dietitian will consider the individual's weight status and goals, age and gender, the reported level of physical activity, and the effect of metabolic stressors [32].

Calcium and Phosphorus

The continuing effects of preexisting secondary hyperparathyroidism after kidney transplantation have been described in the literature [33]. This sets the stage for hypercalcemia when the functioning transplanted kidney provides normal reabsorption of calcium [25, 26]. At the same time, corticosteroids decrease the intestinal absorption of elemental calcium by approximately 42 % while they also increase calcium excretion in the urine [34]. Some transplant centers individualize calcium and vitamin D supplementation to maintain bone mineral metabolism.

Vitamins and Other Minerals

Typically, vitamin supplementation is not required after kidney transplantation if the recipient regularly consumes a balanced and adequate diet. However, some transplant programs recommend a general multivitamin with supplemental minerals.

Pharmacology Update

Advances in immunosuppressive therapies have greatly improved the success of kidney transplantation. Immunosuppression is used to prevent rejection and maintain long-term graft survival. The typical immunosuppressive regimen consists of a CNI, such as CsA or tacrolimus; an antiproliferative agent (azathioprine or mycophenolate mofetil—MMF); and a corticosteroid (prednisone). In multidrug therapy, each drug mediates the immunocompetence cascade at a different point. The mechanism of immunosuppression is to inhibit the adaptive immune response while allowing nonspecific immune functions to remain intact [25, 26]. Immunosuppressive agents also have non-immunologic side effects, many of which must be considered in nutrition care. Multidrug regimens allow lower doses of individual agents to minimize side effects. Immunosuppressive therapy is continually evolving, with standard regimens monitored by the kidney transplant team at regularly scheduled intervals. Of course, novel regimens are investigated in ongoing research. Table 12.2 summarizes immunosuppressant medications most commonly seen in transplant centers in the United States at this time. Major agents are also discussed below.

Cyclosporine A or CsA (Sandimmune/Neoral)

CsA (Neoral, Novartis Pharmaceuticals, East Hanover, NJ; Sandimmune, Novartis Pharmaceuticals; Gengraf, Abbott, Abbott Park, IL) is described as a first-generation CNI. Introduced in the early 1980s, it led to significant reductions in chronic rejection and became the gold standard for maintenance immunosuppression [35]. CsA selectively inhibits adaptive immune responses but has several side effects, which may include gingival hyperplasia, GI disturbances, hyperglycemia, hyperkalemia, hypophosphatemia, hypomagnesemia, hepatotoxicity, and nephrotoxicity. This drug is absorbed in the upper small intestine and can be affected by food, drug–drug interactions, bile flow, and the lipoprotein and hematocrit status [36]. In order to assure efficacy and to minimize the nephrotoxic side

Table 12.2 Nutritional side effects of immunosuppressive medications

Medication/category	Complication	Suggested interventions
ATGAM, thymoglobulin[a]/ antilymphocyte globulin	Fever and chills	Provide nutrient-dense foods
	Increased risk of infection, profound leucopenia, thrombocytopenia	Ensure patient is receiving adequate protein
Azathioprine (Imuran)[b]/ antiproliferative	Nausea/vomiting	Try antiemetic medications if vomiting does not subside
	Diarrhea	Review medications and substitute for potential medications that may be causing diarrhea, make sure patient is receiving adequate fluid to replace losses
	Mucositis	Provide foods that will not irritate the throat
	Macrocytic anemia	Make sure patient is receiving adequate folate intake
	Pancreatitis	Initiate parenteral nutrition if pancreatitis is severe
Basiliximab (Simulect)[c]/monoclonal antibody	None reported	
Prednisone[d], prednisolone[d], methylprednisolone[d]/ corticosteroids	Hyperglycemia	Monitor blood sugar and need for hypoglycemia agents and CHO-controlled diet
	Sodium retention	Limit high-sodium foods
	Ulcers	Ensure adequate intake of calcium, vitamin D, vitamin A, C, and zinc
	Osteoporosis	
	Hyperphagia	
	Impaired wound healing and increased risk of infection	Behavior modification to prevent overeating
	Hypertension	
	Pancreatitis (rare)	
Cyclosporine (Neoral, Sandimmune[c]; Gengraf[e])/ calcineurin inhibitors (CNIs)	Hyperkalemia	Restrict high-potassium foods
	Hypomagnesemia	Limit high-sodium foods
	Hypertension	Monitor blood sugar and need for hypoglycemic agents and CHO-controlled diet
	Hyperglycemia	Limit fat to <30 % of total calories during the long-term phase
	Dyslipidemia	
	Gingival hyperplasia	
	GI disturbances	
	Hypophosphatemia	
	Hepatotoxicity	
	Nephrotoxicity	
Muromonab-CD3 (Orthoclone OKT3)[g]/monoclonal antibody	Nausea, vomiting	Try antiemetic medications
	Diarrhea	Review medications and substitute for those that may cause diarrhea; make sure the patient receives adequate fluid to replace losses
	Anorexia	Offer frequent meals of nutrient-dense foods
	Fever, chills, myalgias	

(continued)

Table 12.2 (continued)

Medication/category	Complication	Suggested interventions
Mycophenolate mofetil (CellCept)[f]/ antiproliferative	Diarrhea Nausea Vomiting	Review medications and substitute for those that may cause diarrhea; make sure the patient receives adequate fluid to replace losses
Sirolimus (Rapamycin)[h]/macrolide antibiotic	Hyperlipidemia	Limit fat intake <30 % of calories as fat during long-term phase, maintain a healthy weight
	GI disorders (constipation, diarrhea, nausea, vomiting, dyspepsia)	Monitor for adequate nutrient intake
	Hypokalemia	
	Increased liver function tests	
	Delayed wound healing	
Tacrolimus (Prograf)[i]/calcineurin inhibitor (*CNI*)	Nausea, vomiting	Try antiemetic medications
	Hyperkalemia	Limit high-potassium foods
	Hyperglycemia	Monitor blood sugar and need for hypoglycemia agents and CHO-controlled diet
	Abdominal distress Diarrhea Constipation	Monitor oral intake; consider alternate methods of nutrition support if intake suboptimal
	Hypophosphatemia	
	Hypomagnesemia	

[a]Genzyme, Cambridge, MA; Pfizer, Inc., New York, NY
[b]Faro Pharmaceuticals, San Diego, CA
[c]Novartis Pharmaceuticals, St. Louis, MO
[d]Multiple providers of generic equivalents
[e]Abbott, Abbott Park, IL
[f]Roche, Nutley, NJ
[g]Ortho Biotech, Bridgewater, NJ
[h]Wyeth Pharmaceuticals, Philadelphia, PA
[i]Astellas Pharma US, Deerfield, IL

effects, CsA levels and kidney function are closely monitored [38]. Neoral is a microemulsion preparation of CsA and has better absorption because it is not dependent on bile. There are usually fewer side effects with Neoral.

Tacrolimus (Prograf/FK506)

Tacrolimus (Prograf; Astellas Pharma US, Deerfield, IL) is a second-generation CNI. Whereas both tacrolimus and CsA inhibit interleukin-2 (IL-2) synthesis and release, each displays a different mechanism at the cellular level. The ingestion of food with tacrolimus affects the rate and extent of the absorption of the drug. Compared to CsA, tacrolimus seems to have lower nephrotoxicity and is linked with lower frequency of steroid-resistant rejection. However, its side effects include insulin resistance, tremor, and headache, as well as GI distress including anorexia, nausea, vomiting, and diarrhea or constipation [37].

Mycophenolate Mofetil or MMF (CellCept/RS-61443)

MMF (CellCept; Roche Laboratories, Nutley, NJ) is mainly used as an adjunctive agent in multitherapy protocols with a CNI and corticosteroids. The primary effect on the immune system is to inhibit T cell proliferation and it has the advantage of being nontoxic to the kidney [25, 26]. There are several side effects of this drug, but the most common are leukopenia and GI distress with diarrhea, nausea, or vomiting [38].

Sirolimus (Rapamycin/Rapamune)

Sirolimus (Rapamune; Pfizer, Inc., New York, NY) is a macrolide antibiotic that is structurally similar to tacrolimus and likewise inhibits the T cell activation, though by a different mechanism [38]. It can be used to replace a CNI, as it is known to cause less kidney damage. Potential side effects include dyslipidemias (hypertriglyceridemia and hypercholesterolemia), mouth ulcers, delayed wound healing, and pneumonitis [25, 26, 38]. There is evidence that sirolimus, among other immunosuppressive agents, carries the highest risk of altered lipid profiles [39].

Azathioprine (Imuran)

Azathioprine (Imuran; GSK, Brentford, UK) is a nonspecific immunosuppressant whose mode of action is to inhibit the proliferation of immunocompetent cells. Thus it is known as an antiproliferative agent. In the pre-CsA era, azathioprine and glucocorticoids were used as dual therapy after kidney transplant; later CsA was added for triple therapy [35]. While it has been replaced by MMF in current treatment regimens, azathioprine continues to be used in patients who have done well on this medication with previous transplants and in patients who do not seem to tolerate MMF [25, 26]. Common side effects include diarrhea and hematologic manifestations such as anemia and leukopenia [25, 26].

Corticosteroids (Prednisone, Prednisolone, Methylprednisolone, Solu-Medrol, Solu-Cortef)

The most commonly prescribed corticosteroids used in transplant programs include prednisone and methylprednisolone, which have anti-inflammatory properties and inhibit the production of lymphokines; they are available from several manufacturers as generically equivalent medications. This class of immunosuppressants can be administered in high doses, either orally or parenterally, for acute rejection; or they may be given as high-dose oral pulses, which are then tapered to maintenance levels or in some cases discontinued [40, 41]. Associated side effects are believed to be dose-dependent and, therefore, have declined in severity as lower doses are used in maintenance immunosuppressive therapy. Patients using corticosteroids are at increased risk for hypertension, osteopenia, NODAT, and dyslipidemias [25, 26].

Other Agents

Monoclonal antibodies, such as OKT-3 (Muromonab-CD3, Orthoclone; Ortho Biotech, Bridgewater, NJ), basiliximab (Simulect; Novartis Pharmaceuticals, Inc., St. Louis, MO), and alemtuzumab (Campath; Genzyme, Cambridge, MA) may be used either perioperatively for induction therapy or for acute rejection episodes. OKT-3, an anti-T cell antibody, may be used for acute cellular rejection particularly in cases of steroid resistance [25, 26]. Basiliximab is an IL-2 receptor antagonist without known side effects, which may be used in combination with traditional immunosuppressive therapy. It is used in combination therapy with CsA and corticosteroids [25, 26, 42]. Research has not yet supported improved outcomes with alemtuzumab, or Campath, in patients with kidney transplant and so it is not widely used in this population [25, 26].

OKT-3 can cause GI distress as well as flu-like symptoms, and appropriate adjustments in nutritional therapy should be made. OKT-3 also presents increased risk of infection and lymphoproliferative disease [41].

Balanced control of the immune system with immunosuppressive therapy is the cornerstone of graft survival. Dietitians should provide important nutrition education to assist transplant recipients in preventing and controlling side effects from their immunosuppressive therapy.

Long-Term Care Challenges

Cardiovascular Disease

Cardiovascular disease is the leading cause of death after kidney transplantation, with an incidence considerably higher than that in the general population due to the high prevalence and accumulation of classical risk factors before and after transplantation. Additional risk may be conferred by immunosuppression regimens. Approximately 70 % of kidney transplant recipients will experience serum lipid abnormalities during the post-transplant course [39, 43].

The serious impact of CKD on risk for cardiovascular disease led experts to recommend that CKD should be considered a coronary heart disease (CHD) risk equivalent in the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) [43, 44]. Altered lipids in post-kidney transplant individuals should be addressed as an integral factor in their care [43]. Contributing factors for dyslipidemias include immunosuppressive therapy (corticosteroids, sirolimus, and CNIs, especially CsA), graft dysfunction, obesity, diuretic or antihypertensive drug therapy, age, gender, diabetes mellitus, and proteinuria [39, 43].

Although most risk factors are not amenable to treatment, diet and obesity are two factors that may be modified. Therapeutic lifestyle changes should be considered as a first step in MNT for obesity and lipid disorders [32]. It involves reducing intake of saturated fat and cholesterol, increasing physical activity, and maintaining a healthy weight [44]. Lipid profiles can improve with dietary intervention, but often patients still require lipid-lowering medications to reach target lipid levels as suggested by the ATP III guidelines. The HMG-CoA reductase inhibitors (statins) are prescribed for treatment of post-transplant hyperlipidemia in combination with therapeutic lifestyle changes that include activity and low-fat, low-cholesterol, higher-fiber meal planning [19, 39].

Hyperhomocysteinemia has been reported in kidney transplant recipients. The mechanism for elevated homocysteine levels in this group is unknown, but potential factors include inadequate folate status and renal dysfunction. Nor is it understood whether elevated serum homocysteine has a causal

role in dyslipidemias in transplant patients. A large double-blinded controlled study of supplemental folic acid and vitamins B_6 and B_{12} in kidney transplant recipients demonstrated successful reduction of serum homocysteine but no impact on cardiovascular outcomes [45].

Obesity

The negative impact of obesity at the time of transplant on subsequent kidney transplant outcomes is controversial though a large analysis of United States Renal Data System (USRDS) data demonstrated increased morbidity, including early allograft loss, in transplant recipients with higher BMI [10]. This is compounded by weight gain which ranges from 8 to 14 kg in the first year after a kidney transplant [14]. Obesity presents increased surgical and clinical risks that affect transplant outcomes, such as delayed wound healing, increased post-transplant infections, increased NODAT, and a higher incidence of DGF [46]. Post-transplant obesity has been shown to have adverse effects on blood pressure, glucose, and lipid metabolism, thereby contributing to dyslipidemias and NODAT [23, 43]. There are multiple causes of post-transplant weight gain, as discussed in this chapter.

With today's lower doses of maintenance corticosteroids, the contribution to post-transplant weight gain from that category of immunosuppressive medications has declined [14]. Other research has suggested, however, that steroid avoidance regimens do produce lower weight gains after transplant [47]. However, there are several non-medication risk factors that continue to be recognized in post-transplant weight gain, including lack of physical activity, prior history of obesity, age at the time of transplant, gender, ethnicity, and socioeconomic status [14].

Weight management is a difficult challenge. Lifestyle changes involving diet, behavior modification, and physical activity are the cornerstone of successful weight control. In one study, the effect of early intensive dietary intervention on recently transplanted kidney patients showed reduced weight gain with intensive individualized MNT [48]. Future studies should investigate whether pre- and post-transplant weight reduction can favorably impact outcomes.

Medications may be combined with lifestyle modification for weight loss after transplant. However, the long-term success of weight loss with pharmacologic treatment is poor, with a high rate of relapse when the medication is stopped [14]. In addition, some medications such as orlistat (Xenical, Roche Laboratories, Nutley, NJ; Alli, GSK, Brentford, UK) are not recommended due to evidence of lower CNI levels which result from altered fat absorption [49]. Alli is available over the counter and so clinicians must be diligent in educating patients about this negative side effect.

Few studies have evaluated the impact of exercise following kidney transplantation [50]. Physical activity offers significant health benefits, including the reduction of cardiovascular risk factors, improvement in diabetes management and bone health, and weight management. Patients are typically cleared to resume exercise 6 weeks after transplant. A Cochrane review of 32 studies that were suitable for their analysis supported these findings and suggested that regular exercise in patients after kidney transplant promotes physical fitness with improved blood pressure and heart rate [51].

Bariatric surgery has become an option for treating morbid obesity in pre- and post-transplant patients. The first report of outcomes in a large number of patients showed BMIs that declined from pre-surgery levels of 47–50 kg/m2 to post-bariatric surgery levels of 32–35 kg/m2. Mortality was significant in these patients with multiple comorbidities [52]. A review of data from the USRDS identified the Roux-en-Y gastric bypass as the most common procedure and reported that weight loss was comparable to that in non-CKD patients, but with a higher mortality [53].

Finally, there are no high-quality clinical trials to demonstrate the positive benefits of weight loss or reduced weight gain in the peri-transplant period. Future research in this area is needed.

New-Onset Diabetes After Transplantation (NODAT)

Since the International Consensus Guidelines appeared in 2003, NODAT has been defined by serum glucose higher than 200 mg/dL or fasting plasma glucose greater than or equal to 126 mg/dL [23]. Data about NODAT prior to that era are difficult to interpret since there was no standardized definition.

A review of NODAT using the USRDS database suggested an incidence of 10 % in transplanted individuals, though the literature has reported figures ranging from 3 to 20 % [54]. Nutrition management of NODAT typically includes a carbohydrate-controlled diet, exercise, and weight management [55]. Hypoglycemic agents may also be prescribed and modifiable risk characteristics, such as immunosuppression, may be adjusted as clinically appropriate [54].

Hypertension

Hypertension occurs in 50–85 % of kidney transplant recipients [56]. The etiology of hypertension is multifactorial and includes genetic predisposition, impaired renal function, uncontrolled renin secretion from the native organ, surgical issues such as anastomotic stenosis, the use of CNIs, and obesity [57]. Poor blood pressure control after a kidney transplant, defined as systolic blood pressure greater than 140 mmHg, can accelerate the loss of allograft function and impact the survival of the transplant recipient [56]. Antihypertensive treatment may include sodium modification, weight management, diuretics, and calcium channel blockers as the first choice for pharmaceutical therapy [58]. While nephrology nutrition experts who reviewed the literature recommend 2,400 mg sodium per day post transplant, the Dietary Guidelines of 2010 set 1,500 mg of sodium per day as the goal for specified subgroups, including individuals with CKD and/or with hypertension [32, 59].

Mineral and Bone Disorder

The extent of post-transplant mineral and bone disorder depends on several variables, including the degree of pre-transplant hyperparathyroidism and the level of function in the allograft kidney [25, 26]. The 1,25-dihydroxy vitamin D levels can be suboptimal in transplant candidates and remain abnormal for at least 6 months following transplantation [60]. Long-term corticosteroid therapy with resultant inhibition of bone formation and the stimulation of bone resorption can also cause osteoporosis [30].

General Considerations

Interactions

Grapefruit juice and grapefruit products can affect absorption of certain medications and should not be consumed by patients taking calcium channel blockers, specific immunosuppressants, antilipidemics, and estrogen products. Grapefruit products inhibit the cytochrome P450 isoenzyme CYP3A4 mechanism in the gastrointestinal tract. The pharmacokinetics of CNIs demonstrates intraindividual

variability when CNIs are administered with grapefruit [21]. The duration of the effect of grapefruit juice varies, but with repeated intake it can have a cumulative effect [21]. Patients are strongly advised to keep the transplant staff informed of all herbals and botanicals after a kidney transplant and to follow the team's advice regarding continued use [20]. Most transplant teams in the United States will advise transplant recipients to avoid herbal medications in general.

Food Safety

Foodborne infections are common and sometimes can be life-threatening, particularly to individuals who are immunosuppressed [61]. There are currently 250 known foodborne diseases, but information is limited on the incidence of infection from food sources in the immunosuppressed patient [62]. Transplant recipients infected with foodborne microorganisms exhibit symptoms ranging from mild intestinal distress to severe dehydration, which can jeopardize immunosuppression. Research has demonstrated that, compared to bone marrow transplant recipients, solid organ transplant recipients are less likely to follow food safety recommendations, including avoiding high-risk foods such as unpasteurized dairy products and high-risk produce [63]. Given these findings and given the increased prevalence of foodborne outbreaks, nutrition education post-transplant should include guidelines on food safety. The United States Department of Agriculture has developed a booklet which addresses the specific topic of food safety for individuals who have had organ transplants [64].

Summary

The nutrition interventions associated with kidney transplantation vary according to the phase of care as well as the nutritional status of the transplant recipient. The RD provides nutrition assessments, determines a nutrition diagnosis (or several), plans and executes nutrition interventions, and provides ongoing monitoring and evaluation throughout the transplant process for recovery and maintenance of transplant function. The RD should also monitor the patient for general health issues and comorbidities, such as DM, obesity, and lipid disorders and provide MNT in accordance with evidence-based guidelines. The RD is a valued member of the transplant team and, by providing timely MNT, he/she can enhance the transplant recipient's ability to prevent or minimize the nutrition-related complications. The entire team should be encouraged to participate in educational activities to increase successful patient outcomes.

Case Study

General: B.G. is a 65-year-old black male with ESRD due to Type 2 DM (T2DM), which was diagnosed 25 years ago. Deceased donor kidney transplant 6 weeks ago.

Food and nutrition-related history:

- His wife prepares meals, avoids added salt and high-sodium seasonings
- Both the patient and his wife attended DM education classes approximately 10 years ago. Uses glucometer which records capillary blood glucose (CBG) readings
- Medications:

  - Thiazolidinedione and sulfonylurea with sliding-scale insulin as needed pre-transplant
  - Atorvastatin (Lipitor) for 6 years pre-transplant
  - Current medications, 6 weeks post-transplant: 5 mg prednisone; 250 mg MMF bid; tacrolimus, 1 mg bid; Os-Cal 500 Plus D tid; MVI daily; metoprolol; gabapentin; esomeprazole; potassium phosphate and sodium phosphate; 800 mg magnesium oxide 2×/day; insulin—glargine 20 U every evening and sliding-scale regular insulin based on CBGs

- Exercise: reduced due to neuropathy. Walks indoor track at recreation center, 30 min, 1–2×/week
- The church community has shown support during their more stressful situations and sometimes provides meals to the family

Anthropometrics:

- Height: 71″ (180 cm)
- Weight: 111.8 kg (246 lb)
- BMI: 34.5, Frame: large
- Weight history: lost 20 lb in 6 months before transplant (as advised after transplant evaluation)

Biochemical data, *medical tests*, *and procedures*:

- CBG 3×/day, before meals (recorded in glucometer)
- Pre-transplant hemoglobin A1c: 6.6 %
- 6 Weeks post-transplant: non-fasting glucose 250 mg/dL; Hgb A1c 8.1 %; creatinine 1.8 mg/dL; blood urea nitrogen (BUN) 25 mg/dL; potassium 6.1 mg/dL; CO_2 20 mEq/L; phosphorus 2.0 mg/dL; calcium 8.5 mg/dL; magnesium 1.8 mg/dL; albumin 3.4 g/L; cholesterol 273 mg/dL; high-density lipoproteins (HDL) 36 mg/dL; TG 352 mg/dL; low-density lipoproteins (LDL) 128 mg/dL; urinary protein negative

Nutrition-related physical findings:

- Obese abdomen
- Describes diarrhea (alternates with constipation; lately more diarrhea)
- No changes in hair, denies altered sense of taste and smell

Client history:

- T2DM diagnosed 25 years before transplant; retinopathy, treated with laser surgery (vision adequate but marginal); neuropathy
- Hypertension diagnosed 12 years before transplant
- In-center hemodialysis for 3 years prior to transplant, most recently 4 h per treatment, 3×/week
- Deceased donor kidney transplant 6 weeks ago, surgical incision healing well
- Smoker, quit 6 years ago
- Supportive wife works part-time in billing office and helps patient with some self-care routines. Two adult children live out of town, have their own families

Case Study Questions

1. What are this patient's protein and calorie needs?
   Answer:

   (a) Adjusted body weight (ABW) = 97 kg.
   (b) Protein (1.3 g/kg ABW) = 126 g/day.
   (c) Calories (30 kcal/kg ABW) = 2,910 cal/day may need to modify for DM and wt loss.

2. Are there suggestions which may help his digestive concerns?
   Answer:
   (a) Discuss with transplant team possible adjusted doses/timing of immunosuppressive drugs (i.e., CellCept qid vs. bid).
   (b) To address long-term concerns which may be related to DM gastroenteropathy, soluble fiber supplements, such as psyllium-based products, could be tried.
3. What types of exercise might be appropriate for this gentleman?
   Answer:
   (a) Walking per ability with slow gradual increase and chair exercises with light hand weights.
   (b) When his incision is completely healed, perhaps water aerobics or stationary cycling will help with his weight management program.
4. How could calcium/phosphorus balance be improved?
   Answer:
   (a) Avoid taking phosphorus supplement at the same time as his calcium supplement.
   (b) Dietary phosphorus intake could be increased, but some high-phosphorus foods are also high in potassium. Patient could be scheduled for bone density studies.
5. What glycemic control issues could be addressed?
   Answer:
   (a) Educate on the timing and action of currently used types of insulin, carbohydrate in foods, and CHO distribution as needed. Diabetes management could be updated.
   (b) HgbA1c is not considered accurate since patient's use of immunosuppressive drugs and the effect on blood glucose levels has been dramatic over the past 6 weeks. Reassess HgbA1c 3 months after prednisone and Prograf doses are at maintenance levels.
   (c) Weight control (an issue for him in the past) may be a significant issue regarding his DM management.
6. Is patient on an appropriate MVI product?
   Answer:
   (a) Evaluate MVI supplement to address megadosing of any component or inclusion of an "immuno-enhancing" item such as ginseng (contraindicated due to his current requirements for immunosuppression).
7. Could patient's edema be related to diet?
   Answer:
   (a) Fluid retention can be affected by steroid use, edema may also be affected by dietary sodium.
8. What are some factors that could be affecting patient's serum potassium?
   Answer:
   (a) Elevated serum levels of Prograf (data not available in this report; check his labs at Transplant Clinic).
   (b) Neutra-Phos, containing 14 mEq/K^+/tab; consider switch to K-Phos Neutral containing 1 mEq K^+/tab.
   (c) Provide education regarding the balance between increased need for phosphorus intake while he still has some hyperkalemia.
   (d) Avoid salt substitutes containing potassium.
   (e) Does MVI contain minerals? It may contribute to excessive potassium intake.

9. How would you deal with patient's hyperlipidemia?
   Answer:

   (a) Participate in team discussion to encourage resuming statin medications after immunosuppressive medications are at maintenance levels.
   (b) Review of dietary fat would and weight management.
   (c) Soluble fiber and plant sterols could be introduced.

References

1. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR annual data report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation. 2011. http://www.srtr.org/annual_reports/2010/. Accessed 17 March 2012.
2. American Diabetic Association. International Dietetics & Nutrition Terminology (IDNT) reference manual: standardized language for the nutrition care process. 3rd ed. Chicago, IL: American Diabetic Association; 2011.
3. Cochran CC, Kent PS. Nutrition management of the adult renal transplant patient. In: Byham-Gray L, Wiesen K, editors. A clinical guide to nutrition care in kidney disease. 3rd ed. Chicago, IL: American Diabetic Association; 2004.
4. Tritt L. Nutritional assessment and support of kidney transplant recipients. J Infus Nurs. 2004;27:45–51.
5. National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;47:S1–201.
6. National Kidney Foundation. KDOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. 2003. http://www.kidney.org/professionals/KDOQI/guidelines_lipids/toc.htm. Accessed April 2012.
7. Hsu C, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med. 2009;169(4):342–50.
8. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr. 2005;81:543–54.
9. Kopple JD, Feroze U. The effect of obesity on chronic kidney disease. J Ren Nutr. 2011;21:66–71.
10. Meier-Kriesche H, Andorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation. 2002;73:70–4.
11. Martins C, Pecoits-Filho R, Riella MC. Nutrition for post-renal transplant recipients. Transplant Proc. 2004;36(6):1650–4.
12. Massarweh NN, Clayton JL, Mangum CA, Florman SS, Slakey DP. High body mass index and short and long-term renal allograft survival in adults. Am J Transplant. 2006;6(2):357–63.
13. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krshnan M, Nissneson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant. 2011;11:725–36.
14. Potluri K, Hou S. Obesity in kidney transplant recipients and candidates. Am J Kidney Dis. 2010;56:143–56.
15. Seagraves A, Moore EE, Moore FA, Weil III R. Net protein catabolic rate after kidney transplantation: impact of corticosteroid immunosuppression. J Parenter Enteral Nutr. 1986;10:453–5.
16. Blue LS. Adult kidney transplantation. In: Hasse JM, Blue LS, editors. Comprehensive guide to transplant nutrition. Chicago, IL: American Diabetic Association; 2002.
17. Hasse JM, Weseman RA. Solid organ transplantation. In: Gottschlich MM, Fuhrman MP, Hammond KA, Holcombe BJ, Seidner DL, editors. Nutrition support dietetics core curriculum. Dubuque, Iowa: ASPEN; 2001. p. 605.
18. Steiber A, Kopple JD. Vitamin status and needs for people with stages 3–5 chronic kidney disease. J Ren Nutr. 2011;21:355–68.
19. Phillips S, Heuberger R. Metabolic disorders following kidney transplantation. J Ren Nutr. 2012;22:451–60.
20. Vivekanand J. Herbal medicines and chronic kidney disease. Nephrology. 2010;15(s2):10–7.
21. Nowak R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John's work—and beyond! Nephrology. 2008;13:337–47.
22. Hasse JM, Matarese LE. Solid organ transplantation. In: Gottschlick MM, editor. The ASPEN nutrition support core curriculum: a case-based approach—the adult patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2009.
23. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, Kasiske B, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell J, van der Woude FJ, Wheeler DC. New-onset diabetes after transplantation: 2003 international consensus guidelines. Transplantation. 2003;75:SS3–24.

24. Ponticello C, Passenni P. Gastrointestinal complications in renal transplant recipients. Transpl Int. 2005;18(6): 643–50.
25. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1–157.
26. 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:S1–130.
27. Schaier M, Wendt C, Zeier M, Ritz E. *Clostridium difficile* diarrhoea in the immunosuppressed patient-update on prevention and management. Nephrol Dial Transplant. 2004;19:2432–6.
28. Helderman J, Goral S. Gastrointestinal complications of immunosuppression. J Am Soc Nephrol. 2002;13: 277–87.
29. Ozgur O, Boyacioglu S, Ozdogan M, Gur G, Telatar H, Haberal M. Helicobacter pylori infection in haemodialysis patients and renal transplant recipients. Nephrol Dial Transplant. 1997;12:289–91.
30. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. J Am Soc Nephrol. 2002;13:551–8.
31. Beto J, Bansal VK. Hyperkalemia: evaluating dietary and nondietary etiology. J Ren Nutr. 1992;1:28–9.
32. American Diabetic Association. Evidence-Based Nutrition Practice Guidelines for chronic kidney disease. http://www.adaevidencelibrary.com/topic.cfm?cat=3929. Accessed 30 March 2012.
33. Rubello D, Giannini S, D'Angelo A, Nobile M, Carraio G, Rigotti P, Marchini F, Zaninotto M, Dalle Carbonare L, Sartori L, Nibale O, Carpi A. Secondary hyperparathyroidism is associated with vitamin D receptor polymorphism and bone density after renal transplantation. Biomed Pharmacother. 2005;59(7):402–7.
34. Haef J, Jakobsen V, Tuedegoard E, Kanstrupl L, Fogh-Anderson N. Dietary habits of nutritional status of renal transplant patients. J Ren Nutr. 2004;14:20–5.
35. Morris PJ. Transplantation—a medical miracle of the twentieth century. N Engl J Med. 2004;351:2678–80.
36. Bennett W, Burdmann E, Andoh T, Houghton D, Lindsley J, Elzinga L. Nephrotoxicity of immunosuppressive drugs. Nephrol Dial Transplant. 1994;9:141–5.
37. Webster AC, Taylor RRS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev. 2005;(4):CD003961.
38. McPartland J, Pomposelli JJ. Update on immunosuppressive drugs used in solid-organ transplantation and their nutrition implications. Nutr Clin Pract. 2007;22:467–73.
39. Ward HJ. Nutritional and metabolic issues in solid organ transplantation: targets for future research. J Ren Nutr. 2009;19:111–22.
40. Starzl T, Marchiono T, Waddell W. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet. 1963;117:385–95.
41. DiCecco SR, Francisco-Ziller N, Moore D. Chapter 1: overview and immunosuppression. In: Hasse JM, Blue LS, editors. Comprehensive guide to transplant nutrition. Chicago, IL: American Diabetic Association; 2002.
42. Ekberg H, Grinyo J, Nashan B, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. Am J Transplant. 2007;7:560–70.
43. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R, Levin A, Masri B, Parekh R, Wanner C, Wheeler DC, Wilson PWF. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant. 2004;4(s7):13–53.
44. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). 2004. http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. Accessed Nov 2012.
45. Bostom AG, Carpenter MA, Kusek JW, Levey AS, Hunsicker L, Pfeffer MA, Selhub J, Jacques PF, Cole E, Gravens-Mueller L, House AA, Kew C, McKenney J, Pacheco-Silva A, Pesavento T, Pirsch J, Smith S, Solomon S, Weir M. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the folic acid for vascular outcome reduction in transplantation trial. Circulation. 2011;123:1763–70.
46. Kent P. Issues of obesity in kidney transplantation. J Ren Nutr. 2007;17:107–13.
47. Elster EA, Leeser DB, Morrissette C, et al. Obesity following kidney transplantation and steroid avoidance immunosuppression. Clin Transplant. 2008;22:354–9.
48. Patel MG. The effect of dietary intervention on weight gains after renal transplantation. J Ren Nutr. 1998;8:137–41.
49. Evans S, Michael R, Wells H, MacLean D, Gordon I, Taylor J, Goldsmith D. Drug interaction in a renal transplant patient: cyclosporine-Neoral and orlistat. Am J Kidney Dis. 2003;41:493–6.
50. Bernadi A, Biasia F, Pati T, Piva M, Scaramuzzo P, Stoppa F, Bucciante G. Factors affecting nutritional status, response to exercise and progression of chronic rejection in kidney transplant recipients. J Ren Nutr. 2005; 15(1):54–7.

51. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev. 2011;(10):CD003236.
52. Alexander JW, Goodman HR, Gersin K, Cardi M, Austin J, Goel S, Safdar S, Huang S, Woodle ES. Gastric bypass in morbidly obese patients with chronic renal failure and kidney transplant. Transplantation. 2006;78:469–74.
53. Modanlou KA, Muthyala U, Xiao H, Schnitzler MA, Salvalaggio PR, Brennan DC, Abbott KC, Graff RJ, Lentine KL. Bariatric surgery among kidney transplant candidates and recipients: analysis of the United States Renal Data System and literature review. Transplantation. 2009;87:1167–73.
54. Shah T, Kasrav A, Huang E, Hayashi R, Young B, Cho YW, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus after kidney transplantation. Clin Transpl. 2006;82:1673–6.
55. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. 2007. http://www.kidney.org/professionals/KDOQI/guideline_diabetes/. Accessed 5 Sept 2011.
56. Chatzikyrkou C, Menne J, Gwinner W, Schmidt BM, Lehner F, Blume C, Schwarz A, Haller H, Schiffer M. Pathogenesis and management of hypertension after kidney transplantation. Hypertension. 2011;29:2283–94.
57. Zeier M, Dikow R, Ritz E. Blood pressure after renal transplantation. Ann Transplant. 2001;6:21–4.
58. Cross NB, Webster AC, Masson P, O'Connell PJ, Craig JC. Antihypertensive treatment for kidney transplant recipients. Cochrane Database Syst Rev. 2009(3):CD003598. doi: 10.1002/14651858.CD003598.pub2.
59. United States Department of Agriculture, Center for Nutrition and Public Policy. Dietary guidelines for 2010. http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm. Accessed 5 April 2012.
60. Querings K, Girndt M, Geisel J, Georg T, Tilgen W, Reichrath J. 25-Hydroxyvitamin D deficiency in renal transplant recipients. J Clin Endocrinol Metab. 2006;91:526–9.
61. Medeiros LC, Chen G, Kendall P, Hillers VN. Food safety issues for cancer and organ transplant patients. Nutr Clin Care. 2004;7:141–8.
62. United States Department of Agriculture. Food safety and inspection service. Fact sheets: foodborne illnesses and disease. http://www.fsis.usda.gov/Factsheets/Foodborne_Illness_&_Disease_Fact_Sheets/index.asp. Accessed April 2012.
63. Chen G, Kendall PA, Hillers VN, Medeiros LC. Qualitative studies of the food safety and knowledge and perceptions of transplant patients. J Food Prot. 2010;73:327–35.
64. United States Department of Agriculture. Food safety and inspection service. Food safety for transplant recipients. 2006. http://www.fsis.usda.gov/PDF/Food_Safety_for_Transplant_Recipients.pdf. Accessed April 2012.

Chapter 13
Protein-Energy Wasting

Kamyar Kalantar-Zadeh

Key Points

- To recognize the prevalence of protein-energy wasting (PEW), its potential causes, and its association with inflammation, anorexia, anemia, and other untoward conditions in CKD (chronic kidney disease) stage 5D
- To understand the clinical associations between markers of PEW, such as hypoalbuminemia, and cardiovascular disease and poor survival in dialysis patients
- To learn the tools and measures used to assess the PEW in CKD-5D and their limitations
- To recognize current and emerging treatment modaliti-es for PEW in dialysis patients

Keywords Protein-energy wasting (PEW) • Uremic malnutrition • Anorexia • Malnutrition-inflammation-cachexia syndrome (MICS) • Cardiovascular disease • Reverse epidemiology • Hypoalbuminemia

Introduction

Among individuals with CKD (chronic kidney disease) stage 5D, who undergo maintenance dialysis treatment to survive, currently one out of every five people dies each year in the USA. This unacceptably high mortality rate has not changed substantially in recent years despite many advances in dialysis techniques and patient care [1]. Maintenance dialysis patients also have a high hospitalization rate and a low health-related quality of life. Cardiovascular diseases (CVD) comprise the bulk of morbidity and mortality in dialysis patients. The dialysis-dependent CKD-5D population grows constantly and fast, almost surpassing over half a million in the USA, and continues to consume a disproportionately large component of the Medicare budget; hence, identifying factors that lead to poor dialysis outcome and their successful management is of outmost importance [1]. It was once believed that the traditional cardiovascular risk factors and/or conditions related to dialysis treatment and technique are the main causes of poor clinical outcome; however, randomized controlled trials have failed to show an improvement of mortality by lowering serum cholesterol [2] or increasing dialysis dose [3, 4]. Whereas frequent

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(such as daily in-center or nocturnal) hemodialysis may have better outcome, it is highly unlikely that this modality ever be offered to more than a small fraction of patients, whereas infrequent (e.g., twice weekly) hemodialysis is practiced more frequently in developing countries [5]. Evidence suggests that conditions other than the traditional cardiovascular risk factors be related to the enormous cardiovascular epidemic and high death rates in this population. Among the potential candidates for the poor clinical outcomes in maintenance dialysis patients, the protein-energy wasting (PEW) continues to be at the top of the list [6]. Observational studies have repeatedly and consistently shown a strong association between measures of nutritional status and survival in maintenance dialysis patients [7–9].

Protein-Energy Wasting (PEW): Definition and Etiology

A workable definition of uremic malnutrition, a main component of the PEW in CKD patients, is the following [10]: *Malnutrition is the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity*, *which is caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which is improved by nutritional repletion in patients with CKD*. The International Society of Renal Nutrition and Metabolism (ISRNM) expert panel has recommended the more inclusive term "protein-energy wasting" (PEW) for loss of body protein mass and fuel reserves, while it has also referred to "kidney disease wasting" for the occurrence of PEW in CKD or AKI regardless of the cause [6]. Cachexia, in its terminal form, is a severe and rare form of PEW. The ISRNM suggests that PEW can be diagnosed for sure if three characteristics are present including laboratory markers (low serum levels of albumin, transthyretin, or cholesterol), reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), and reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference). Measures of chronic inflammation or other developing tests can be useful clues for the existence of PEW but do not define it [6]. The uremic malnutrition, a core component of PEW, is engendered when the body's need for protein or energy fuels or both cannot be satisfied by the current dietary intake. Various studies using different criteria have been used to establish the presence of PEW in the dialysis population. Its reported prevalence varies between 18 and 75 % among dialysis patients according to the type of dialysis modality, nutritional assessment tools, and the origin of patient population [6, 11]. Although per definition the PEW should not involve micronutrients that are believed to be adequate or even abundantly retained in the setting of renal insufficiency, many protein-energy malnourished dialysis patients may also have a relative deficiency in vitamins and trace elements [12].

The etiology of PEW in dialysis patients is not clear, but some probable causes are listed in Table 13.1 and shown in Fig. 13.1. Uremia, endocrine and gastrointestinal disorders, volume overload, and oxidative and carbonyl stress may lead to the CKD-associated malnutrition. The origin of PEW appears to precede dialysis treatment, because it is observed progressively as the glomerular filtration rate (GFR) falls below 60 mg/min, i.e., the CKD stage 3 and greater [13]. Diminished appetite (anorexia) is a main cause of PEW and may be related to elevated circulating levels of cytokines or may be engendered via signaling through the central melanocortin system [14]. Dialysis patients with a poor appetite have higher levels of inflammatory markers, including C-reactive protein (CRP), an interleukin-6 (IL-6), and several-fold increased risk of death [15]. Moreover, dietary restrictions imposed by nephrologists and/or dietitians to prevent hyperphosphatemia or hyperkalemia may lead to low protein intake and poor outcomes [16].

Dialysis treatment and techniques may also contribute to engendering or worsening PEW. Nutrient loss may happen through hemodialysis membrane or via peritoneal membrane, although its contribution to PEW may not be substantial. High prevalence of comorbid conditions and metabolic disorders including insulin resistance and acidosis may also lead to hypercatabolism and/or wasting. A higher than normal resting energy expenditure is also reported in dialysis patients independent of comorbidity [17] (Table 13.1).

Table 13.1 Potential contributors of the protein-energy wasting in CKD-5 and dialysis patients

A. Inadequate nutrient intake
  1. Anorexia, secondary to:
    (a) Uremic toxicity
    (b) Impaired gastric emptying (e.g., in diabetes mellitus)
    (c) Inflammation with or without comorbid conditions*
    (d) Emotional and/or psychological disorders
  2. Dietary restrictions
    (a) Prescribed restrictions: low-potassium, low-phosphate regimens
    (b) Social constraints: poverty, inadequate dietary support
    (c) Physical incapacity: inability to acquire or prepare food or to eat
B. Nutrient losses during dialysis
  1. Loss through hemodialysis membrane into hemodialysate
  2. Adherence to hemodialysis membrane or tubing
  3. Loss into peritoneal dialysate
C. Hypercatabolism due to comorbid illnesses
  1. Cardiovascular diseases*
  2. Diabetic complications
  3. Infection and/or sepsis*
  4. Other comorbid conditions*
D. Hypercatabolism associated with dialysis treatment
  1. Negative protein balance
  2. Negative energy balance
E. Endocrine disorders of uremia:
  1. Resistance to insulin
  2. Resistance to growth hormone and/or IGF-1
  3. Increased serum level of or sensitivity to glucagons
  4. Hyperparathyroidism
  5. Other endocrine disorders
F. Acidemia with metabolic acidosis
G. Concurrent nutrient loss with frequent blood losses

* Indicates that the given factor may also be associated with inflammation; adapted from [10]
IGF-1 insulin-like growth factor 1

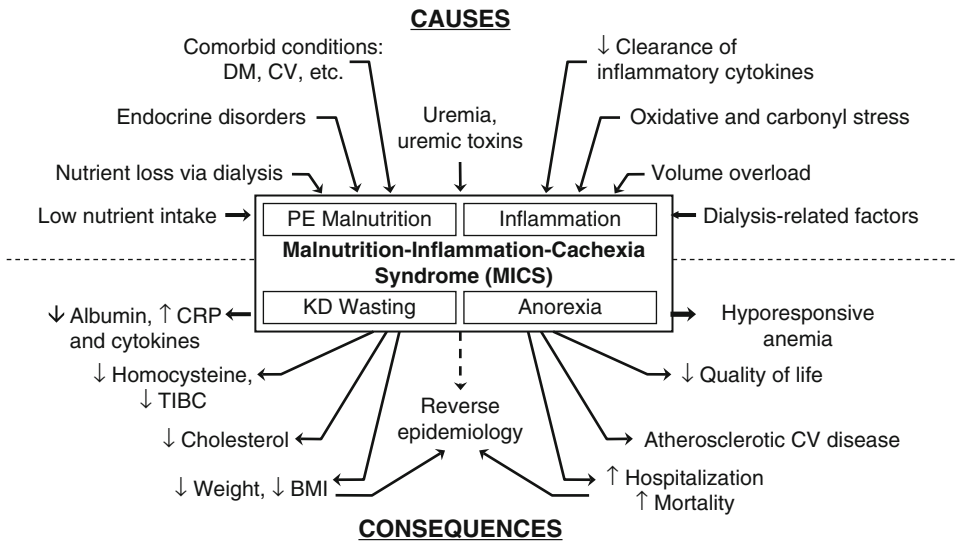

Fig. 13.1 Schematic representation of the causes and consequences of malnutrition-inflammation-cachexia (or complex) syndrome (MICS). *DM* diabetes mellitus, *CV* cardiovascular, *PE* protein-energy, *KD* kidney disease, *CRP* C-reactive protein, *TIBC* total iron-binding capacity (also known as transferring), *BMI* body mass index

Assessment of Protein-Energy Wasting

Methods and tools to assess PEW in CKD patients are classically divided into four major categories: (1) assessment of appetite and dietary intake, (2) biochemical measures, (3) body composition, and (4) scoring systems (Table 13.2). A normal appetite is essential to maintain adequate food intake and to avoid undernourishment. Even though a diminished appetite (anorexia) is one of the early signs of uremia progression in CKD and is implicated as one of the underlying etiologies of PEW in dialysis patients [18], its uniform assessment may not be reliable because of its inherent subjectivity. It has been argued that inflammation is a cause of diminished appetite in dialysis patients [15]. If this hypothesis should be true, then the inflammation may be causally linked to the PEW in CKD patients.

A traditional nutritional evaluation is dietary assessment, because both the quality and quantity of the ingested nutrients can be assessed with a high degree of reproducibility [19]. However, dietary assessment methods including 24-h recall and 3-day food diary with interview and food frequency questionnaires are difficult to accurately implement or interpret in dialysis patients. A dialysis patient-specific food frequency questionnaire has recently been developed [20]. A more routinely used and readily available method is the estimation of the weight-normalized protein equivalent of total nitrogen appearance (nPNA), also known as the normalized protein catabolic rate (nPCR), which is derived from the rate of urea generation between the two subsequent hemodialysis treatment sessions. This urea-kinetic estimate of the protein intake is associated with survival, with the lowest mortality

Table 13.2 Proposed classification of the assessment tools for evaluation of protein-energy wasting in maintenance dialysis patients

A. Nutritional intake
1. Appetite assessment
2. Direct: diet recalls and diaries, food frequency questionnaires
3. Indirect, based on urea nitrogen appearance: nPNA (nPCR)
B. Body composition
1. Weight-based measures: BMI, weight-for-height, edema-free fat-free weight
2. Skin and muscle anthropometry via caliper: skinfolds, extremity muscle mass
3. Total body elements: total body potassium, total body nitrogen
4. Energy-beam-based methods: DEXA, BIA, NIR
5. Other methods: underwater weighing
C. Laboratory values
1. Visceral proteins (negative acute phase reactants): albumin, prealbumin, transferring
2. Somatic proteins and nitrogen surrogates: creatinine, SUN
3. Lipids: cholesterol, triglycerides, other lipids and lipoproteins
4. Growth factors: IGF-1, leptin
5. Peripheral blood cell count: lymphocyte count
D. Scoring systems
1. Conventional SGA and its modifications (e.g., DMS [28], MIS [29], CANUSA version [45])
2. Other scores: HD-PNI [46], others (e.g., Wolfson [47], Merkus [48], Merckman [49])

Adapted from [10, 11]

nPNA normalized protein nitrogen appearance, *nPCR* normalized protein catabolic rate, *BMI* body mass index, *DEXA* dual energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis, *NIR* near-infrared interactance, *SGA* subjective global assessment of nutritional status, *DMS* Dialysis Malnutrition Score [28], *MIS* Malnutrition-Inflammation Score [29], *CANUSA* Canada-USA study-based modification of the SGA [45], *HD-PNI* hemodialysis prognostic nutritional index [46], *SUN* serum urea nitrogen, *IGF-1* insulin-like growth factor 1, *CRP* C-reactive protein, *IL* interleukin (e.g., IL1 and IL6), *TNF-α* tumor necrosis factor alpha, *SAA* serum amyloid A

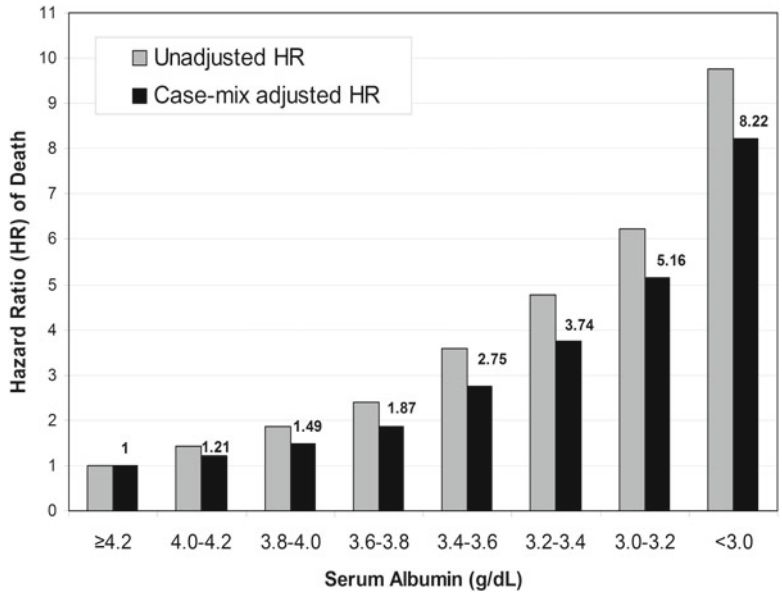

Fig. 13.2 Association between serum albumin levels (averaged over 3-month intervals) and subsequent 2-year death risk in 58,058 maintenance hemodialysis patients 2001–2003 (based on data published data [7, 11])

between 1.0 and 1.4 g/kg/day protein intake [21]. However, nPCR (nPNA) is not an accurate estimate of dietary protein intake if there is appreciable residual renal function (urine output) or if the patient is in negative or positive nitrogen balance. Hence, in hypercatabolic states such as chronic infection or in anabolic states such as muscle and fat buildup, nPCR (nPNA) may be inaccurate.

Anthropometry and body composition measures are among traditional indicators of nutritional status in dialysis patients. Weight-for-height and body mass index (BMI = weight/height^2) can be conveniently calculated and are also known to predict outcomes in dialysis patients. However, the reliability of these measures to represent the true body composition is questionable, especially since a high BMI can occur with both high total body fat and very high muscle mass [22]. Caliper anthropometry including mid-arm muscle mass and skinfold thickness has a less-than-perfect reproducibility [23]. More reliable methods such as underwater weighing and total nitrogen or potassium measurements are costly and rarely if ever used in dialysis patients, although they are considered gold standards. Energy-beam methods may provide more pragmatic alternatives. Portable devices such as those based on the bioelectrical impedance analysis (BIA) or near-infrared interactance (NIR) technology are evaluator and patient friendly, whereas dual energy X-ray absorptiometry (DEXA) is a more elaborate and costly method that requires both resources and expertise [24].

Serum concentrations of albumin, prealbumin (transthyretin), transferrin (total iron-binding capacity or TIBC), cholesterol, urea nitrogen, and creatinine can be evaluated as markers of nutritional status and outcome predictors in dialysis patients. However, these laboratory values may significantly be confounded by such non-nutrition factors as inflammation, oxidative stress, iron stores, liver disease, or residual renal function. Serum albumin is one of the most sensitive mortality predictors in both HD and PD patients (Fig. 13.2) [25]; a fall in serum albumin concentration by as low as 0.6 g/dL from baseline over a 6-month interval is associated with the doubling of the death risk in hemodialysis patients [26].

In the past few years, several scoring systems have been introduced or developed to assess the overall nutritional aspects of CKD patients. The *Subject Global Assessment* (SGA) is probably the most known scoring tool, which has also been recommended by the KDOQI Nutrition guidelines for the periodic assessment of dialysis patients [27]. Among the limitations of the SGA are the inherently "subjective" characteristics of the assessment components and the semi-quantities scoring. Fully quantitative versions of the SGA that have been developed for dialysis patients include the *Dialysis Malnutrition Score* (DMS) [28] and the *Malnutrition-Inflammation Score* (MIS) [29]. The reproducibility and objectivity of the DMS and MIS may be superior to the conventional SGA [27, 30].

Inflammation and Kidney Disease Wasting

Inflammation is defined as a protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or sequester both the injurious agent and the injured tissue [10]. This important defense mechanism, which is inherently "acute" and should happen on an "as-needed" basis, may become harmful to the organism if it becomes "chronic." Evidence suggests that dialysis patients with PEW are more likely to have abnormally high circulatory levels of inflammatory markers and pro-inflammatory cytokines such as CRP and IL-6, both known to be strong predictors of poor outcome [31]. It is not clear why chronic inflammation occurs commonly in CKD patients but some potential causes have been listed in Table 13.3.

Inflammatory markers are associated with anorexia in dialysis patients [32]. Chronic inflammation may also lead to increased rate of protein depletion in skeletal muscle and other tissues, muscle and fat wasting, hypoalbuminemia, and hypercatabolism, leading to the so-called PEW or *kidney disease wasting*. Since both the PEW and inflammation are usually concurrent, act on the same direction on laboratory markers and body proteins, and are both associated with the KDW and atherosclerotic CVD in dialysis patients, a so-called malnutrition-inflammation complex (or cachexia) syndrome (MICS) has been defined to underscore the close link between these two conditions (Fig. 13.1) [10]. However, there is currently no conclusive consensus with regard to the nature or direction of the association between the PEW and inflammation and their pathophysiologic link to the KDW and survival [33]. Indeed, a low serum albumin <3.8 g/dL in hemodialysis patients is more likely with a low dietary protein intake (nPCR < 1.0 g/kg/day) and a high serum IL-6 level, indicative of both malnutrition and inflammation [34].

Consequences of PEW

In addition to anorexia, hypoalbuminemia, and the muscle and fat wasting, PEW may have other clinically important consequences in chronic dialysis patients.

Refractory Anemia

Anemia appears to be more common in those dialysis patients who also suffer from PEW and/or inflammation [35]. A blunted response to *erythropoiesis-stimulating agents* (ESA) is usually associated with increased levels of pro-inflammatory cytokines such as IL-6 [36]. An inverse association between such markers of nutritional state as serum prealbumin, transferrin, and total cholesterol

Table 13.3 Possible causes of inflammation in CKD patients

A. Causes of inflammation due to CKD or decreased GFR
1. Decreased clearance of pro-inflammatory cytokines
2. Volume overload with or without concomitant endotoxinemia*
3. Oxidative stress (e.g., oxygen radicals)*
4. Carbonyl stress (e.g., pentosidine and advanced glycation end products)
5. Decreased levels of antioxidants (e.g., vitamin E, vitamin C, carotenoids, selenium, glutathione)*
6. Deteriorating protein-energy nutritional state and food intake*
B. Coexistence of comorbid conditions
1. Inflammatory diseases with kidney involvement (e.g., SLE or HIV disease)
2. Increased prevalence of comorbid conditions (CVD, DM, advanced age, etc.)*
3. Remnant allograft from a previous solid organ transplantation*
C. Additional inflammatory factors related to dialysis treatment
I. Hemodialysis:
1. Exposure to dialysis tubing
2. Dialysis membranes with decreased biocompatibility
3. Impurities in dialysis water and/or dialysate
4. Back filtration or back diffusion of contaminants
5. Foreign bodies (such as PTFE) in dialysis access grafts
6. Intravenous catheter
II. Peritoneal dialysis:
1. Episodes of overt or latent peritonitis*
2. PD catheter as a foreign body and its related infections
3. Constant exposure to PD solution

* Indicates that the given factor may also be associated with protein-energy wasting; adapted from [10]
CKD chronic kidney disease, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *SLE* systemic lupus erythematosus, *HIV* human immune deficiency virus, *CVD* cardiovascular disease, *DM* diabetes mellitus

concentration and blood lymphocyte count and the required ESA dose has also been reported [35]. In a meta-analysis, L-carnitine administration that is used to improve nutritional state was associated with improved hemoglobin and a decreased ESA dose and in anemic dialysis patients [37]. Moreover, anabolic steroids have also been used successfully to simultaneously improve both nutritional state and anemia in dialysis patients.

Atherosclerotic Cardiovascular Disease

Dialysis patients with more frequent and more impactful cardiovascular events often have hypoalbuminemia and elevated levels of inflammatory markers [38]. Epidemiologic evidence suggests that inflammation may be linked to CVD in malnourished or cachectic dialysis patients. Emerging data even in the general population imply that such indicators of inflammation as an increased serum CRP level are stronger predictors of cardiovascular events than LDL hypercholesterolemia [39]. The association between elements of MICS and atherosclerosis has been underscored by some investigators who have chosen the term "malnutrition-inflammation-atherosclerosis" (MIA) syndrome for this entity. Chronic inflammation may be the *missing link* that causally ties PEW to poor outcome and high death rate in these individuals.

Reverse Epidemiology

In highly industrialized, affluent countries, *under*-nutrition is an uncommon cause of poor outcome in the general population, whereas *over*-nutrition is associated with a greater risk of CVD and shortened survival. In contrast, in maintenance dialysis patients, *under*-nutrition is one of the strongest risk factors for adverse cardiovascular events and mortality. Similarly, certain markers which predict a low likelihood of cardiovascular events and an improved survival in the general population, such as decreased body mass index (BMI) or lower serum cholesterol levels, are risk factors for increased cardiovascular morbidity and death in dialysis patients. Hence, obesity, hypercholesterolemia, and hypertension appear paradoxically or counterintuitively to be *protective* features that are associated with a greater survival among dialysis patients [10]. The association between *under-nutrition* and adverse cardiovascular outcome in dialysis patients, which stands in contrast to that seen in the general population, has been referred to as "reverse epidemiology" [40]. Possible causes of these paradoxical findings include the time discrepancy between competitive risk factors, i.e., under-nutrition, which is the short-term killer, vs. over-nutrition, which needs much longer time to cause death. It is possible that new standards or goals for such traditional risk factors as body mass, serum cholesterol, and blood pressure be considered for dialysis patients, especially if they suffer more frequently from PEW.

Management of PEW

Because PEW and inflammation are powerful predictors of death risk in dialysis patients, it is possible that nutritional and anti-inflammatory interventions improve poor outcome in dialysis patients. Ample evidence suggests that maintaining an adequate nutritional intake in patients with a number of acute or chronic catabolic illnesses may improve their nutritional status irrespective of its etiology. However, evidence as to whether nutritional treatment may improve morbidity and mortality in dialysis patients is quite limited [11]. There are no large-scale, randomized prospective interventional studies that have examined these questions. However, secondary data analyses have indicated that a high protein intake, e.g., between 1.2 and 1.4 g/kg body weight per day, is associated with the best survival in dialysis patients [21]. According to the KDOQI guidelines on nutrition, dialysis patients can receive at least 35 cal/kg body weight per day of energy and 1.2 g/kg body weight per day of protein [41].

Table 13.4 shows selected nutritional interventions that have been tried or recommended in dialysis patients. Enhancing food intake by either dietary counseling or positive reinforcement may be helpful, especially if renal dietitians take a proactive role to this end. Many nephrologists and dietitians advocate oral supplementations as an adjunct therapy. However, it is important to appreciate that simultaneously imposed dietary restrictions to control potassium, phosphorus, and/or calcium intake or to manage diabetes mellitus or dyslipidemia may interfere with or even contradict the foregoing efforts and lead to confusion for both patients and health-care providers.

Tube feeding and parenteral interventions may reinforce protein and energy intake even among anorectic patients. A metabolic study demonstrated that intradialytic parenteral nutrition (IDPN) promoted a large increase in whole-body protein synthesis and a significant decrease in proteolysis in non-inflamed but malnourished hemodialysis patients [42]. Hormonal or pharmacological interventions may be associated with many side effects that mitigate the enthusiasm of using them, although emerging data suggests dietary supplements with anti-inflammatory interventions [43], especially if associated with simultaneous appetite-stimulating properties (such as megestrol acetate [44] or pentoxifylline), may improve nutritional status and outcomes in dialysis patients. A number of other techniques have been employed or recommended for the prevention or treatment of PEW before the onset of dialysis therapy, maintenance of an adequate dose of dialysis, avoidance of acidemia, and aggressive treatment of superimposed catabolic illness.

Table 13.4 Overview of nutritional/anti-inflammatory interventions for dialysis patients with protein-energy wasting

A. Oral interventions
1. Increasing food intake (including meals during hemodialysis treatment)
2. Oral nutritional supplements
B. Enteral interventions
1. Tube feeding
C. Parenteral interventions
1. Intradialytic parenteral nutrition
2. Other parenteral interventions
D. Hormonal interventions
1. Androgens
2. Growth factors/hormones
E. Nonhormonal medications
1. Anti-inflammatory agents (e.g., borage oil, pentoxifylline)
2. Antioxidants (e.g., vitamin E, acetylcysteine)
3. Appetite stimulators (e.g., megestrol)
4. Carnitine
5. Others (e.g., fish oil)
F. Dietary counseling
1. In-center supervision/counseling
2. In-center supervision/counseling
G. Dialysis treatment related
1. Dialysis dose and frequency
2. Membrane compatibility

Adapted from [11, 50]

Summary

In CKD-5D patients who undergo maintenance dialysis treatment, PEW, with or without concurrent inflammation, is undoubtedly one of the most challenging and unresolved issues of the contemporary medicine and nephrology. PEW and its concomitant muscle and fat wasting are very common and associated with inflammation and hypoalbuminemia. Malnutrition may be a major cause of poor outcome and high death rate in the fast-growing dialysis patient population. The impact of malnutrition on deteriorating the short-term survival in dialysis patients is so massive that it overwhelms and even reverses the conventional associations between such traditional risk cardiovascular factors as obesity and survival. There is currently no uniform assessment tool for the detection or accurate grading of the PEW in CKD patients, although emerging scoring systems appear promising. There is a paucity of information concerning the effect of nutritional therapy, appetite-stimulating agents, or anti-inflammatory modalities on morbidity and mortality in dialysis patients. Simultaneous dietary restrictions to avoid hyperkalemia or hyperphosphatemia in CKD patients may handicap efforts to prevent or treat malnutrition in this patient population. Randomized clinical trials are needed to compare the effect of the nutritional support and anti-inflammatory agents, with or without appetite-stimulating effects, in individuals with CKD who suffer from PEW. The most optimal nutritional intervention that can overcome the high death rate linked to the enormous cardiovascular epidemic and poor outcome in CKD patients is yet to be determined.

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References

1. United States Renal Data System (USRDS). USRDS 2012 annual data report. In: Atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2012. www.usrds.org
2. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
3. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–9.
4. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13:1307–20.
5. Rhee CM, Unruh M, Chen J, Kovesdy CP, Zager P, Kalantar-Zadeh K. Infrequent dialysis: a new paradigm for hemodialysis initiation. Semin Dial. 2013 (in press).
6. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
7. Colman S, Bross R, Benner D, Chow J, Braglia A, Arzaghi J, Dennis J, Martinez L, Baldo DB, Agarwal V, Trundnowski T, Zitterkoph J, Martinez B, Khawar OS, Kalantar-Zadeh K. The Nutritional and Inflammatory Evaluation in Dialysis patients (NIED) study: overview of the NIED study and the role of dietitians. J Ren Nutr. 2005;15:231–43.
8. Kovesdy CP, Shinaberger CS, Kalantar-Zadeh K. Epidemiology of dietary nutrient intake in ESRD. Semin Dial. 2010;23:353–8.
9. Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? Semin Nephrol. 2009;29:3–14.
10. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003;42:864–81.
11. Kalantar-Zadeh K, Cano NJ, Budde K, Chazot C, Kovesdy CP, Mak RH, Mehrotra R, Raj DS, Sehgal AR, Stenvinkel P, Ikizler TA. Diets and enteral supplements for improving outcomes in chronic kidney disease. Nat Rev Nephrol. 2011;7:369–84.
12. Kalantar-Zadeh K, Kopple JD, Deepak S, Block D, Block G. Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. J Ren Nutr. 2002;12:17–31.
13. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57:1688–703.
14. Cheung W, Yu PX, Little BM, Cone RD, Marks DL, Mak RH. Role of leptin and melanocortin signaling in uremia-associated cachexia. J Clin Invest. 2005;115:1659–65.
15. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol. 2004;43:1439–44.
16. Shinaberger CS, Greenland S, Kopple JD, Van Wyck D, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? Am J Clin Nutr. 2008;88:1511–8.
17. Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients. J Am Soc Nephrol. 1996;7:2646–53.
18. Kalantar-Zadeh K, Block G, Humphreys MH, McAllister CJ, Kopple JD. A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients. J Am Soc Nephrol. 2004;15:442–53.
19. Bross R, Noori N, Kovesdy CP, Murali SB, Benner D, Block G, Kopple JD, Kalantar-Zadeh K. Dietary assessment of individuals with chronic kidney disease. Semin Dial. 2010;23:359–64.
20. Kalantar-Zadeh K, Kovesdy CP, Bross R, Benner D, Noori N, Murali SB, Block T, Norris J, Kopple JD, Block G. Design and development of a dialysis food frequency questionnaire. J Ren Nutr. 2011;21:257–62.
21. Shinaberger CS, Kilpatrick RD, Regidor DL, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. Am J Kidney Dis. 2006;48:37–49.
22. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, Nissenson AR, Krishnan M, Kopple JD, Mehrotra R, Anker SD. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc. 2010;85:991–1001.

23. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim JJ, Murali SB, Luna A, Gomez M, Luna C, Bross R, Nissenson AR, Kalantar-Zadeh K. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2010;5:2258–68.
24. Bross R, Chandramohan G, Kovesdy CP, Oreopoulos A, Noori N, Golden S, Benner D, Kopple JD, Kalantar-Zadeh K. Comparing body composition assessment tests in long-term hemodialysis patients. Am J Kidney Dis. 2010;55:885–96.
25. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, Kalantar-Zadeh K. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. Am J Kidney Dis. 2011;58:418–28.
26. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr. 2005;81:543–54.
27. Steiber AL, Kalantar-Zadeh K, Secker D, McCarthy M, Sehgal A, McCann L. Subjective Global Assessment in chronic kidney disease: a review. J Ren Nutr. 2004;14:191–200.
28. Kalantar-Zadeh K, Kleiner M, Dunne E, Lee GH, Luft FC. A modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant. 1999;14:1732–8.
29. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A Malnutrition-Inflammation Score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38:1251–63.
30. Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. Am J Kidney Dis. 2009;53:298–309.
31. Kovesdy CP, Kalantar-Zadeh K. Novel targets and new potential: developments in the treatment of inflammation in chronic kidney disease. Expert Opin Investig Drugs. 2008;17:451–67.
32. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80:299–307.
33. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis. 2001;38:1343–50.
34. Kim Y, Molnar MZ, Rattanasompattikul M, Hatamizadeh P, Benner D, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis. Int Urol Nephrol. 2013;45(1):215–27.
35. Kalantar-Zadeh K, McAllister CJ, Lehn RS, Lee GH, Nissenson AR, Kopple JD. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. Am J Kidney Dis. 2003;42:761–73.
36. Rattanasompattikul M, Molnar MZ, Zaritsky JJ, Hatamizadeh P, Jing J, Norris KC, Kovesdy CP, Kalantar-Zadeh K. Association of malnutrition-inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. Nephrol Dial Transplant. 2013;28(7):1936–45.
37. Hurot JM, Cucherat M, Haugh M, Fouque D. Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review. J Am Soc Nephrol. 2002;13:708–14.
38. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn Jr H, Kopple JD, Greenland S. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant. 2005;20:1880–8.
39. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347:1557–65.
40. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63:793–808.
41. K/DOQI, National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35(6 Suppl 2):S1–140.
42. Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. J Clin Invest. 2002;110:483–92.
43. Kalantar-Zadeh K, Braglia A, Chow J, Kwon O, Kuwae N, Colman S, Cockram DB, Kopple JD. An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: a pilot/feasibility study. J Ren Nutr. 2005;15:318–31.
44. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossein C. Megestrol acetate in a moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. J Ren Nutr. 2005;15:345–55.
45. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol. 1996;7:198–207.
46. Beto JA, Bansal VK, Hart J, McCarthy M, Roberts D. Hemodialysis prognostic nutrition index as a predictor for morbidity and mortality in hemodialysis patients and its correlation to adequacy of dialysis. Council on Renal Nutrition National Research Question Collaborative Study Group. J Ren Nutr. 1999;9:2–8.
47. Wolfson M, Strong CJ, Minturn D, Gray DK, Kopple JD. Nutritional status and lymphocyte function in maintenance hemodialysis patients. Am J Clin Nutr. 1984;39:547–55.

48. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT. Predictors of poor outcome in chronic dialysis patients: The Netherlands Cooperative Study on the Adequacy of Dialysis. The NECOSAD Study Group. Am J Kidney Dis. 2000;35:69–79.
49. Marckmann P. Nutritional status and mortality of patients in regular dialysis therapy. J Intern Med. 1989;226:429–32.
50. Kalantar-Zadeh K, Ikizler TA. Let them eat during dialysis: an overlooked opportunity to improve outcomes in maintenance hemodialysis patients. J Ren Nutr. 2013;23(3):157–63.

Chapter 14
Acute Kidney Injury

Marcia A. Kalista-Richards

Key Points

This chapter will enable the reader to:

- Identify metabolic changes that occur with acute kidney injury (AKI).
- List the impact of renal replacement therapy options for the patient with AKI.
- Evaluate nutritional requirements for the patient with AKI.
- Define modalities used for the provision of specialized nutrition support for the patient with AKI.
- Identify considerations in the provision of nutrition support for the patient with AKI.

Keywords Acute kidney injury • Acute renal failure • Nutrient requirements • Parenteral nutrition • Enteral nutrition • Metabolism

Function of the Kidneys

The primary function of the kidneys is to excrete end products of metabolism, regulate electrolytes and mineral concentrations, and maintain fluid and electrolyte balance [1]. Other functions include urine production, dilution, and concentration; maintenance of blood pressure; concentration of extracellular and intracellular fluids; gluconeogenesis; maintenance of calcium phosphorus balance; and activation of vitamin and hormone synthesis [1].

The kidney has approximately one million nephrons, each of which is composed of several functional segments including the glomeruli, proximal tubules, distal tubules, loop of Henle, and collecting duct which drains into the renal pelvis. The nephron clears plasma of the end products of metabolism (urea, creatinine, uric acid, inorganic and organic acids). Electrolytes (sodium, potassium, chloride, bicarbonate), minerals (calcium, phosphorus, magnesium), and micronutrients (zinc, selenium) are filtered through the glomeruli and are reabsorbed or excreted based on needs. Small nutrients such as glucose, small protein, amino acids, and vitamins are filtered through the glomerulus and reabsorbed via active transport in the proximal tubule of the kidney [1].

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Acute Kidney Injury

Acute kidney injury (AKI) has replaced the term acute renal failure. AKI is characterized by an abrupt reduction of kidney function which results in failure to maintain electrolyte, acid–base, and fluid homeostasis. AKI may present with normal or abnormal urine outputs with abnormal levels being classified according to the following urine volumes: anuria (<100 mL/day), oliguria (100–400 mL/day), and nonoliguria (>400 mL/day) [2, 3]. AKI can occur as a result of multiple organ dysfunctions (MODS) or may be restricted to the kidney alone. Depending on the etiology, permanent damage can occur or if the underlying problem is corrected, the nephrons can recover. AKI can occur along with preexisting chronic kidney disease. Mortality is highly associated with the diagnosis [2, 4–7].

Categories of AKI include prerenal, renal (intrarenal and intrinsic), and postrenal. Decreased renal perfusion related to volume depletion or redistribution, burns, pancreatitis, peritonitis, hypoalbuminemia, and decreased cardiac output or embolus are related to the onset of prerenal AKI [2]. Early diagnosis and improving glomerular filtration and blood flow are beneficial in reversing prerenal AKI over a few days, unless the patient had underlying preexisting kidney disease or a considerable decline of baseline kidney function [8]. People taking numerous medications such as nonsteroidal anti-inflammatory drugs (NSAIDS) or angiotensin 2 receptor blockers (ARDS), the elderly, those with renal insufficiency, and liver disease are high-risk groups [4]. Nutritional requirements and the need for specialized nutrition support would be based on concurrent diagnosis and patient status.

An obstruction of the urine flow related to stricture, malignancy, inflammatory processes, vascular diseases, papillary necrosis, or intratubular crystals can result in postrenal AKI [2]. The goal is to correct the obstructive process and provide adequate fluids. Nutrition intervention would be directed towards any other comorbid factors associated with the development of postrenal AKI.

Intrarenal AKI (also referred to as intrinsic AKI) is associated with renal parenchyma damage. Prerenal AKI can trigger the problem, but a major cause of intrarenal AKI is acute tubular necrosis (ATN) and damage to the renal tubules as a result of ischemia or nephrotoxins [2]. Predisposing factors to ATN are renal ischemia from prolonged prerenal azotemia, nephrotoxins such as radiocontrast and chemotherapy agents, interstitial nephritis, infections, and pigmenturia [2]. Trauma, major surgery, hypotension, and sepsis are also associated with ATN [2, 8].

International experts representing intensive care and nephrology societies collaborated to establish the Acute Dialysis Quality Initiative (ADQI). ADQI developed a definition and staging system known as the RIFLE system, which classifies AKI into three severity categories based on increased serum creatinine and urine output, R = risk, I = injury, and F = failure, and two clinical categories, L = loss and E = end-stage renal disease [9, 10]. The Acute Kidney Injury Network (AKIN) later made modifications to the RIFLE categories and established a three-level staging system based on serum creatinine and urine output [10–12]. More recently international guidelines by Kidney Disease: Improving Global Outcomes (KDIGO) unified the ADQI and AKIN guidelines with the goal to establish a global definition and guidelines [10–12] (Tables 14.1 and 14.2).

AKI generally occurs concurrently with another disease state or critical illness. Treatment for AKI includes elimination of the causative factor, treatment of the disease process, volume repletion in hypovolemic patients, use of renal replacement therapy (RRT), and maintenance of nutrition status.

Over the years, nutrition support was considered to have a more negative effect on the patient including azotemia, fluid overload, and electrolyte disturbances. This posed challenges in providing adequate nutrition; therefore, nutrition intervention was often postponed so not to worsen the kidney failure in non-dialyzed patients and to delay the start of dialysis [7]. Given the catabolic nature of AKI and comorbidities, it is now recognized that nutrition supplementation should not be withheld. The development and utilization of RRT over the years has permitted the judicious use of nutrition support while limiting or removing previous concerns [7].

Table 14.1 AKI definition [11]

Increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h
Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days (or)
Urine volume of <0.5 mL/kg/h for 6 h

Source: http://www.kdigo.org. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International supplements. 2012;2:1–138

Table 14.2 Staging of AKI [11]

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline or Increase in serum creatinine to ≥4.0 mg/dL (≥353.65 μmol/L) or Initiation of renal replacement therapy or In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h or Anuria for ≥12 h

Source: http://www.kdigo.org. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International supplements. 2012;2:8–12

Renal Replacement Therapy

RRT options in AKI include continuous or intermittent therapy. Continuous renal replacement therapy (CRRT) also referred to as continuous extracorporeal blood therapy (CEBT) refers to outside the body purification therapy and is applied for 24 h per day. CRRT includes continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), and slow continuous ultrafiltration (SCUF) [8].

Intermittent therapy or hemodialysis treatments, also an outside the body purification therapy, is generally administered three times per week. Peritoneal dialysis therapy is another form of RRT which is performed daily using the peritoneal cavity; however, it is not routinely used for the critically ill patient with AKI. All modalities used as RRT have nutrition implications requiring consideration by the clinician in developing a nutrition support plan. Refer to the chapter on dialysis for additional information.

Nutrition Management of the AKI Patient

Nutrition Assessment

It is agreed that the diagnosis of AKI creates numerous metabolic derangements that can lead to deterioration of an individual's nutritional status; therefore, a referral should be made to the dietitian for evaluation [12]. No one tool or parameter can be used in the evaluation of the patients' nutritional status.

Available parameters require analysis of trends and an evaluation of how the underlying disease state will potentially skew results of such values. This is particularly important for the individual with AKI.

Fluid status of the patient will significantly impact in the evaluation of weight status. Fluid shifts resulting in weight gain due to volume excess related to oliguria or anuria is common with AKI. Use of RRT can result in significant reductions in a patient's overall body weight that correlates to fluid removal and not loss of muscle or fat mass. The "normal" and dry weight should be considered to prevent overfeeding. Body mass index records can help provide data regarding pre-illness weight status when available.

A physical assessment of the patient should be performed to check for signs of nutrient deficiencies and hydration status. A patient may present with lower extremity edema yet have muscle or fat wasting, evidenced by temporal indentation or prominence of the rib cage. Techniques for physical examination include inspection, palpation, percussion, and auscultation. A nutrition-focused physical exam can help identify skin lesions, wounds, or pressure ulcers, all of which need to be factored in the assessment and determination of nutritional requirements. Refer to chapter on the nutrition-focused physical exam.

Laboratory parameters are of value in the assessment process but they are not without limitations. Transport protein values in the intensive care unit (ICU) setting provide more relevance to the acute status rather than the overall protein level of the patient. Serum albumin is a prognostic indicator of overall disease-related outcome; however, profound hypoalbuminemia occurs in a critically ill patient. Serum albumin, thyroxine-binding prealbumin (PA), retinol-binding protein (RBP), and transferrin are negative acute phase reactants that will decrease as a result of the stress and inflammatory response related to injury and illness. C-reactive protein (CRP) and serum ferritin levels are positive acute phase reactants that inversely increase during this process. These important values are related to inflammatory metabolism which contributes to anorexia, lean body mass loss, risk for complications including infection, increased length of stay, and mortality [13]. Cytokines including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) may also be measured; however, interpretation of these results in the AKI patient have not been standardized.

Nitrogen balance evaluation can be used to help determine the degree of catabolism and establish protein goals for the critically ill patient. A creatinine clearance of >50 mL/min/1.78 m^2 is needed for accurate determination [14], therefore limiting the use of this parameter to the patient with oliguria and anuria. Nitrogen balance can be determined by calculating the urea nitrogen appearance (UNA) or the protein catabolic rate (PCR) in patients with AKI and on CRRT [5, 14–16]. However, it also has limitations due to protein fluctuations and catabolism that can result in errors with interpretation [14] (Table 14.3).

Blood urea nitrogen values reflect rate of urea synthesis by the liver and excreted by the kidney, and serum creatinine reflects the nitrogenous waste product of muscle metabolism and is proportional to the body's muscle mass. Both values are elevated in AKI [17].

Electrolyte balance is affected by AKI, which requires careful evaluation. Metabolic acidosis can result in hyperkalemia, whereas hyponatremia occurs with overhydration. Changes in glomerular function, medications, exogenous sources of electrolytes, quality of urine production, nutrition support, and RRT will each alter serum values.

Oral Intake and Supplements

A patient who is not critically ill with AKI can receive an oral diet; however, many factors impact an individual's ability to consume adequate oral nourishment such as taste changes, gastrointestinal (GI) disorders, and conditions related to comorbid disease. The clinician needs to be skillful in optimizing a balance between dietary needs and restrictions through the individualization of the nutrient

Table 14.3 Urea nitrogen appearance and protein catabolic rate equations [15, 16]

Urea nitrogen appearance, g/day = UUN + [(BUN2 − BUN1) × 0.6 × BW1] + [BW2 − BW1 × BUN2]
Where net protein breakdown = UNA × 6.25
BUN1 = initial concentration of BUN, postdialysis (g/L)
BUN2 = final concentration of BUN, predialysis (g/L)
BW1 = postdialysis weight (kg)
BW2 = predialysis weight (kg)
PCR, g/day = UNA × 6.25

prescription for the person with AKI. Goals of the nutrition treatment plan should include meeting the demands of catabolic conditions including comorbid states to limit any unnecessary restrictions and to prevent worsening of laboratory values and overall status. When suboptimal intake is noted, nutrition supplements should be added.

Specialized Nutrition Support

For the ICU patient, nutrition support using enteral or parenteral nutrition is warranted to meet the nutritional demands and it attempts to mitigate the metabolic and immunologic disturbances and improve outcomes. Malnutrition has been identified as a predictor of hospital mortality for AKI patients independent of complications and comorbidities [18]. Enteral nutrition support is the preferred route of feeding for these patients provided GI function is adequate, as this method has been associated with fewer infectious and metabolic complications in comparison to parenteral nutrition (PN) [12, 19–22]. An individual's clinical condition, the presence and severity of malnutrition, the degree of food inadequacy, and time period (days to weeks) that oral intake is less than optimal will influence when enteral tube feeding should be initiated. Guidelines from the Society of Critical Care Medicine (SCCM) and American Society of Parenteral and Enteral Nutrition (ASPEN) suggest that enteral nutrition is considered safe and practical and should be started within the first 24–48 h for the critically ill patient after admission once the patient is hemodynamically stable [19]. Patients who require high-dose catecholamine agents and those who are receiving blood products or large fluid volumes during resuscitation periods require careful attention [19]. For those individuals considered unstable based on factors including hypotension, risk for gastric dysmotility, or who are septic, enteral feedings should be withheld to avoid ischemia or reperfusion injury involving the intestinal microcirculation [19]. Complication risk or injury must always be weighed against potential benefits of feeding.

The route of enteral support can either be gastric or into the small bowel based on the patients' GI anatomy, current disease state, and motility function. Gastric feedings rely on adequate GI function without problems of delayed gastric emptying, obstruction, or fistula [22]. For individuals with gastroparesis, gastric reflux conditions, gastric outlet obstruction, pancreatitis, or risk of aspiration, small bowel feedings should be considered [22]. Critically ill patients who are being fed into the small bowel and who require simultaneous gastric decompression can utilize a dual-lumen gastrojejunal tube [22].

Tolerance to tube feedings is assessed by presence of abdominal distention, rigidity or firmness, absence of stools, or vomiting [22]. According to SCCM/ASPEN, a standard enteral formula can be used for patients with AKI unless significant electrolyte imbalances and fluid status require specialty formulas [19].

Tube Feeding Formulas

Formulas used for tube feeding range from those that require complete digestion to predigested formulas developed for individuals with digestive disorders, such as malabsorption or short gut syndrome. These formulas provide 1–1.2 kcal/mL to more concentrated products of 1.5–2 kcal/mL. Products have also been developed to meet specialty needs of individuals with disease-specific disorders such as liver or kidney disease. As products evolve and outcome-based research advances, it is necessary for the clinician to appropriately match the needs of the patient with the best product available in a safe and cost-effective manner.

Enteral products developed specifically for renal patients on dialysis require digestion and are lower in sodium, potassium, and phosphorus with a concentrated source of calories and protein. Vitamin and mineral contents are designed to match the needs of the dialysis patient with added amounts of folic acid and pyridoxine and limited amounts of vitamins C and A. The Dietary Reference Intakes (DRIs) for most nutrients are met using 1 L of formula. Enteral formulas contain vitamin K and are a consideration for patients receiving warfarin. The dose may need to be adjusted and coagulation protocols monitored with tube feedings, any oral intake, or transition to oral intake [23].

Renal products may need to be used cautiously or replaced with nonrenal specific products when an individual has been undernourished and is at risk for refeeding syndrome. Individuals with a history of poor intakes, chronic alcoholics, and malnourished patients, particularly those with marasmus or obese patients with significant weight loss, are at risk for refeeding syndrome [24–26]. This syndrome can be defined as severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing aggressive refeeding, whether enterally or parenterally [25]. Hypokalemia, hypophosphatemia, hypomagnesemia, abnormal glucose metabolism, fluid-balance abnormalities, and thiamine deficiency can occur. Prevention of refeeding syndrome includes the slow administration of nutrients at a caloric level below maintenance needs, with careful attention to phosphorus, potassium, and magnesium as it should be anticipated that these values drop [24, 25, 27]. Low serum potassium, magnesium, or phosphorus is generally not expected in patients with kidney disease; therefore, it is of particular importance to be aware of the problems related to refeeding syndrome. The lower potassium, phosphorus, and magnesium content of renal formulas may actually precipitate a serious decline in serum electrolytes once nutrition support is initiated. It is advantageous if the clinician is familiar with the individual's previous dietary intake before the start of nutrition support in order to select the most appropriate product and to manage the patient wisely. If refeeding syndrome characteristics are present (low magnesium, potassium, and phosphorus), then a concentrated nonrenal specific formula should be used rather than a renal product that is low in potassium, magnesium, and phosphorus. Once serum values normalize, the need for a renal specific formula can be reassessed with selection of the most appropriate enteral product to meet the patient's needs. Other nonrenal concentrated formulas that provide 1.5–2 kcal/mL may also be used depending on the individual's status, RRT, fluid, and laboratory results. Modular protein sources are available and can be used to tailor individual needs.

Over the years, closed enteral systems have become more widely used in the hospitalized setting. These products contain sterile tube feeding, are ready-to-hang for up to 24–72 h, have been associated with less contamination, and require less nursing intervention time [28]. The closed system solutions generally are 1–1.5 L of volume and are concentrated formulas (i.e., 2 kcal/mL).

Tube Feeding Management

The management of GI complications including diarrhea, malabsorption, nausea, and vomiting, along with mechanical complications such as tube occlusions, is similar to other individuals who require enteral support. The AKI patient requires further monitoring of fluid status, electrolyte management,

and GI status. The amount of free water flushes with feedings or with the administration of medications needs to be strictly limited when urine output is reduced.

Tube occlusions are a potential problem particularly when the tube is used for the administration of medications. In general, feeding tubes should be flushed routinely with about 20–30 mL of water every 4 h during continuous feeding and before and after each intermittent or bolus feedings and medication administration [27, 29]. Flushes contribute extra water and can be a challenge for the renal patient. Calorically dense and fiber-containing products are more viscous, and formulas that are administered at very low rates can potentially aggravate the problem, since the formula may not flow easily through the tube [27]. In addition to water, carbonated beverages such as cola and cranberry juice have been used to flush feeding tubes; however, these products are not recommended [27] and can negatively change serum potassium and phosphorus levels. Cranberry juice has also been reported to interfere with warfarin metabolism and therefore may predispose the patient to coagulation problems [30]. Liquid irrigants, enzyme solutions, and mechanical devices have also been used to unclog a tube [27]. Implementation of practices that would prevent clogging is recommended.

Fluid restriction is determined by whether the patient is anuric, oliguric, or has some residual renal function; the ability of the type of RRT to remove unwanted fluid; and other comorbid factors ranging from heart failure to the presence of an ileostomy. Strict fluid restrictions would require the use of 1.8–2 kcal/mL formula; serum potassium and phosphorus values would dictate which enteral product would best meet the needs of the patient. Acute or chronic diarrhea or vomiting can decrease serum potassium levels, which need to be factored into the decision regarding product selection.

Gastroparesis is common in individuals with diabetes and is associated with dialytic procedures, elevated BUN values, and hyperglycemia thereby necessitating close monitoring of the tolerance to enteral tube feedings [27]. Placement of the tube in the stomach versus small bowel will also affect GI tolerance. Tube feeding volume should be assessed and whether promotility agents such as metoclopramide or erythromycin are being used to promote gastric emptying [27]. The patient's position during dialysis should be considered to determine whether the tube feeding can be given. For example, if a patient needs to be in a supine position because of hypotensive episodes during RRT, the feeding needs to be held in order to prevent the risk of aspiration. A semirecumbent position (>30° elevation) is recommended to prevent aspiration for individuals requiring tube feeding [27].

AKI may require medications with noted side effects such as constipation, diarrhea, nausea, or vomiting. Tube feedings have been associated with similar side effects; therefore, it is important to identify the etiology of the symptoms and to treat the problem based on the actual cause rather than an assumption. Prokinetic agents and those medications containing sorbitol, as well as *Clostridium difficile* colitis, are also common causes of diarrhea [29].

Metabolic complications can occur in individuals on tube feedings; therefore, the health care team must assess each laboratory value independently to determine potential reasons for increased or decreased values. Baseline metabolic and nutrition assessment parameters should be obtained with the initiation of enteral feedings, and follow-up parameters should be based on the individual's needs and clinical condition.

Guidelines for Administration

Initiation of enteral feedings is generally 25–50 mL/h or may be started at goal rate [31] based on patient tolerance and status. It is important to be attentive to the caloric density of the product selected. When a 2 kcal/mL formula is used, nutrient needs can be met at lower doses than if a 1.2 kcal/mL formula is used. A 2 kcal/mL formula at 50 mL/h equals 1,200 mL or 2,400 kcal and 85 g of protein, whereas a standard 1.2 kcal/mL formula at 80 mL/h equals 1,920 mL or 2,304 kcal and 106 g of protein. This is a difference of 720 mL.

Parenteral Nutrition Support

Use of Parenteral Nutrition (PN)

Parenteral nutrition is the administration of nutrients using an intravenous (IV) method intended for individuals who do not have a functional GI tract or in situations where administration of nutrients using the GI tract was not tolerated or could not be safely used. Parenteral nutrition can be administered either centrally or peripherally; however, in the patient with AKI, a central access would be used.

PN solutions may be provided as a "2-in-1" solution which the carbohydrate, protein, vitamins, electrolytes, minerals, additives, and sterile water are combined in one solution. Intravenous fat emulsions (IVFEs) can be administered separately from the "2-in-1" solution. When IVFE are added to the PN solution it forms a total nutrient admixture (TNA) or a "3-in-1" solution.

Intradialytic Parenteral Nutrition Support

Patients with ESRD receiving hemodialysis can receive nutritional support while on dialysis using the direct blood access used for the dialysis treatments. This method of nutritional support allows for the infusion of amino acids, dextrose, IVFE, and additives via the venous side of the extracorporeal circuit during dialysis.

This method of support has been used primarily for patients who are considered malnourished with inadequate oral intake of food and supplements. Overall goals of therapy include provision of added nutrients without causing volume overload. The ultrafiltration of dialysis can be used to control fluid volume and the patient weight status.

Advantages to the intradialytic parenteral nutrition support (IDPN) infusion include the ability to administer hypertonic solutions without dangers of phlebitis and ease of infusion using the available access. Calorie, protein, and fat intake is dependent on formula designed; calories up to 1,600 can be infused using a combination of 70 % dextrose, 15 % amino acids, and 20 % lipids.

A disadvantage to the system includes the inability to consistently meet patient total nutritional requirements as the nutrition is only given during dialysis treatments which generally is three times per week. Thus, IDPN is considered more supplemental rather than total nutrition limiting reimbursement and overall favorable outcomes. IDPN is also being provided to individuals with functional gastrointestinal tract, whereas any parenteral nutrition is most often recommended in the absence of GI function. Labs, weight status, and tolerance issues need to be monitored closely as with total parenteral nutrition with added consideration being given to shortened infusion times based on number of hours the patient is on hemodialysis. Glycemic control often requires insulin therapy during infusion to prevent hyperglycemia, and postdialysis hypoglycemia may require tapering of formula in addition to a carbohydrate containing snack posttreatment [32].

Some studies have supported benefits including improved protein synthesis, energy metabolism, serum albumin levels, and weight gain with those patients who are more malnourished with greater improvement of albumin values [32]. IDPN is not considered for routine use in the hemodialysis patient.

Intraperitoneal nutrition (IPN) which uses a peritoneal dialysate solution containing amino acids has been used in end-stage renal patients on peritoneal dialysis [33]. Although this allows for the infusion of amino acids in one bag of dialysate, limitations include the inability to provide complete nutrition adequacy therefore IPN is considered supplemental placing severe limits on reimbursement.

Nutrient Substrates

Protein

Protein is provided in the PN formula to provide a source of nitrogen. Crystalline amino acid (AA) is the source of protein with commercial solutions being available in concentrations of 3.5–20 %. The concentration used will be based on an individual's protein requirements, fluid allowance, and availability in the formulary. The AKI patient with increased protein requirements and limited fluid allowance generally would use the more concentrated solutions such as 10, 15, or 20 %. Standard amino acid (AA) solutions include a balance of essential amino acids (EAA) and nonessential amino acids (NEAA) and are appropriate for the AKI patient. There is insufficient evidence to support the use of only EAA solutions in the treatment of AKI [20]. EAA use alone does not offer benefits and in fact has been noted to be potentially harmful for patients due to hyperammonemia and metabolic encephalopathy [29]. NEAA including ornithine, citrulline, and arginine are needed to enable detoxification of ammonia via the urea cycle [29].

Carbohydrate

Carbohydrates provide a source of calories and are supplied as an anhydrous dextrose monohydrate in sterile water. It is available in concentrations ranging from 5 to 70 % and provides 3.4 kcal/g of dextrose. Dextrose supports the energy needs of the individual but requires careful consideration in achieving good glycemic control and prevents overfeeding by minimizing the carbohydrate load, particularly for individuals who require ventilatory support. Although exact carbohydrate requirements have not been clearly identified, a minimum of 50 g/day is required to avoid ketone production [34]. Suggested carbohydrate intake for critically ill patients is ≤4 mg/kg/min/day [35]. Fluid limits and the targeted plasma glucose of 110–149 mg/dL (6.1–8.3 mmol/L) [36] impact selection of dextrose and volume used. The more concentrated 40–70 % dextrose is usually selected based on allowed volume and needs.

Fat

Lipids provide a source of essential fatty acids and a concentrated source of calories. Long-chain fatty acid emulsions are made from either soybean oil or a combination of safflower and soybean oils. IVFE are available as either 10, 20, or 30 % solutions; the 30 % solution is reserved for TNA. IVFE contains egg phospholipids as an emulsifier with glycerol to adjust the osmolarity; therefore, they are contraindicated in individuals who have an egg allergy or potential soy allergy. IVFE contributes to the phosphorus and vitamin K intake.

Lipids should be limited to 1 g/kg/day in the critically ill patient [37]. To prevent essential fatty acid deficiency, provide IVFE as 2–4 % of total energy intake with 1–2 % linoleic acid [38]. This can be accomplished by giving 250 mL 20 % IVFE administered separately over 8–10 h, twice weekly in a 2-in-1 PN formulation [39]. Triglycerides should be monitored to assess lipid clearance; desired values are less than 400 mg/dL in adult patients [29]. Overfeeding or rapid infusion of IVFE can cause hypertriglyceridemia, leading to altered immune and pulmonary response, and increased risk of pancreatitis [39].

Other lipid sources such as propofol contribute fat calories and should be calculated in the individual's overall caloric and lipid intake. Propofol provides 1.1 kcal/mL and 0.1 g fat/mL.

Parenteral Additives

Fluid and Electrolytes

Impaired kidney function impacts the kidney's ability to maintain normal fluid and electrolyte balance. Daily fluid intake allowance usually corresponds to fluid output. If urine output is less than 1 L/day, fluid intake of 1–1.5 L/day is recommended [40]. With patients who are oliguric (i.e., urine output declines to ≤400 mL/day) or anuric (urine output <100 mL/day), tighter fluid management is needed.

Electrolyte requirements have been established for individuals with normal kidney function along with suggested values for individuals with kidney failure [41]. Body weight, nutritional status, residual kidney function, comorbid diseases, and medications can influence both fluid and electrolyte status. Serum potassium, magnesium, and phosphorus levels will likely increase with poor kidney function due to impaired excretion. Management of electrolytes requires careful monitoring of laboratory values to minimize the potential risk of complications and to meet the patient's needs.

Sodium and potassium may be available as chloride, acetate, or phosphate; calcium gluconate and magnesium sulfate are preferred [42]. Parenteral AA solutions may include small amounts of electrolytes and acetate, which need to be calculated into the total solution. Acetate, a bicarbonate precursor, is used for PN rather than bicarbonate itself because of potential pH changes and the risk of insoluble precipitation with calcium and magnesium [42]. Acetate can be metabolized to bicarbonate by the liver. Individuals with acidosis may be treated with the addition of acetate; however, the amount will be dependent on sodium and potassium additives. Bicarbonate may also be used to treat acidosis but would require access using a separate line. The amount of calcium and phosphorus requires careful monitoring as excess amounts added to the PN solution can result in insoluble precipitation causing crystal deposition that may lead to death [42].

Vitamins and Trace Minerals

The American Medical Association (AMA) Nutrition Advisory Committee has made recommendations for the inclusion of multivitamins (MVI) and trace elements (TE) with PN use [29]. Commercially available PN MVI adult preparations contain 12 or 13 of the known vitamins; vitamin K has been added to create MVI 13, which contains 150 μg vitamin K. IVFE also contains vitamin K due to soybean or safflower oils of which it is made of. Daily vitamin K requirements for adult PN is 150 μg daily [26]; however, use of coagulation therapy needs to be considered with vitamin K use.

Parenteral MVI contains 1 mg vitamin A, whereas oral vitamins used for dialysis patients do not contain vitamin A. Total vitamin A intake, whether oral or parenteral, should be monitored, particularly in individuals who require long-term PN support as toxicity may develop. Adult MVI preparations contain 200 mg daily vitamin C [42], whereas an oral renal vitamin contains 60–100 mg [43].

Daily TE supplementation for adult PN formulations have also been established [29]; however, exact requirements for AKI patients have not. Trace elements may be withheld, given several times per week, administered in a half dose, or selected trace elements ordered based on route of excretion, risk for toxicity, and needs. A combination of clinical judgment, assessment of symptoms, and evaluation of laboratory data is needed when deciding to administer trace elements and amounts. Ongoing research and reporting of outcomes and observations which helps strengthen evidence-based guidelines are needed in this area.

Initiation and Monitoring of Parenteral Nutrition Support

Parenteral nutrition orders should consider the patient's fluid, electrolyte, and acid–base balance status; glycemic control; access availability; and risk for refeeding syndrome when starting and monitoring PN. The total volume can be delivered safely; however, hypervolemic patients with fluid limits are likely to be restricted to 1–1.5 L/day. Achievement of RRT goals, urinary output, and overall hydration status will determine fluid allowances when starting PN and identifying a safe total volume allowance. Initial adult carbohydrate dose is usually 150–200 g/day; those with diabetes mellitus or hyperglycemia, 100–150 g/day [29]. PN can be increased to meet nutritional requirements to achieve goals in 72–96 h [35] or as best tolerated by the patient.

Correction of electrolyte disturbances is recommended prior to starting PN. Refeeding syndrome can be avoided by limiting the amount of carbohydrate in feedings [29]. Refeeding syndrome can cause laboratory abnormalities; however, RRT may correct some of these abnormalities and should be monitored as the nutrition support formula is developed. For example, if an individual is at risk for refeeding syndrome (which can lower serum potassium), the same individual may have hyperkalemia because of kidney failure; therefore, the dialysate solution can be adjusted to a low potassium bath. Caution should be taken that the potassium does not fall to an undesirable level with the initiation of PN. Thus, it is important to assess the whole picture.

Protein can be administered at full dose without dose reduction. IVFE may be started at full dose provided serum triglyceride levels are within normal range [42].

Acid–base abnormalities may be a result of the individual's underlying condition, although nutrition support can also influence the values as well. Manipulation of the acetate and chloride content of the PN may aid in the correction of such abnormalities.

Discontinuing Parenteral Nutrition

Hypoglycemia can occur if the solution is discontinued abruptly in patients who are not receiving other sources of nutrition. Prevention strategies include tapering the PN solution, hanging 10 % dextrose at the same rate as the PN, monitoring serum glucose levels when insulin is being given, and assessing other sources of nutrition (IV, tube feedings, or oral intake).

Monitoring Clinical and Laboratory Parameters

General guidelines for monitoring clinical and laboratory parameters in patients receiving PN include obtaining a baseline comprehensive metabolic panel, daily weights, intakes and output, daily laboratory values until stable then weekly thereafter, and serum glucose three times per day until stable. Serum triglyceride levels should be checked prior to the infusion of lipids. Liver enzymes, bilirubin, and a complete blood count (CBC) should be checked when PN is initiated, then 2–3 times per week until stable, then weekly [41]. Frequency of monitoring will be based on acuity and results. Less frequent monitoring can be used as stabilization occurs.

Nutritional Requirements in AKI

It has been well established that AKI presents protein calorie malnutrition and an inflammatory and pro-oxidative state with all of its known complications [11, 21, 44–47]. Nutrition support should be aimed towards attenuating and counteracting the negative nitrogen balance and loss of lean body mass

that occurs in most patients with critical illness. The goals of nutrition support for the AKI patient are similar if not the same as for other ICU patients with normal renal function. Obviously, renal impairment adds challenges while attempting to provide nutritional adequacy, prevent malnutrition, support immune function, accelerate recovery, and prevent mortality.

Metabolic derangements have been observed in the AKI population. AKI has been found to increase metabolism in some studies; however, some clinical conditions of AKI are not associated with increased catabolism [48, 49]. The underlying comorbid conditions and degree of critical illness will impact on the overall level of catabolism of the patient. Negative nitrogen balance also results from uremic toxins, endocrine factors, metabolic acidosis, inadequate protein intake, and RRT loses [48–50].

Impaired lipolysis causes plasma lipid changes with noted decreased production of lipoprotein lipase, especially with acidosis and hepatic triglyceride lipase reduction [48–50]. This is of particular importance when PN containing IVFE or lipid-based medication use is required. The triglyceride content of lipoproteins including very-low-density and low-density lipoprotein levels is increased with AKI and cholesterol, and high-density lipoproteins are decreased [48].

Insulin resistance occurs with AKI leading to an imbalance of glycemic parameters. Hyperglycemia complications include risk of infection, poor wound healing, and mortality [51]. Tight glycemic control is recommended with avoidance of swings to hypoglycemia [36].

Energy Requirements

The energy needs for critically ill patients, including those with AKI, will depend much on the nutritional status prior to kidney injury, acute and chronic comorbid conditions, and the severity of the underlying disease, more so than on the syndrome of renal injury itself [21, 52–54]. When available, indirect calorimetry should be used to determine energy requirements [20]. The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines on Enteral Nutrition in Renal Failure and KDIGO recommend an energy intake of 20–30 kcal/kg/day with AKI [21]. ESPEN adds that calories should be adapted according to the individual's needs in cases of obesity or underweight status [21]. When calorie levels of 40 kcal/kg/day were used in comparison to 30 kcal/kg/day combined with 1.5 g/protein/kg/day, the higher calorie infusion did not show differences in positive nitrogen balance but did result in elevated glucose and triglyceride levels along with insulin needs [44].

Protein Requirements

Non-catabolic, nonoliguric, milder cases of AKI that require RRT and are likely to regain renal function within a short period of time can generally receive up to 0.8 g/kg/day of protein during this time provided adequate calories are provided (30 kcal/kg/day) [20, 48, 52]. KDIGO also supports administering 0.8–1.0 g/kg/day of protein in non-catabolic AKI patients who are not in need of dialysis [11]. Consideration must be given to concurrent events that may increase needs based on protein breakdown or losses. Protein restriction with the intent to prevent or delay initiation of RRT should be avoided [11].

Losses of protein and amino acids via the extracorporeal circulation of RRT are approximately 0.2 g amino acid per liter of ultrafiltrate or 10–15 g amino acid per day [21, 50, 52]. An added 5–10 g/day of protein is needed per day above the 1.5 g/kg/day for AKI to replace losses when treatments are daily or when high flux filters and/or high-efficiency modalities including CRRT and sustained low-efficiency dialysis (SLED) are used [21, 50, 52].

KDIGO recommendations include 1.0–1.5 g/kg/day protein in AKI patients on RRT, and up to a maximum of 1.7 g/kg/day in patients on CRRT and in hypercatabolic states [11]. ASPEN/SCCM recommends an increased protein load of 1.5–2 g/kg/day of protein up to a maximum of 2.5 g/kg/day in order to achieve positive nitrogen balance with CRRT treatments [19, 20, 55, 56]. Other studies have suggested that protein intake during CRRT should range between 1.8 and 2.5 g/kg/day [20]. The patient's catabolic rate, renal function, and dialysis losses should be evaluated to best determine protein needs in order to promote positive nitrogen balance [20].

Fat Requirements

Lipid requirements parallel those that avoid development of EFAD in at risk patients receiving PN and to avoid overfeeding. Lipids are recommended at 1 g/kg/day or 35–30 % of total energy in the critically ill patient and should not exceed 2.5 g/kg/day in parenteral solutions [29, 37]. Use of propofol or amphotericin B housed in a lipid emulsion needs to be factored into the lipid dose provided.

Vitamins and Trace Elements

There are numerous consequences of AKI including disruption of both vitamin and trace element balance. Various recommendations have been made for fat soluble vitamins. Plasma levels of vitamins A and E were found to be low in experimental AKI [11, 44] and the kidney's inability to degrade RBP may lead to increased retinol levels [49]. Oral renal MVI do not contain vitamin A; however, adult multivitamin products contain 1 mg or 3,300 IU of vitamin A as retinol. Current evidence does not support added supplementation of vitamin A or E and retinol may require limitations [57]. Vitamin K levels may be normal or elevated [11] and vitamin D3 activation is impaired in AKI [21, 48, 52]. Water soluble vitamins including C, thiamine, and folic acid may be lower due to extracorporeal excretion [49]; however, vitamin C should be limited to 100 mg with IHD and should not exceed 200 mg with CRRT [46, 48, 58].

Numerous factors impact TE needs in the AKI patient. The route of excretion, use of solutions containing contaminant or TE sources, TE in PN solution, GI excretory or protein bound losses, conditions that require elimination due to potential of toxicity, illness-related deficiencies, and the use of RRT should be evaluated. Both TE and vitamins can be altered with the AKI inflammatory activity. Another concern is that although it is known that AKI patients are at risk for depletion, exact requirements have not been established [50].

PN commonly contains zinc, copper, chromium, manganese, and selenium. In cases of cholestasis, copper and manganese are reduced or deleted due to excretion route and toxicity potential. Fluids used in the CRRT may have trace element contamination. The CRRT fluid does not have an appreciable amount of selenium or copper, but losses occur in the effluent [59, 60]. If the copper has been removed due to cholestasis and the patient requires continued RRT, deficiency may be of concern [57]. Zinc was found in effluent fluid in CVVHDF; however, there was positive zinc balance due to the zinc content of replacement fluid solutions and PN and as a contaminant in anticoagulant solutions [50]. Patients who have concurrent GI problems such as diarrhea or colocutaneous fistula may require zinc supplementation based on such losses. Selenium levels have been noted to be low in patients with AKI [61].

Fluid, Electrolytes, and Mineral Needs

The amount of fluid that can be excreted by the injured kidney and the selection of RRT dictate the daily fluid intake. Intermittent dialysis generally necessitates fluid limits, whereas the use of continuous therapy allows for a full nutrition support prescription to be given.

AKI causes electrolyte imbalances that can be related to the underlying disease, hypermetabolic conditions, medications, nutritional refeeding issues, kidney failure, RRT use as well as the use of specialized nutritional support. Standard daily electrolyte requirements have been published for adult EN and PN formulations [29].

Hyperkalemia is common with AKI with acidosis and reduced kidney clearance; however, gastrointestinal disease can cause losses. In the absence of RRT, potassium would need to be restricted. AKI can cause hypocalcemia related to hyperphosphatemia, hypoalbuminemia, losses with CRRT, and citrate anticoagulation [62]. The renal replacement prescription can be used to manage potassium and calcium levels. Hyperphosphatemia seen in AKI can be treated using phosphorus binders and restricting intake. Hypermagnesemia occurs with AKI due to impaired excretion requiring limits of intake; however, the use of CRRT typically causes loss of phosphorus and magnesium requiring supplementation [14]. Recommendations for electrolyte and micronutrient requirements are based on serum concentrations [20].

Summary

Nutrition support in the patient with AKI is usually required to prevent deterioration of nutritional status during the catabolic events of multiple organ disease syndrome. There are alterations in the metabolism of protein, carbohydrate, and fat and changes in fluid and electrolyte balance. A thorough nutritional assessment needs to be performed with the development of a nutrition care plan based on the individual's needs and limitations of AKI. Specialized nutrition support requires skillful monitoring with ongoing evaluation of the patient's status to avoid complications.

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References

1. Biggs JP, Kriz W, Schnermann JB. Overview of kidney function and structure. In: Greenberg A, editor. Primer on kidney disease. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 2–19.
2. Holley JL. Clinical approach to the diagnosis of acute renal failure. In: Greenberg A, editor. Primer on kidney disease. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 287–92.
3. Peacock PR, Sinert R. Renal failure, acute. Emedicine from WebMD.
4. Campbell D. How acute renal failure puts the brakes on kidney function. Nursing. 2003;33:59–64.
5. Goldstein-Fuchs DJ, McQuiston B. Renal failure. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia, PA: Saunders; 2003. p. 460–83.
6. Chertow GM, Soroko SH, Paganin EP, Cho KC, Himmelfarb J, Ikizler TA, et al. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int. 2006;70:1120–6.
7. Star RA. Treatment of acute renal failure. Kidney Int. 1998;54(6):1817–31.
8. Mindell JA, Chertow GM. A practical approach to acute renal failure. Med Clin North Am. 1997;81(3):731–48.
9. Bellamo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. ADQI workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) group. Crit Care. 2004;8(4):R204–12.

10. Kidney Disease: Improving Global Outcomes. Clinical practice guidelines on acute kidney injury. 2011. www.kdigo.org
11. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:8–16. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf
12. Lewington A, Kanagasundaram S. Acute kidney injury. The Renal Association. 2011. www.renal.org/Clinical/Guidelines/Section/AcuteKidneyInjury.aspx
13. Russel MK, Mueller C. Nutrition screening and assessment. In: Gottschlich MM, editor. The A.S.P.E.N. nutrition support core curriculum: a case-based approach-the adult patient. Silver Spring, MD: A.S.P.E.N.; 2007. p. 163–86.
14. Gervasio JM, Garmon WP, Holowaty M. Nutrition support in acute kidney injury. Nutr Clin Pract. 2011; 26:374–80.
15. Blumenkrantz MJ, Kopple JD, Gutman RA, Chan YK, Barbour GL, Roberts C, et al. Methods for assessing nutritional status of patients with renal failure. Am J Clin Nutr. 1980;3:1567–85.
16. Druml W. Nutrition support in acute renal failure. In: Mitch WE, Klahr S, editors. Handbook of nutrition and the kidney. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 191–213.
17. Traub S. The kidneys. In: Traub SL, editor. Basic skills in interpreting laboratory data. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacist; 1996. p. 131–57.
18. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortella G, Borghetti A. Prevalence and clinical outcome associated with pre-existing malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol. 1999;10:581–93.
19. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G; A.S.P.E.N. Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–313.
20. Brown RO, Compher C; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support in adult acute and chronic renal failure. JPEN J Parenter Enteral Nutr. 2010;34(4):366–77.
21. Cano N, Fiaccadori E, Tesinski P, Toigo G, Druml W; DGEM, Kuhlmann M, Mann H, Horl WH. ESPEN guidelines on enteral nutrition: adult renal failure. Clin Nutr. 2006;25:295–310.
22. A.S.P.E.N. enteral access devices: selection, insertion, maintenance, and complications. In: Boullata J, Nieman Carney L, Guenter P, editors. Enteral nutrition handbook. The American Society for Parenteral and Enteral Nutrition; 2010. p. 159–203.
23. Singh H, Duerksen DR. Vitamin K and nutrition support. Nutr Clin Pract. 2003;18:359–65.
24. Beyer PL. Complications of enteral nutrition. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia: Saunders; 2003. p. 215–26.
25. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.
26. Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28:S39–70.
27. Lord L, Harrington M. Enteral nutrition implementation and management. In: Merritt R, editor. A.S.P.E.N. nutrition support practice manual. 2nd ed. Silver Spring, MD: A.S.P.E.N.; 2006. p. 76–89.
28. Vanek WV. Closed versus open enteral delivery systems: a quality improvement study. Nutr Clin Pract. 2000;15:234–43.
29. A.S.P.E.N. Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr. 2002;26 Suppl 1:1SA–38.
30. Nyffeler MS, Frankel E, Hayes E, et al. In: Merritt R, editor. A.S.P.E.N. nutrition support practice manual. 2nd ed. Silver Spring, MD: A.S.P.E.N.; 2006. p. 118–36.
31. Heyland DK, Cahill NE, Dhaliwal R, Wang M, Day AG, Alenzi A, Aris F, et al. Enhanced protein—energy provision via the enteral route in critically ill patients: a single center feasibility trial to the PEP uP protocol. Crit Care. 2010;14(2):R78. http://ccforum.com/content.14/2/R78
32. Wolk R, Foulks C. Renal disease. In: Mueller CM, editor. The A.S.P.E.N. adult nutrition support core curriculum. 2nd ed. Silver Spring, MD: The American Society of Parenteral and Enteral Nutrition; 2012. p. 491–510.
33. Wilkens KG, Juneja V, Shanaman E. Medical nutrition therapy for renal disorders. In: Mahan LK, Escott-Stump S, Raymond J, editors. Krause's food and the nutrition care process. 13th ed. St Louis, MO: Elsevier. p. 799–831.
34. Ling P, McCowen KC. Carbohydrates. In: Gottschlich MM, editor. The A.S.P.E.N. nutrition support core curriculum: a case-based approach-the adult patient. Silver Spring, MD: A.S.P.E.N.; 2007. p. 33–47.
35. A.S. P.E.N. how to write parenteral nutrition orders. In: Canada T, Grill C, Guenter P, editors. A.S.P.E.N. parenteral nutrition handbook; 2009. p. 163–85.
36. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:43–6.

37. Seidner DL, Mascioli EA, Istfan NW, Porter KA, Selleck K, Blackburn GL, et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. JPEN J Parenter Enteral Nutr. 1989;13:614–9.
38. Driscoll DF. Lipid injectable emulsions. Nutr Clin Pract. 2006;21:381–6.
39. A.S.P.E.N. complications of parenteral nutrition. In: Canada T, Grill C, Guenter P, editors. A.S.P.E.N. parenteral nutrition handbook; 2009. p. 197–234.
40. Fuhrman MP. Parenteral nutrition in kidney disease. In: Byham-Gray L, Wiesen K, editors. Clinical guide to nutrition in kidney disease. 1st ed. Chicago: The American Dietetic Association; 2004. p. 159–74.
41. Skipper A. Parenteral nutrition. In: Matarese LE, Gottschlich MM, editors. Contemporary nutrition support practice: a clinical guide. 2nd ed. Philadelphia: Saunders; 2003. p. 227–41.
42. A.S.P.E.N. parenteral nutrition formulations. In: Canada T, Grill C, Guenter P, editors. A.S.P.E.N. parenteral nutrition handbook; 2009. p. 129–61.
43. National Kidney Foundation. Nutrient prescription. In: McCann L, editor. Pocket guide to nutrition assessment of the patient with chronic kidney disease. 4th ed. New York: National Kidney Foundation; 2009. p. 4-1–4-18.
44. Fiaccadori E, Maggiore U, Rotelli C, Giacosa R, Picett E, Parenti E, et al. Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study. Nephrol Dial Transplant. 2005;20:1976–80.
45. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
46. Fiaccadori E, Parenti E, Maggiore U. Nutrition support in acute kidney injury. J Nephrol. 2008;21:645–56.
47. Heng AE, Cano NJM. Nutritional problems in adult patients with stage 5 chronic kidney disease on dialysis (both haemodialysis and peritoneal dialysis). NDT Plus. 2010;3:109–17.
48. Druml W. Nutrition management of acute renal failure. Am J Kidney Dis. 2001;37(1 Suppl 2):S89–94.
49. Kopple JD. Nutrition management. In: Massry SG, Glassock RJ, editors. Massry & Glassock's textbook of nephrology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 1449–73.
50. Fiaccadori E, Regolisti G, Cabassi A. Specific nutritional problems in acute kidney injury, treated with non-dialysis and dialytic modalities. NDT Plus. 2010;3:1–7.
51. van den Berghe G, Woutersn P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359–67.
52. Cano N, Aparicio M, Brunori G, et al. ESPEN guidelines on parenteral nutrition. Parenteral nutrition in adult renal failure. Clin Nutr. 2009;28(4):401–14.
53. Toigo G, Aparicio M, Attman PO, et al. Export working group report on nutrition in adult patients with renal insufficiency. Clin Nutr. 2000;19:281–91.
54. Faisy C, Guerot E, Diehl JL, et al. Assessment of resting energy expenditure in mechanically ventilated patients. Am J Clin Nutr. 2003;78:241–9.
55. Wooley JA, Btaiche IF, Good KL. Metabolic and nutritional aspects of acute renal failure in critically ill patients requiring continuous renal replacement therapy. Nutr Clin Pract. 2005;20(2):176–91.
56. Frankenfield DC, Reynolds HN. Nutritional effect of continuous hemodiafiltration. Nutrition. 1995;11(4):388–93.
57. Gervasio JM, Cotton AB. Nutrition support therapy in acute kidney injury: distinguishing dogma from good practice. Curr Gastroenterol Rep. 2009;11:325–31.
58. Strejc JM. Considerations in the nutritional management of patients with acute renal failure. Hemodial Int. 2005;9:135–42.
59. Berger MM, Shenkin A, Revelly JP, Roberts E, Cayeux MC, Baines M, et al. Copper, selenium, zinc and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. Am J Clin Nutr. 2004; 80(2):410–6.
60. Story DA, Ronco C, Bellomo R. Trace element and vitamin concentration and losses in critically ill patients treated with continuous venovenous hemofiltration. Crit Care Med. 1999;27:220–3.
61. Metnitz GH, Fischer M, Bartens C, Steltzer H, Lang T, Druml W. Impact of acute renal failure on antioxidant status in multiple organ failure. Acta Anaesthesiol Scand. 2000;44:236–40.
62. Fall P, Szerlip HM. Continuous renal replacement therapy: cause and treatment of electrolyte complications. Semin Dial. 2010;23(6):581–5.

Chapter 15
Bone and Mineral Disorders

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Key Points

- To identify the mechanisms and consequences of CKD-mineral and bone disorder (CKD-MBD)
- To describe the effects of bone and mineral abnormalities in chronic kidney disease (CKD)
- To discuss current therapies and treatment recommendations for bone and mineral abnormalities in CKD

Keywords Uremic or renal osteodystrophy (RO) • Chronic kidney disease-mineral and bone disorder (CKD-MBD) • Vitamin D • 1,25-Dihydroxyvitamin D • Secondary hyperparathyroidism • Parathyroid hormone (PTH) • Phosphate • Calcium • Vitamin D analogs • Calcimimetics • FGF23 • Vitamin D receptor (VDR) • Calcium-sensing receptor (CaSR) • Calcidiol • Nutritional vitamin D • KDOQI • KDIGO • Evidence-based practice guidelines

Introduction

Abnormal bone and mineral metabolism is a common complication of chronic kidney disease (CKD) and has been the subject of concern and controversy throughout the world [1–5]. Mounting evidence suggests that disorders of bone and mineral metabolism are associated with an increased risk for cardiovascular calcification, morbidity, and mortality [6, 7]. As kidney function declines, mineral homeostasis deteriorates leading to changes in the levels of various hormones such as parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, other vitamin D metabolites, fibroblastic growth factor-23 (FGF23), and growth hormone. Eventually, serum and tissue concentrations of calcium and phosphorus become abnormal. The discovery of FGF23 has changed the understanding of abnormal phosphorus and vitamin D metabolism in CKD. FGF23 is a bone-derived hormone that increases phosphaturia and decreases the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

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Increased secretion of $1,25(OH)_2D$ and high dietary phosphorus intake are considered to be the main stimuli of FGF23 secretion [8]. FGF23 levels increase early (CKD stage 2 or 3) and steadily increase as CKD progresses. This hormone stimulates an appropriate physiologic adaptation to maintain normal phosphorus balance. It helps to augment urinary phosphate excretion, increase PTH levels, and lower $1,25(OH)_2D$ production by decreasing phosphorus absorption from the Gastrointestinal (GI) tract. Over time this adaptation fails causing a progressive decline in $1,25(OH)_2D$ levels with additional consequences such as secondary hyperparathyroidism (SHPT). High FGF23 levels have been independently linked with adverse outcomes in CKD, such as cardiovascular disease and mortality. Additionally, treatment with activated vitamin D compounds stimulates FGF23 which has reinforced the need to consider the risks and benefits of using activated vitamin D and to determine the optimal doses to treat CKD-mineral and bone disorder (CKD-MBD) [8].

With the decreased conversion of 25-hydroxyvitamin D to the active form, intestinal calcium absorption drops and PTH secretion increases. The diseased kidney does not respond appropriately to PTH or FGF-23. There is also evidence of downregulation of vitamin D receptors (VDRs) and resistance to the actions of PTH at the tissue level. While all the interrelated mechanisms and consequences are not fully understood, the import of these abnormalities has generated considerable interest and controversy [2].

Evidence-based practice guidelines for CKD-mineral and bone disorder management were published by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) in 2003 [1]. In 2005, an international group, Kidney Disease Improving Global Outcomes, sponsored a controversies conference entitled "Definition, Evaluation and Classification of Renal Osteodystrophy" [9]. The resulting position statement, published in 2006, provided a broader definition of bone and mineral abnormalities which was labeled as CKD-MBD [9]. CKD-MBD was defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by one or a combination of (1) abnormal calcium, phosphorus, PTH, or vitamin D metabolism; (2) abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and (3) vascular or other soft tissue calcification. It was suggested that the term renal osteodystrophy (RO) be applied only to alterations in bone morphology in CKD that are quantifiable by histomorphometry of bone biopsy. There was also agreement within the consensus group that an international guideline was warranted to help clinicians understand and treat this disorder [9]. KDIGO evidence-based practice guidelines for CKD-MBD were developed and published in 2009 [2]. These guidelines have been reviewed and embraced by experts around the world [2–5]. The KDIGO recommendations and biochemical targets are less prescriptive than previous guidelines due to the lack of high-quality evidence indicating that achievement of specific biochemical targets translates directly into improved outcomes [2]. KDOQI reviewed the KDIGO guidelines and essentially agreed that the majority of the international guidelines were applicable to the US CKD population [3]. A comparison of KDOQI and KDIGO guideline biochemical targets can be found in Table 15.1.

In the years since dialysis became routinely available, the profile of bone and mineral abnormalities has changed, molded by the dialysis process and various therapies. The focus on hyperparathyroid bone disease and osteomalacia has expanded to include concern for low-turnover bone abnormalities, mixed bone disease, and soft tissue mineralization [1, 2]. Abnormalities of bone and mineral metabolism, in those individuals on dialysis therapy, are typically asymptomatic until late in the course of the disease, and even then, symptoms may be nonspecific and unobtrusive [10, 11]. Common symptoms such as pruritus, bone pain, fractures, deformities, and muscle weakness [2, 9] have been overshadowed by metastatic and extraskeletal calcifications which have the potential to affect many areas of the body. Extraskeletal calcification can be localized in arteries, in the eyes, in visceral organs, around joints, and in the skin [1, 2]. Manifestations of abnormal bone and mineral metabolism can be found in Table 15.2 [2, 7, 10–12]. It is important to understand the widespread incidence and impact of bone and mineral abnormalities in CKD and to use caution in applying therapies, always weighing the risks and benefits.

Table 15.1 Comparison of guideline biochemical targets

	KDOQI 2003		KDIGO 2009		
Parameter	Stages 3–4	Stage 5D	Stages 3–5	Stage 5D	KDOQI 2010 commentary
Calcium	Within reference range for laboratory	Corrected total calcium within reference range	Within reference range	Within reference range	Applicable to the USA; levels outside reference range require evaluation for treatment effects or other causes
Phosphorus	2.7–4.6 mg/dL	3.5–5.5 mg/dL	Within reference range	Toward laboratory reference range	Applicable to USA; discretionary recommendations allow clinicians to assess benefits/harms of drug therapy and base decisions on clinical circumstances/patient preferences
PTH	3: 35–70 pg/mL 4: 70–110 pg/mL	150–300 pg/mL	If above upper reference range/increasing, correct modifiable factors/treat with calcitriol or analogs	Within 2–9 times upper reference limit; marked change within the range or outside range should trigger treatment to avoid extremes	Recommendation give US practitioners flexibility to use and adjust treatments that are effective in decreasing PTH levels despite lack of proof that attaining a specific PTH range translates to better outcomes

Table 15.2 Manifestations of abnormal bone and mineral metabolism in CKD

Manifestation	Characteristics/description
Altered vitamin D metabolism	Elevated FGF23 Deficiency in calcitriol Defective intestinal absorption of calcium Hypocalcemia Stimulation of PTH synthesis
Abnormal handling of calcium, phosphorus, and magnesium by the kidneys	Elevated FGF23 Hyperphosphatemia Hypocalcemia
Secondary hyperparathyroidism	Decreased skeletal response to PTH Altered degradation of PTH Abnormal regulation of calcium-dependent PTH secretion Impaired skeletal response to PTH Increased parathyroid gland chief cell proliferation Bone disease
Metastatic and extraskeletal calcifications	Calcification of coronary arteries and cardiac valves Potential skin ulceration or soft tissue necrosis
Fractures	Incidence is increased in CKD and associated with increased mortality
Bone pain	Uncommon since decrease in aluminum bone disease, expressed as general ache
Pruritus	Associated with high PTH levels, hypercalcemia, high CaP, and metastatic calcification; self-reported by 40–50 % of hemodialysis patients
Dialysis-related amyloidosis	Disabling arthropathy after long duration of dialysis
Proximal myopathy and muscle weakness	Usually limited to proximal muscles, caused by SHPT, phosphorus depletion, aluminum toxicity, or low vitamin D levels

Data from [1, 2, 7, 10–12]

Pathogenesis of Bone and Mineral Abnormalities in CKD

Progressive loss of kidney function causes disturbances in mineral metabolism and bone integrity. The cascade of events that leads to bone and mineral abnormalities begins early in CKD. The kidneys help maintain the balance of calcium and phosphorus in the body by regulating the net excretion of these minerals in the urine. Balance is also maintained by changes in calcium and phosphorus absorption in the intestines and through the exchange of ions between bone and the extracellular fluid. Bone-level calcium and phosphorus stores help support metabolic and homeostatic requirements. PTH, calcitriol, and phosphatonins like FGF23 coordinate the responses of the kidneys, intestines, and bones [1, 2, 10, 12].

Mineral and endocrine derangements begin earlier in CKD than bone-level changes [9]. In response to increasing phosphate load and decreasing calcitriol levels, FGF-23 and PTH increase the per-nephron phosphate excretion via sodium-dependent phosphate cotransporters NPT2a and NPT2c [13, 14]. FGF-23 and PTH levels increase as CKD progresses (stage 2 CKD) with compensatory adaptations striving to maintain normophosphatemia [13, 14]. In healthy volunteers, dietary phosphate loading stimulates FGF23 synthesis, while restricting dietary phosphate has the opposite effect [15]. Increased FGF-23 is an early biochemical marker of mineral derangement, although commercial assays for FGF23 or its biologic activator, Klotho, are not yet available for routine clinical use [16]. In the prospective Chronic Renal Insufficiency Cohort (CRIC) [17], elevated FGF-23 was independently associated with mortality risk at all stages of CKD and with risk of progression to ESRD in patients with baseline GFR ≥30 mL/min. FGF23 levels are positively correlated with serum phosphate and negatively associated with serum calcitriol and PTH. The role of FGF23 in development of SHPT is due to both direct and indirect effects. FGF23 has a counter-regulatory effect on calcitriol; thus, in

CKD it has the potential to reduce vitamin D activity. It can also stimulate local expression of 1α hydroxylase in the parathyroid (PT) glands which may indirectly downregulate PTH synthesis through increased local production of calcitriol [18]. It has also been demonstrated that there is a downregulation of the FGF23 signaling pathway in the PT glands with a decreased expression of FGFR1 and Klotho. Klotho, a single-pass transmembrane protein, has wide biologic effects and is expressed mainly in the kidneys and the PT glands but has also been detected in other tissues. It is central to FGF23 biologic activity and seems to be required for the FGF23-mediated receptor activation that stimulates phosphorylation pathways. Klotho also has a role in regulation of phosphate and calcium metabolism leading to increased calcium reabsorption [18] and directly regulates PTH synthesis [19]. Many other general metabolism roles have also been attributed to Klotho, and it is believed that other new roles for Klotho will be identified in the future [18].

Once the glomerular filtration rate (GFR) drops below 60 (stage 3 CKD), PTH levels begin to rise in the blood [1], setting in motion the development of SHPT [9]. This rise in PTH appears to be in response to several factors, including increasing FGF23 levels, vitamin D deficiency, increasing phosphate retention, and a skeletal resistance to PTH, all of which lead to hypocalcemia and further stimulation of PTH. With progressive loss of kidney function, there seems to be a decrease in the number of VDRs and calcium-sensing receptors (CaSRs) in the PT glands, making them resistant to the actions of vitamin D and calcium. Dietary phosphorus modification may modulate PTH [10, 11] and FGF23 [8, 9, 15] levels even when serum phosphorus levels are within the normal range. Hyperphosphatemia occurs later in the progression of CKD, usually when GFR drops to about 20–30 mL/m^3, and significantly influences the function and growth of parathyroid glands [1, 11].

By the time dialysis is required, most CKD patients have some degree of SHPT which is characterized by hypersecretion of PTH and eventually hyperplasia of the parathyroid glands. The historic trade-off hypothesis [1, 2, 8, 10] suggests that as GFR declines, production of calcitriol is inadequate to meet physiologic needs, serum calcium levels decline, phosphorus excretion declines, and serum phosphorus levels increase. Reduced calcitriol levels hinder the absorption of calcium from the intestines. These factors lead to hypocalcemia, a primary stimulus for increased production and secretion of PTH. Increased PTH levels stimulate phosphorus excretion and calcitriol production to correct the hypocalcemia. However, research on FGF23 challenges this trade-off hypothesis and indicates that elevated FGF23 is one of the first abnormalities and that it decreases 1,25-vitamin D production and starts the cascade of events that lead to SHPT [8].

In the later stages of CKD, increased PTH production and secretion can no longer counterbalance the abnormal serum levels of calcium, phosphorus, and FGF23 [1, 8, 10, 11]. In addition, the kidneys lose their ability to adequately degrade and clear PTH from the body. Increased PTH production and secretion along with decreased PTH degradation lead to SHPT [9, 10, 20].

Phosphate is a key element for many physiologic pathways such as skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling [18]. The kidneys are central to its regulation, mainly through two hormonal regulators, FGF23 and PTH. Both of these hormones have hypophosphatemic effects through decreased phosphate tubular reabsorption. The third regulator of phosphate metabolism is 1,25-vitamin D which increases intestinal calcium and phosphate absorption and inhibits PTH synthesis [18]. Hyperphosphatemia helps regulate the production of calcitriol by reducing the activity of the enzyme that activates 25(OH) vitamin D [20]. Hyperphosphatemia also has an effect on PTH gene expression and indirectly increases PTH production [21]. In those without CKD, higher PTH levels, along with increased FGF23 levels [18], decrease phosphorus reabsorption to restore serum phosphorus levels to normal. In the late stages of CKD, this compensatory mechanism is inadequate to maintain the serum phosphorus levels [18, 21]. Additionally, with significant SHPT, phosphorus is released directly from the bone into the blood contributing to hyperphosphatemia [22]. Chronically elevated phosphorus levels are associated with parathyroid gland size and are central to parathyroid gland hyperplasia and continued high PTH levels [10, 20, 21].

In CKD, production of calcitriol by the kidney is reduced in response to high FGF23 [8]. Low levels of calcitriol contribute to SHPT both directly and indirectly [23, 24]. Calcitriol exerts a direct negative feedback control on the parathyroid gland, inhibiting preproPTH production and gene transcription [10, 11]. Indirectly, low calcitriol levels hinder the absorption of calcium from the intestine and mobilization of calcium from the bone. These actions suggest that calcium, rather than vitamin D, predominantly regulates PTH [23].

Hypocalcemia results from increased calcium-phosphate complexes and from a decrease in absorption of dietary calcium from the intestine [24–26]. In addition, the ability of the bone to release calcium into the blood is hindered. The CaSR provides a regulatory mechanism involving release of PTH to maintain calcium homeostasis [20]. Even slight physiologic, within normal range, changes in serum calcium seem to modulate the development of SHPT.

Skeletal resistance to the calcemic action of PTH is also a factor in the development of SHPT. As CKD progresses, increasingly higher levels of PTH are needed to induce PTH effects and to maintain normal bone remodeling activity [27]. Skeletal resistance is thought to be multifactorial, perhaps from altered regulation of PTH receptors in the bone that makes them less sensitive to PTH as well as from phosphorus retention and calcitriol deficiency [11, 28].

As hypocalcemia, hyperphosphatemia, increased FGF23, and calcitriol deficiency continue, the parathyroid glands continually increase production of PTH leading initially to parathyroid cell hypertrophy. With chronic stimulation, the parathyroid cells proliferate and diffuse hyperplasia develops. This proliferation of parathyroid cells makes it difficult to modulate PTH levels. Nodular hyperplasia is characterized by cells that have fewer CaSRs and VDRs and are significantly resistant to vitamin D therapy [11, 20, 21].

Bone Manifestations

The traditional types of RO have been defined on the basis of turnover, mineralization, and volume (TMV). Two general characteristics define the state of the bone—high turnover and low turnover. SHPT, considered high-turnover disease, is characterized by abnormal and increased bone remodeling, including osteitis fibrosa and mixed bone disorders. Low-turnover bone states are characterized by decreased bone mineralization and formation, including osteomalacia and adynamic bone disorder (ABD) [1, 10]. The spectrum of possible manifestations, from low to high turnover, from low to high volume, and with or without mineralization abnormalities, can be found in Table 15.3 [2].

Osteitis fibrosa is caused by SHPT and historically has been the most common form of bone abnormality in CKD [23, 29]. It is characterized by marrow fibrosis and increased bone turnover due to both bone resorption and bone formation. The bone resorption is caused by an increase in the number and activity of osteoclasts, and changes in bone formation are due to increased osteoblasts and osteoid deposition [1, 10, 12]. While mixed bone disease has features of both high- and low-turnover abnormalities, it is generally classified as a high-turnover disease. Mixed bone disease has been associated with aluminum accumulation, hypocalcemia, and variable levels of serum phosphorus [10, 23].

Table 15.3 Types and characteristics of renal osteodystrophy

Type	Bone turnover	Mineralization	Volume
Mild SHPT	Slightly high	Normal	Normal
Osteitis fibrosa	High	Normal	High
Osteomalacia	Low	Abnormal	Normal
Adynamic bone disorder	Low	Acellularity	Low
Mixed	High	Abnormal	Normal

Bone strength can be impaired in all of the above [2, 10]

Osteomalacia, characterized by low bone turnover, due to aluminum overload was common in the 1970s and early 1980s secondary to aluminum levels in the dialysate and the use of aluminum hydroxide phosphate binders. With the change in dialysate standards and limitations of aluminum ingestion, aluminum-related osteomalacia is uncommon, but toxicity can still occur [10, 23]. The KDOQI guidelines recommend that aluminum-based phosphate binders be used only in extreme hyperphosphatemia and for a short duration [1]. KDIGO did not directly address aluminum toxicity other than to suggest avoiding long-term exposure to aluminum sources and indicating toxicity can be diagnosed with a bone biopsy [2].

There is also a potential for developing osteomalacia related to vitamin D deficiency, metabolic acidosis, hypophosphatemia, and deficiencies in the trace elements, fluoride and strontium [10]. Osteomalacia is characterized by a decreased bone formation rate, widened osteoid seams, as well as decreased formation and resorption surfaces [10, 23].

ABD is characterized by a lack of new bone formation, low cellular activity, low numbers of osteoblasts, and normal or reduced osteoclasts. Increased bone matrix is the primary defect. Mineralization is usually decreased, without excess osteoid deposition or abnormal thickness. The reduction in osteoblasts and limited bone formation may be a result of a relative deficiency in PTH. Other systemic PTH inhibitory factors may also play a role in ABD [23, 24, 30]. Several subgroups of CKD stage 5 dialysis (CKD stage 5D) patients may be more likely to have ABD. These include peritoneal dialysis patients, elderly patients, and those with diabetes [24, 31, 32].

Plasma levels of PTH are generally higher than normal in CKD, even when associated with ABD. In uremia, a relative reduction in PTH is able to induce a low-turnover bone state even at laboratory normal PTH levels [32, 33]. There are also racial differences in response to PTH. Blacks tend to have reduced skeletal sensitivity to PTH and less likelihood of developing overt osteitis fibrosa despite higher plasma levels of PTH [33].

Most of the studies of bone histomorphometry have not been designed to fully evaluate the relationship between fractures and types of renal osteodystrophy. Evidence is mixed regarding the relationship between low-turnover bone state and increased fractures, but some research suggests that fractures are more common in osteomalacia and adynamic bone state. It is well established that fractures in those with CKD are associated with a higher mortality rate [2].

In addition to bone abnormalities, extraskeletal calcification is a significant finding in CKD-MBD [1, 2]. Arterial calcification is found early in CKD and progresses over time. Early research suggests that coronary calcification is more likely to occur in individuals who have higher serum phosphorus, higher calcium times phosphorus product (CaP) levels, and a higher daily calcium load [34, 35]. Guérin et al. found that the severity of calcification is correlated with age, dialysis vintage, fibrinogen levels, and the prescribed dose of calcium-based phosphate binders [36]. Vascular calcification is associated with increased stiffness of the large capacity arteries such as the carotid artery and the aorta [35–37]. Other research shows that the presence and severity of arterial calcifications predict cardiovascular and all-cause mortality [36]. The full pathology of extraskeletal calcification in CKD is not fully understood, but FGF23 is also considered to be contributory to this process [38, 39].

Calcific uremic arteriolopathy (CUA), previously termed calciphylaxis, is a rare but severe form of medial calcification of the small, cutaneous arteries. It is associated with painful skin lesions, subcutaneous nodules, tissue ischemia, and necrosis of the skin or subcutaneous tissue of the extremities. Disturbances in mineral metabolism, SHPT, and vascular calcification appear to play a role in the genesis of CUA [40–42]. Proposed risk factors for calciphylaxis include female gender, Caucasian ethnicity, obesity, diabetes, liver disease, local trauma, hypotension, hypoalbuminemia, elevated mineral levels, protein C and protein S deficiencies, malnutrition, iron deposition, and hyperparathyroidism. There are discrepancies in reported risk factors because of the relatively small numbers of patients in many of the studies [43]. While the incidence of CUA is low and limited research has failed to fully explain the mechanisms, it can be a life-threatening complication of bone and mineral abnormalities in CKD [10].

Another abnormality in CKD is atypical accumulation of β_2-microglobulin (β_2MA), a polypeptide that is involved with lymphocyte-mediated immune response. Accumulation is progressive due to decreased catabolism and excretion by the kidneys. Symptoms seldom occur until the patient has been on dialysis therapy for a long time, i.e., 5–15 years. The most common first symptom is carpal tunnel syndrome. Kidney transplantation is currently the only therapy that stops the progression of β_2MA. Current treatment focuses the use of biocompatible dialyzer membranes to enhance clearance of β_2MA during dialysis and on easing joint pain and inflammation [12, 44–46].

Osteoporosis is a skeletal disorder commonly found in the elderly. Since a large percentage of those receiving dialysis are over the age 65, osteoporosis may occur as an adjunct problem to CKD-MBD. Traditional therapies used to treat osteoporosis in otherwise healthy adults are thought to be inappropriate for dialysis patients, especially without benefit of a bone biopsy [2]. Diagnosis of osteoporosis in CKD is more complicated since CKD-MBD may have similar manifestations [47, 48]. KDIGO suggests that patients in stages 1–3 with osteoporosis or high risk of fracture be treated in accordance with World Health Organization (WHO) recommendations for the general public. In stage 3 with biochemical abnormalities of CKD-MBD, low bone mineral density (BMD), and/or fragility fractures, it is suggested that treatment choices be made with consideration of the magnitude and reversibility of the biochemical abnormalities and the progression of CKD. In stages 4–5D, routine use of antiresorptive agents is not recommended without a bone biopsy [2, 48].

Bone Biopsy

Bone biopsy is the most accurate diagnostic tool for determining bone lesions in CKD. All other assessment parameters should be compared to bone biopsy as the gold standard for assessing bone metabolism [1, 2]. Historically, bone biopsy has been viewed as significantly invasive and potentially painful. Additionally appropriate sample processing techniques, expert interpretation, and standardized reporting terminology have been lacking. As bone biopsy becomes more common, these limitations may diminish. Biopsy with tetracycline labeling allows the classification of bone pathology based on static and dynamic parameters that diagnose RO [11, 12]. Routine bone biopsy is not recommended for CKD stage 5D patients unless the clinical picture or symptoms are inconsistent with the biochemical profile [1, 2, 12].

Radiography, Pulse Pressure, and Electron Beam Computed Tomography

While X-rays provide limited information on CKD stage 5D-specific bone abnormalities, they do help in the assessment and identification of extraskeletal calcification and osteoporosis. Lateral abdominal X-rays are a simple low-cost way to detect vascular calcification [2, 10]. Pulse pressure (PP) (the difference between systolic and diastolic blood pressure) has been shown to predict arterial stiffness, and cardiac calcification contributes to arterial stiffness in CKD and dialysis patients. Increased pulse pressure in dialysis patients is also associated with increased mortality risk. PP may help identify CKD patients with subclinical CAC who need further evaluation. High PP indicates vessel wall alterations that may lead to adverse outcomes [2, 10].

Another method of identifying soft tissue calcification is electron beam computed tomography (EBCT); however, EBCT is not routinely available. EBCT studies have shown that dialysis patients have coronary artery calcium scores that are severalfolds higher than individuals without CKD [2, 10].

Bone Mineral Density

BMD is most commonly measured by dual X-ray absorptiometry (DEXA). This procedure measures the mineral content and the density of the bone but does not provide information about bone turnover and does not correlate well with bone histology or identify the type of lesion in CKD stage 5D [48]. The KDOQI/KDIGO bone and mineral work groups did not find evidence that BMD was helpful in guiding therapy for CKD-MBD, except for the evaluation of osteoporosis and in patients who have fractures [2].

Biochemical Markers of Bone and Mineral Metabolism in CKD

With some limitations, a number of biochemical parameters can assist in the diagnosis and management of CKD-MBD. Much of the current research is focused on correlating specific biochemical parameters to bone biopsy, thus enhancing their clinical value. Concomitant, serial monitoring of several biomarkers is useful. These include total serum calcium, corrected calcium, serum phosphorus, alkaline phosphatase, and plasma PTH [1, 2, 10–12].

Ionized calcium is the fraction of blood calcium that is critical to physiologic processes. It is more difficult to accurately measure than total calcium but is the most indicative of an individual's true calcium status. Routine monitoring of total calcium over ionized calcium is recommended because it is usually more reproducible, less costly, and adequate, especially in the presence of normal plasma proteins [2, 10, 49].

Total calcium may underrepresent ionized calcium in protein-compromised patients. Since a significant portion of serum calcium is bound to protein, predominately albumin, it has been suggested that correcting total calcium for low albumin may more accurately estimate ionized calcium. Adjusting total calcium downward in patients with normal albumin levels greater than 4.0 g/dL is questionable at best [10]. A myriad of formulas have been proposed to make this correction. Most major renal laboratories correct total calcium for low measured albumin, and while recent data does not show any superiority of using corrected calcium over total calcium alone, the KDIGO bone and mineral work group did not recommend abandoning this practice [2].

High serum calcium is associated with bone abnormalities as well as morbidity and mortality in CKD patients on dialysis [1, 6, 10]. KDIGO recommends maintaining serum total calcium within the laboratory reference range but does not provide goals or limitations for dietary calcium or calcium from phosphate binders [2]. The guidelines do suggest that hyperphosphatemia be treated with phosphate binders and that the choice of binders be made while considering the stage of CKD, the presence of other CKD-MBD complications, concomitant therapies, and the side effect profiles. Additionally, it is suggested that calcium-based binders be limited in the presence of recurrent hypercalcemia [2]. After an exhaustive review of the literature, the Institute of Medicine recognized that excessive calcium intake can lead to hypercalcemia, hypercalciuria, vascular and soft tissue calcification, nephrolithiasis, prostate cancer, interactions with iron and zinc, progression of CKD, and constipation. It is noted that excessive calcium intake is rarely from foods alone but is more likely to be from supplements and calcium-fortified foods. The report notes that those with CKD may be more sensitive or susceptible to the effects of excess calcium or vitamin D intakes. Thus, it is reasonable for those with CKD to avoid total calcium intake above the upper tolerable limit. The NIH tolerable upper limits for elemental calcium based on life stages for those without CKD can be found in Table 15.4 [50].

Phosphorus, one of the most common chemical elements in the body, is involved with a wide variety of metabolic and enzymatic processes. It circulates and is measured as phosphate ions in the serum but is usually reported as elemental phosphorus concentrations [12]. Concentration of phosphorus in the serum varies significantly depending on the time of day and recent dietary phosphorus intake. This may

Table 15.4 Tolerable upper limits for calcium by age range

Age	Males (mg)	Females (mg)
9–18	3,000	3,000
19–30	2,500	2,500
31–50	2,000	2,500
51–70	2,000	2,000
>70	2,000	2,000

Data from [50]

help explain the significantly high and variable levels seen in individual CKD patients. Fasting phosphorus measures are ideal but unlikely in chronic dialysis patients. Falsely high levels may be due to breakdown of blood cells if specimens are processed incorrectly [11]. Chronic hyperphosphatemia is associated with bone and mineral abnormalities, worsening SHPT, as well as morbidity and mortality [1, 2, 6, 51]. Hyperphosphatemia is also aggravated by severe SHPT, where bone phosphorus is released directly into the blood and is unavailable to phosphate binders [11]. KDIGO suggests maintaining serum phosphorus in the normal reference range for stages 3–5 and lowering elevated phosphorus toward the normal reference range in stage 5D [2]. Methods for control of serum phosphorus include dietary modification, adequate dialysis, and the use of phosphate binders [1, 2, 12, 51].

Calcium and phosphorus product has predictive power for abnormal mineral metabolism, morbidity, and mortality [6, 7]. However, KDIGO recommends evaluating the individual values of serum calcium and phosphorus together rather than using the mathematical construct of calcium times phosphorus [2].

PTH is an important biomarker for the evaluation of CKD-MBD even though there is a lack of standardization of assays to measure serum levels. Additionally, serum levels change quickly in response to changes in ionized calcium, and it is possible to see wide variations in the values from measurement to measurement. KDIGO recommends using trends rather than single values to guide therapy [2]. PTH plays a critical role in the regulation of mineral and bone homeostasis, and its secretion is regulated by serum ionized calcium. Levels of phosphorus and vitamin D also affect synthesis and secretion of PTH. There are some studies that relate intact PTH (iPTH) levels to various states of bone turnover. Malluche et al. and others have found significant predictive power for high-turnover bone state at iPTH level >400–500 pg/mL [12], and low-turnover bone state is highly likely when iPTH levels are <100 pg/mL [11, 12]. However, when the iPTH is lower than 100 or greater than 500 pg/mL, a definitive diagnosis requires a bone biopsy [1, 11, 52]. There are inconsistencies in published data correlating PTH levels to bone turnover. Qi et al. found that PTH failed to predict bone turnover in 30 % of HD patients and 51 % of PD patients [52]. Based on available evidence, KDIGO suggests maintaining iPTH between 2 and 9 times the upper reference level. Additionally, it is suggested that significant changes even within that range should trigger evaluation and intervention to avoid those extremes [2].

Biologically active PTH (1-84) polypeptide is synthesized and secreted by the parathyroid cells. However, along with 1-84 PTH, varied PTH fragments are released. As previously discussed, many factors modulate PTH gene expression, PTH production, PTH secretion, and parathyroid cell proliferation [52]. Calcium is the primary determinant of minute-to-minute PTH secretion, whereas calcium, FGF23, phosphorus, and vitamin D levels regulate PTH production and cell proliferation. The 1-84 molecule is degraded into smaller fragments within minutes of release [11, 23]. This degradation is modulated by parathyroid cells and the serum calcium concentration. Thus, when serum calcium is low, PTH degradation decreases, and when calcium is high, PTH breakdown increases. PTH fragments have varying half-lives [52]. They also have diverse biologic activity on PTH receptors. Elimination of PTH fragments is primarily through glomerular filtration and tubular degradation; therefore, they accumulate in CKD. These variable circumstances have generated questions regarding the predictive value and interpretation of plasma iPTH [11, 52, 53].

It is known that iPTH assays capture both 1-84 and other fragments. The metabolic significance of PTH fragments is not fully understood. The action of the largest known PTH fragment (7-84) may oppose the action of the 1-84 molecule and contribute to the PTH resistance seen in CKD stage 5D. Bio-intact or whole PTH assays that capture the 1-84 PTH are generally about 50 % lower than iPTH, but KDIGO does not recommend routine use of these assays [2, 53–55]. In general, results from these two generations of assays are highly correlated across a wide spectrum of PTH concentrations, but individual patient correlations may vary. Further research is needed to fully elucidate the opposing action of PTH fragments and to correlate second-generation assay results to bone histology [2, 54–57].

The normal range of iPTH, 10–65 pg/mL (1.1–7.15 pmol/L), reflects normal bone turnover in those without CKD. In CKD, with progressive skeletal resistance to PTH, normal bone turnover more closely correlates with higher plasma iPTH levels. Thus, a normal PTH is not normal in CKD patients on dialysis. On the basis of observational studies, the KDIGO work group considered that levels less than two or greater than nine times the upper normal limit for the PTH assay in use represent extreme ranges of risk [2].

Alkaline phosphatase (AP) can also add information about the state of bone turnover [2]. AP is an isoenzyme that is produced primarily in the liver and by osteoblasts in the bone. Other sites of AP production are the intestines, placenta, and kidneys, although these sources contribute negligible amounts under normal conditions. With normal liver function, AP is a useful indicator of bone cell activity. Most research indicates that in CKD, elevated serum AP levels are due to bone AP and correlate with other markers of high-turnover bone disease [57]. The KDIGO guidelines suggest using total AP as an adjunct test to PTH in providing information about the state of bone turnover, particularly when PTH levels are high [2]. Parallel consideration of AP with PTH has the potential to increase the predictive power of PTH; however, the specificity and sensitivity for identifying RO with AP alone or together with PTH have not been fully demonstrated [2].

Bone-specific AP (BSAP) is the fraction of AP that is generated by the osteoblasts. BSAP correlates well with iPTH and other indices of SHPT. However, the KDIGO bone and mineral work group did not find evidence that BSAP adds significant information above the total AP measurement in CKD patients when liver function is normal [2, 10].

In the past, aluminum exposure was a complicating factor in CKD-mineral and bone disorder. Primary causes of aluminum toxicity have been eliminated; thus, serum aluminum is measured less frequently than in the past. Measures of serum aluminum reflect recent aluminum exposure and the potential for accumulation. They may identify hidden sources of aluminum to which a patient is exposed. Serum levels of aluminum should be <10 μg/L [10]. In CKD patients on dialysis, serum aluminum levels of >60 μg/L have notable specificity, sensitivity, and predictive value for the diagnosis of aluminum-related bone disease [1, 2].

Treatment of CKD-MBD

Evidence-based practice guidelines serve to promote standardized, best practice management of bone and mineral abnormalities as a way to improve patient outcomes. They are meant to help clinicians in decision making, but not to dictate practice or set absolute standards. KDIGO found a paucity of high-quality evidence to support generally accepted practice patterns for the treatment of CKD-MBD. The KDIGO clinical practice guidelines for bone and mineral disorder allow flexibility for clinicians to apply those guidelines and recommendations based on evaluation of an individual patient's status and needs [2].

Treatment approaches are intended to normalize FGF23, phosphorus, and calcium and to optimize PTH levels for normal bone turnover while minimizing complications such as extraskeletal calcification. The evidence that achieving very specific target ranges of these biochemical markers will absolutely alter hard outcomes is lacking [2]. However, it seems reasonable to keep the levels as close to

normal as possible to prevent or reduce progression of CKD-MBD. The following treatment options are available for the treatment of CKD-MBD [2, 10–12]:

- Limit dietary phosphate intake while providing adequate protein.
- Avoid sources of inorganic phosphate (highly bioavailable), such as food additives.
- Optimize renal replacement therapy (adequate dialysis).
- Prescribe and titrate phosphate binders as needed to prevent or minimize abnormal levels of CKD-MBD biomarkers including serum phosphorus.
- Limit calcium-based binders in patients who have recurrent hypercalcemia, low iPTH, or indications of soft tissue calcification.
- Evaluate elemental calcium intake, and do not exceed the NIH tolerable upper limit for calcium. Monitor the patient for signs of hypocalcemia and supplement calcium if symptoms are present.
- Prescribe and titrate calcitriol or its analogs to control PTH, but alter doses if hypercalcemia or hyperphosphatemia occurs.
- Prescribe and titrate calcimimetics to control PTH while maintaining serum calcium and/or phosphorus within acceptable ranges.
- Attempt to achieve PTH levels that have the potential to promote normal bone turnover, avoiding the extremes of less than two or greater than nine times the upper limit of the assay being used.
- Educate patients on all aspects of bone and mineral management including the rationale for various treatments and the consequences of nonadherence.
- Consider parathyroidectomy (PTX), if all other treatments fail or surgery is deemed most appropriate for the patient.
- Above all consider the effects of various therapies and weigh the risk-to-benefit profiles.

Dietary Modification

Modifying dietary phosphorus can be a challenge when combined with meeting protein needs for those on dialysis [1, 2]. Primary food sources of organic dietary phosphorus are phosphorus protein-rich foods such as dairy products, meat, poultry, eggs, fish, legumes, and nuts. Food additives supply significant amounts of inorganic phosphorus. Typically about 30–60 % of organic phosphorus is hydrolyzed in the gastrointestinal tract and then absorbed into the circulation as inorganic phosphate [58, 59]. Absorption rates are affected by the digestibility of dietary nutrients and bioavailability of dietary phosphorus as well as the degree of activation of VDR in the GI tract. The presence of compounds that bind phosphorus or interfere with GI absorption, such as phosphate binders, also affects absorption rates [60–62].

A majority of the dietary phosphorus in the typical western diet comes from animal proteins which have a higher bioavailability than plant-based proteins. The phosphorus in animal proteins is easily hydrolyzed and readily absorbed [60–63]. The phosphorus-to-protein ratio is also quite variable [2]. Additionally, meat and dairy products often contain phosphate additives which add to the total phosphorus content.

While most fruits and vegetables have small amounts of organic phosphate, others such as plant seeds, nuts, and legumes are quite high in phosphorus [61, 62]. Plant-based organic phosphates, especially in beans, peas, nuts, and cereals, are generally in the form of phytic acid or phytate [61–63]. Phytate is the primary storage form of both phosphate and inositol in plant seeds. The bioavailability of plant-based organic phosphorus is limited, usually less than 50 %, because humans do not make phytase, the enzyme needed to degrade phytate. This complex renders plant-based, high-phosphorus foods less phosphatemic than animal-based protein sources. Despite reported high-phosphorus content of many plant protein sources in food composition databases, patients (mean GFR 32 mL/min) who consumed a metabolic lab-prepared vegetarian diet (grain and soy based) for 1 week had

significantly lower serum phosphate and FGF-23 levels than those consuming equivalent protein and calories in a meat- and dairy-based diet [64]. Thus, plant sources of protein may have lower phosphorus bioavailability than their in vitro-measured phosphorus content. More research is required to fully understand the variability of phosphate bioavailability and patient-specific absorption [58–64].

While phosphorus from plant-based proteins is generally less available, there are exceptions such as leavened breads that contain yeast-based phytase. Probiotics may also enhance phytase-associated phosphorus release and availability. Processing techniques, such as soaking, germination, malting, and fermentation, reduce phytate content by increasing activity of naturally present phytase. Phytic acid also has potential to reduce the digestibility and utilization of protein and various minerals [61–63]. One must also consider that plant-based proteins generally have a lower biologic value than animal proteins; thus, care must be taken to ensure adequate protein intake in CKD patients if shifting toward a diet of mainly plant derivative foods [63].

Phosphorus, in its inorganic form, is the main component of any food additives and preservatives that are used to extend shelf life, improve color, retain moisture, and enhance flavors of processed foods. Because the inorganic phosphorus in additives is not protein bound, the salts break apart and become readily absorbed in the GI tract. These additives are commonly used in processed foods, frozen meals, enhanced meats, colas, snack bars, cereals, spreadable cheese, instant products, and many bakery products. Unfortunately, there is very little information to estimate the amount of phosphorus that is contributed by additives, nor is there a method to fully distinguish between organic and additive-based inorganic phosphorus that is contained in traditional foods. Inorganic phosphorus is estimated to be over 90 % absorbed, while about 40–60 % of animal-based phosphorus and even less plant-based phosphorus is absorbed in the GI tract [63–67].

The IOM guidance for phosphorus intake, which has not been revised since 1997 and does not address the specific needs of CKD patients, provides an estimated average requirement of 580 mg/day and a recommended daily allowance of 700 mg/day for all adults [63]. The upper tolerable limit, 4,000 mg/day, should not be approached even by those without CKD given recent information that associates high phosphate intake and cardiovascular disease in the general public. Since intakes exceeding metabolic requirements directly increase serum phosphate, it is important to advise CKD patients to avoid exceeding the recommended daily phosphorus allowance [68].

Improving awareness of foods high in phosphorus and understanding differences in phosphorus absorption between animal, plant, and additive sources is essential for the dietitian [62, 63].

Dietitians are key to patient education about the dangers of bone and mineral abnormalities in CKD. While there is little evidence for long-term success of educational interventions to improve serum phosphorus, several studies have shown at least short-term success. The extent to which dietitian-to-patient staffing ratios support intense CKD-MBD counseling is important. Phosphorus sources are an important educational topic along with making patients aware of inadequate food labeling and hidden phosphorus sources such as processed-food additives, which are underrepresented in nutrition labels and databases [2, 64, 65]. Significant underestimations of phosphorus content by as much as 350 mg/day have been reported in Europe, Japan, and the USA [64–66]. Analysis of chicken products in the USA showed actual phosphorus contents exceeding those estimated from a nutrient database [60]. The use of additives that increase phosphorus by twofold or more, together with a lack of information on the nutritional label, has motivated nephrology dietitians to discourage manufacturers' indiscriminate use of phosphorus additives and to call for greater transparency regarding the phosphorus content of foods [60, 62]. While dietitians have taken an active role in treating hyperphosphatemia with phosphate binders, dietary counseling becomes an even more critical intervention considering the significant contribution of food additives to the daily phosphorus load.

Calcium intake may also be modified in CKD-MBD. While calcium content of the traditional "renal" diet is fairly low, calcium-fortified foods may add to the daily calcium load. Calcium-based binders can also cause patients to exceed the upper tolerable limit of elemental calcium [69, 70].

Phosphate removal on dialysis depends on the serum phosphorus concentration at the beginning of treatment, the ultrafiltration rate, the dialyzer capabilities, as well as the frequency and duration of dialysis. The majority of phosphorus clearance takes place early in the treatment and is followed by a slow equilibrium from the intracellular compartment. While phosphorus removal continues throughout the treatment, it is removed more slowly as serum concentrations decline. Patients who are unable to control serum phosphorus with a conventional dialysis schedule may benefit from one or more extra days of dialysis [71, 72].

A typical 4 h dialysis treatment, three times per week, does not maintain a net zero balance between phosphorus intake and clearance. Approximately 800–1,000 mg of phosphorus (2,400–3,000 mg/week) is removed by high-flux dialysis each treatment [70, 71]. If the patient controls dietary intake to the recommended level of 800–1,000 mg/day, there is still a significant positive balance of phosphorus which generally requires the use of phosphate binders. In severe SHPT, hyperphosphatemia may be aggravated by excessive bone turnover with the release of phosphorus directly into the blood. Thus, hyperphosphatemia may not always be due to dietary excess or binder nonadherence [2, 10].

The most appropriate phosphate binders are patient specific and readily available. They must be well tolerated, without creating other problems or adding an excessive pill burden [1, 2]. Appropriate prescription of phosphate binders requires an assessment of dietary phosphate intake and titration of the dose to control serum phosphorus in the target range. Prior to each modification of the binder prescription, it is critical to assess patient adherence to that binder prescription. The binder dose should be titrated to the phosphate content of the meal(s) and include binders for additional sources of phosphate such as snacks. Commonly available phosphate-binding compounds can be found in Table 15.5.

The move toward more frequent and longer-duration dialysis holds great promise for ameliorating CKD-MBD [2, 72]. Patients who dialyze more frequently than three times per week and longer hours seldom have trouble controlling phosphorus, and some require supplementation. While phosphorus clearance is better with more frequent dialysis, phosphate binder doses may not change since many of these patients eat more heartily.

The KDOQI target range for serum calcium was based primarily on a consensus of expert opinion and retrospective studies that suggested potential for higher mortality with elevated serum calcium and phosphorus [1]. Upon reviewing the evidence, the KDIGO work group concluded that serum calcium should be maintained within normal limits for the laboratory [2]. Maintaining serum calcium in the target range involves regulating the calcium in the dialysate, as well as monitoring and modifying the calcium load from the diet and medications such as calcium-based binders or antacids [73]. Many foods are fortified with calcium and can significantly add to the dietary calcium load. It is important that patients be made aware of calcium sources and recommendations for the daily elemental calcium load.

Generally, the use of 2.5 mEq/L dialysate calcium concentration minimizes the movement of calcium from blood to dialysate or dialysate to blood [1, 2, 73]. With 3.5 mEq/L calcium dialysate concentrations, most patients have a positive flux of calcium. Conversely, lower concentrations of dialysate calcium promote negative calcium flux. As with phosphorus, the movement of calcium depends on serum levels, dialysate levels, and the duration of exposure to dialysate. Serum calcium is affected by calcium load, the presence of active vitamin D, and circulating PTH. Severe SHPT promotes release of calcium from the bone, adding another source for hypercalcemia. Serum calcium may also be elevated when PTH levels are low and blood calcium is not being incorporated into the bone. Various retrospective studies suggest that elevated serum calcium levels may be associated with increased mortality [1, 6].

Vitamin D products are commonly used to control PTH levels in CKD-MBD. Vitamin D, vitamin D analogs, and vitamin D derivatives are found in Table 15.6. Each of these vitamin D products has specific structure and actions. Vitamin D doses are typically based on the elevation of plasma PTH.

Table 15.5 Available phosphate binder compounds (Package Inserts)

Binder source	Rx	Available forms	Content (mineral/metal/element)	Potential advantages	Potential disadvantages
Aluminum hydroxide	No	Liquid, tablet, capsule	Aluminum (varies from 100 mg to >200 mg)	Effective, high phosphate-binding capacity; various forms	Aluminum overload; altered bone mineral integrity, dementia
Calcium acetate	Yes	Capsule, tablet	25 % elemental Ca^{2+} (169 mg elemental Ca^{2+}/667 mg cap)	Effective, potentially better binding capability than $CaCO_3$ with less Ca^{2+} absorption	Adds to Ca^{2+} load; potential for hypercalcemia, soft tissue calcification, and PTH suppression; prescription, more costly than $CaCO_3$; GI sx
Calcium carbonate	No	Liquid, tablet, chewable, capsule, gum	Contains 40 % elemental Ca^{2+} (200 mg elemental Ca^{2+}/ 500 mg $CaCO_3$)	Effective, inexpensive, readily available	Additional Ca^{2+} load with potential hypercalcemia, soft tissue calcification, PTH suppression; GI symptoms
Calcium citrate	No	Tablet, capsule, liquid	Contains 22 % elemental Ca^{2+}	Not recommended	Citrate enhances aluminum absorption
Magnesium carbonate and Calcium carbonate*	No	Tablet	Approx 28 % Mg^{2+}/total Mg carbonate and 25 % elemental Ca^{2+}/total $CaCO_3$	Effective; potential for lower calcium load than calcium-based binders	GI symptoms, potential for hypermagnesemia
Sevelamer HCl	Yes	Caplet	None	Effective; no calcium/metal; not absorbed; potential to reduce coronary/aortic calcification compared to calcium-based binders; reduces plasma lipid	Cost; potential for decreased bicarbonate levels; may require calcium supplement if symptoms of hypocalcemia are present; GI symptoms
Sevelamer carbonate	Yes	Tablets, powder	None	Same as above	Cost; may require calcium supplement if symptoms of hypocalcemia are present; GI symptoms
Lanthanum carbonate	Yes	Wafer, chewable	250 or 500 mg elemental lanthanum	Effective, chewable wafers	Potential for lanthanum accumulation although effect is not fully elucidated; GI symptoms

*Some formulations of Magnesium Carbonate and Calcium carbonate with extra nutrients may be prescription only

Table 15.6 Vitamin D products (USA)

Product	Brand name	Format	Target CKD population
Calcitriol 1α,25(OH)D_3	Calcitriol generic	Oral, IV	Stages 3–5
First-generation D_3 molecule; chemically different from D_2 analogs	Rocaltrol® (Roche)	Oral	Stage 5D
	Calcijex® (Abbott)	IV	Stage 5D
Doxercalciferol 1α (OH)D_2	Hectorol® capsules	Oral	Stages 3–5
Prohormone, activated by liver	Hectorol® (Sanofi)	IV	Stage 5D
Synthetic D2			
Paricalcitol 1α $(OH)_2$ 19-nor-D_2	Zemplar® capsules	Oral	Stages 3–4, 5D
Synthetic D2	Zemplar® (Abbott)	IV	Stage 5D

Package Inserts

Calcitriol is the naturally occurring form of vitamin D hormone. It is used to treat hypocalcemia and SHPT and is available in oral and IV forms. It has been associated with hypercalcemia, partly due to increased gastrointestinal calcium absorption.

Paricalcitol [19-nor-1,25$(OH)_2$] is a sterol derived from vitamin D_2. It is missing a carbon-19 methylene group that is present in all natural vitamin D metabolites. Paricalcitol has been reported to have a lower calcemic effect through VDR selectivity at the tissue level of bone and intestine while having greater activity in the parathyroid tissue. Clinical trials have demonstrated the effectiveness of paricalcitol at controlling PTH [74, 75]. Additionally, it has been suggested that the use of paricalcitol provides a survival advantage over calcitriol [76].

Doxercalciferol [1α-hydroxyvitamin D_2] is a prohormone that requires hepatic conversion to its active form, 1,25$(OH)_2D_2$. Doxercalciferol, IV or oral forms, has been shown to be clinically effective in controlling PTH in CKD patients [77].

Dihydrotachysterol$_2$ (DHT_2) is one of the first vitamin D derivatives used to treat CKD-MBD, but there are few convincing reports on its efficacy and safety. It is available for oral administration in tablet and liquid forms [78]. There are several other vitamin D products that are used outside the USA which will not be discussed here but can be reviewed in the literature [78].

Nutritional Vitamin D

Navaneethan et al. performed a systematic review and meta-analysis of both observational and randomized controlled trials in respect to vitamin D supplementation in CKD [79]. The prevalence of vitamin D deficiency is well documented in the general public and increases with extremes of age, postmenopausal state, black race, women, and the presence of CKD. It is estimated as many as 80 % of those with CKD are vitamin D deficient in some parts of the world. Although the kidneys are the primary site for hydroxylation of vitamin D to its active form, many other extrarenal conversion sites have been identified, including the parathyroid gland. There is renewed interest in the use of calciferols to affect bone and mineral metabolism in CKD. The interest has been intensified by studies demonstrating nonskeletal benefits of vitamin D. An association between mortality and vitamin D deficiency has been shown in those with CKD both before and after dialysis dependence. The observational and randomized controlled studies indicate that vitamin D supplementation improves biochemical end points (increased 25(OH)D and 1,25$(OH)_2$D levels, reduced PTH levels) without increasing the frequency of hypercalcemia or hyperphosphatemia. Like other interventions, future research will need to determine whether supplementation and improved biochemical end points translate into better CV and skeletal outcomes in CKD [79, 80].

Vitamin D is not commonly found in plants and animal food sources except for oily fish. Most vitamin D is obtained through ultraviolet B radiation acting on the 7-dehyrdrocholesterol in the skin to form previtamin D_3 which is quickly converted to D_3. Vitamin D_2 is similarly produced by solar irradiation of marine plankton or yeasts and molds. Because of the endocrine functions and the ability of mammals to synthesize vitamin D, it is not truly a vitamin but is a prehormone.

Vitamin D, whether ingested or derived from the skin, is hydroxylated to 25-hydroxyvitamin D_2 or D_3 in the liver. 25-Vitamin D concentration in the blood is a reliable measure of vitamin D deficiency because it is stable in the circulation and has a half-life of about 2 weeks. The major site of activation is the kidneys, but there are other sites of vitamin D activation, all of which are influenced by serum levels of PTH, FGF23, calcium, and phosphorus. The Institute of Medicine was charged with conducting a review of existing literature to determine the optimal intake of vitamin D and calcium for the general public. There were pitfalls with each of the potential outcome measures (variability of PTH level and assays, fractures, calcium absorption) as well as a mixture of study designs without the ability to factor in the effect of sun exposure and seasonal variations. The IOM found a paucity of data demonstrating any causal benefit of vitamin D for most health outcomes but suggested that most children and adults would have adequate vitamin D levels (20 ng/mL) with 600 IU/day for those between 1 and 70 years of age (800 IU/day for those over 70). Many have taken issue with this recommendation and suggest that it is too low. Vitamin D intoxication is rare in adults who are supplemented with 1,000–2,000 IU vitamin D daily. Hypercalcemia, the primary manifestation of toxicity, is generally not seen until vitamin D levels exceed 115–200 ng/mL (375–500 nmol/L). Without more definitive research, the IOM recommendations may be reasonable, but as clinicians we must consider individual patient characteristics that might dictate a different approach [79, 80].

Calcimimetics

Calcimimetics are a class of compounds that act on the CaSRs in the parathyroid cells. They lower the threshold for receptor activation by extracellular calcium ions and suppress PTH secretion. Unlike vitamin D products, calcimimetics reduce plasma PTH with either no change or a decrease in serum calcium and phosphorus levels. Cinacalcet HCl (Sensipar™) has been shown to be effective in lowering PTH, even in patients who have been unresponsive to vitamin D due to gland hyperplasia. The action of cinacalcet is rapid with peak reduction of PTH levels in 2–6 h after administration. The drug is taken orally and is generally well tolerated [81, 82]. The pharmacologic actions of calcimimetics compared to vitamin D analogs can be found in Table 15.7.

With the potential decrease in serum calcium, it is important for patients to have normal serum calcium levels before starting calcimimetic therapy. Patient response to cinacalcet is varied, and biochemical markers should be measured routinely; calcium and phosphorus should be checked within

Table 15.7 Actions of pharmacologic agents used to treat SHPT

Vitamin D/analogs	Calcimimetic
Acts on the genomic receptor	Acts of the cell surface receptor
Slow onset and recovery (days to weeks)	Rapid onset (minutes) and recovery (hours to days)
Inhibits PTH synthesis	Decreases serum levels of Ca^{2+} and P
Potential for increasing serum Ca^{2+} and P	Inhibits PTH synthesis and secretion
Little or no impact on hyperplasic/nodular glands	Inhibits gland hyperplasia Can work even when glands are nodular

Data from [10, 71, 81]

1 week and PTH within 1–4 weeks after initiation of therapy. The initial dose is 30 mg/day with titration every 4 weeks up to a maximum dose of 180 mg/day (Product Insert). Cinacalcet can be used in conjunction with phosphate binders and vitamin D products to maximize treatment of CKD-MBD [81–83].

Alternative Dialysis Therapies

More frequent hemodialysis sessions and longer session lengths may offer improved phosphorus control and potentially improvements in bone and mineral status. An analysis of the Frequent Hemodialysis Network Daily and Nocturnal Trials examined the effects of treatment assignment on predialysis serum phosphorus and on prescribed dose of phosphorus binder. While frequent hemodialysis did not have major effects on calcium or PTH, these trials showed that frequent hemodialysis helps control serum phosphorus and extended session lengths may allow more liberal diets and freedom from phosphorus binders. Of the therapies offered, more frequent, long nocturnal dialysis had the most profound effect and eventually required more than 40 % of patients to have phosphorus added to the dialysate to maintain normal serum P levels [84].

Patient Education

Patient education is a vital part of the long-term management of CKD-MBD. Adherence to treatment regimens depends partially on the patient's understanding of their importance. While the ultimate choice of following the advice of the healthcare team resides with the patient, the clinical team must provide information at the level the patient can understand, utilizing a common message and varied teaching techniques.

Parathyroidectomy

PTX, subtotal or total, is an option for those patients who do not respond to medical or pharmacologic management of SHPT [1, 2]. Postsurgical management of the patient is critical [85, 86]. With the sudden reduction in plasma PTH after surgery, flux of calcium and phosphorus into the bone can be remarkable. This condition is referred to as "hungry bone syndrome" which results in significant hypocalcemia that requires close monitoring and often IV calcium and vitamin D administration [85, 86].

Treatment Options for Adynamic Bone

Patients with adynamic bone have an increased risk for fracture [2, 6], hypercalcemia, and extraskeletal calcifications. In dialysis patients with biopsy-documented adynamic bone or iPTH levels below 100 pg/mL, bone turnover can be stimulated by allowing the iPTH to rise. This may be accomplished by decreasing the total calcium load, by lowering serum calcium, and/or by reducing or discontinuing agents that suppress PTH synthesis and secretion [31, 32].

Summary

Whether treating biopsy-documented RO or CKD-MBD, identified by abnormal biomarkers, bone and mineral abnormalities, or extraskeletal calcifications, the issues are complex. There have been significant advances in the understanding of bone and mineral abnormalities in CKD patients, including their significant potential for increasing morbidity and mortality. Additionally, techniques for monitoring and treating these abnormalities continue to evolve. Improving patient outcomes requires early identification of abnormalities and appropriate utilization of all the therapeutic options—nutritional, pharmacologic, and dialytic to minimize the progression and complications of RO or CKD-MBD. Furthermore, successful management of bone and mineral abnormalities in CKD requires the full commitment and participation from the entire healthcare team, most importantly the patient.

Case Presentation

The patient is a 55-year-old male who has been on dialysis for 3 years. He has had a slow decline in urine output, and a recent collection shows that the output is now insignificant. He has been adherent to his dialysis and medication regimens. His bone and mineral parameters have been well controlled as shown in the history below with the following medications (Table 15.8):

Considering KDIGO recommendations (assuming no financial limits) and based on his most recent biochemical parameters, what course of action would you take?

Action 1: Evaluate phosphorus intake, counsel the patient, and increase binders as appropriate.
Action 2: Increase Hectorol dose by 1–2 μg per treatment.
Action 3: Start cinacalcet at 30 mg/day

☐ Action 1 and 2 ☐ Action 1 and 3 ☐ Action 1 only
☐ Action 2 only ☐ Action 3 only ☐ Action 2 and 3.

Key

Based on KDIGO guidelines, the most appropriate actions are 1 and 2. His serum phosphorus is increasing, possibly from dietary intake and loss of urinary phosphorus clearance. His phosphorus intake should be evaluated and binders increased as appropriate to control the serum phosphorus toward the normal range.

The iPTH has had a significant change even though it does not exceed either extreme limit (high or low). Additionally, the increased alkaline phosphatase suggests (in alignment with PTH) increased bone turnover. Additional suppression of iPTH is warranted to avoid the upper extreme level.

Table 15.8 Three Renagel per meal and 2 μg Hectorol per treatment

Date	Calcium (mg/dL)	Phosphorus (mg/dL)	Alkaline phosphatase	iPTH (pg/mL)
7/1/2011	8.8	4.5	92	215
10/4/2011	9.0	4.6	89	206
1/7/2012	8.9	4.8	102	243
4/5/2012	8.4	5.5	120	310
7/12/2012	8.2	6.0	130	430

The serum calcium is below the level at which one should initiate cinacalcet. If the serum calcium was above 8.4 mg/dL, cinacalcet would be an appropriate action, with the potential to reduce the serum phosphorus and reduce the secretion of PTH.

References

1. National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42 Suppl 3:S1–202.
2. 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:S1–130.
3. Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, Sprague SM, Goldfarb S. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of CKD-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2010;55(5):773–99.
4. Manns BJ, Hodsman A, Zimmerman DL, Mendelssohn DC, Soroka SD, Chan C, Jindal K, Klarenbach S. Canadian Society of Nephrology commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of CKD-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2010;55(5):800–12.
5. Goldsmith DJA, Covic A, Fouque D, Locatelli F, Olgaard K, Rodriquez M, Spasovski G, Urena P, Zoccali C, London GM, Vanholder R. Editorial review: endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement. Nephrol Dial Transplant. 2010;10:1093.
6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie E, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208–18.
7. Young EW, Akia T, Albert J, McCarthy J, Kerr PG, Mendelssohn DC, Jadoul M. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients on Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44:S34–8.
8. Gutierrez OM. Fibroblast growth factor 23 and disordered vitamin D metabolism in chronic kidney disease: updating the "trade-off" hypothesis. Clin J Am Soc Nephrol. 2010;5(9):1710–6.
9. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69:1945–53.
10. Olgaard K, editor. Clinical guide to bone and mineral metabolism in CKD. New York, NY: National Kidney Foundation; 2006.
11. Llach F, Yudd M. Pathogenic, clinical, and therapeutic aspects of secondary hyperparathyroidism. Am J Kidney Dis. 1998;32 Suppl 2:S3–12.
12. Malluche H, Faugere D. Hyperphosphatemia: pharmacologic intervention yesterday, today, and tomorrow. Clin Nephrol. 2000;54(4):309–17.
13. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, et al. Regulation of fibroblast growth factor-23 signaling by Klotho. J Biol Chem. 2006;281:6120–3.
14. Jüppner H. Phosphate and FGF-23. Kidney Int. 2011;79 Suppl 121:S24–7.
15. Burnett SM, Gunawardene SC, Bringhurst FR, Jüppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. J Bone Miner Res. 2006;21(8):1187–96.
16. Isakova T, Gutierrez OM, Wolf M. A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. Kidney Int. 2009;76(7):705–16.
17. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011;305(23):2432–9.
18. Bacchetta J, Fouque D. FGF23 and Klotho. 2011. www.tecomedical.com
19. Razzaque MS. Klotho and Na^+, K^+-ATPase activity: solving the calcium metabolism dilemma. Nephrol Dial Transplant. 2008;23:459–61.
20. Silver J, Levi R. Cellular and molecular mechanisms of secondary hyperparathyroidism. Clin Nephrol. 2005;63(2):119–26.
21. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, MacDonald PN, Brown AJ. Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. J Clin Invest. 1996;97(11):2534–40.
22. Malluche HH, Mawad H, Monier-Faugere M-C. Effects of treatment of renal osteodystrophy on bone histology. Clin J Am Soc Nephrol. 2008;3 Suppl 3:S157–63.

23. Sutton AL, Cameron EC. Renal osteodystrophy: pathophysiology. Semin Nephrol. 1992;12(2):91–100.
24. Slatopolsky E, Brown A, Dusso A. Calcium, phosphorus, and vitamin D disorders in uremia. Contrib Nephrol. 2005;149:261–71.
25. Coburn JW, Koeppel MH, Brickman AS, Massry SG. Study of intestinal absorption of calcium in patients with renal failure. Kidney Int. 1973;3:264–72.
26. Rodriguez M, Martin-Malo A, Martinez ME, Torres A, Felsenfeld AJ, Llach F. Calcemic response to parathyroid hormone in renal failure: role of phosphorus and its effect on calcitriol. Kidney Int. 1991;40:1055–62.
27. Massry SG, Stein R, Garty J, Arueff AI, Coburn JW, Norman AW, Friedler RM. Skeletal resistance to the calcemic action of parathyroid hormone in uremia: role of 1,25 $(OH)_2$ D_3. Kidney Int. 1976;9:467–74.
28. Hoyland JA, Picton ML. Cellular mechanisms of renal osteodystrophy. Kidney Int Suppl. 1999;73:S8–13.
29. Couttenye MM, D'Haese PC, Verschoren WJ, Behets GJ, Schrooten I, De Broe ME. Low bone turnover in patients with renal failure. Kidney Int Suppl. 1999;73:S70–6.
30. Salusky IB, Goodman WG. Adynamic renal osteodystrophy: is there a problem? J Am Soc Nephrol. 2001;12:1978–85.
31. Coen G. Adynamic bone disease: an update and overview. J Nephrol. 2005;18(2):117–22.
32. Sanchez C, Auziliadora BM, Selgas R, Mate A, Millan I, Eugenia Martinez M, Lopez-Barea F. Parathormone secretion in peritoneal dialysis patients with adynamic bone disease. Am J Kidney Dis. 2000;36(5):953–61.
33. Gupta A, Kallenback LR, Zasuwa G, Devine GW. Race is a major determinant of secondary hyperparathyroidism in uremic patients. J Am Soc Nephrol. 2000;11(2):330–4.
34. Galassi A, Spiegel DM, Bellasi A, Block GA, Raggi P. Accelerated vascular calcification and relative hypoparathyroidism in incident hemodialysis diabetic patients receiving calcium binders. Nephrol Dial Transplant. 2006;21(11):3215–22.
35. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary artery calcification in young adults with end stage renal disease who are undergoing hemodialysis. N Engl J Med. 2000;342:1478–83.
36. Guérin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end stage renal disease. Nephrol Dial Transplant. 2000;15:1014–21.
37. Blacher J, Guérin AP, Pannier B, Marchais SJ, London GM. Arterial calcification, arterial stiffness, and cardiovascular risk in end stage renal disease. Hypertension. 2001;38:938–42.
38. Desjardins L, Liabeuf S, Renard C, Lenglet A, Lemke HD, Choukroun G, Drueke TB, Massey ZA. FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages. Osteoporos Int. 2012;23(7):2017–25.
39. Memon F, El-Abbadi M, Nakatani T, Taguchi T, Lanske B, Razzaque MS. Does FGF23-klotho activity influence vascular and soft tissue calcification through regulating phosphate homeostasis? Kidney Int. 2008;74(5):566–70.
40. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, Stehman-Breen CO. Risk factors and mortality associated with calciphylaxis in end stage renal disease. Kidney Int. 2001;60:324–32.
41. Ahmed S, O'Neill KD, Hood AF. Calciphylaxis is associated with hyperphosphatemia and increased osteopontin expression by vascular smooth muscle cells. Am J Kidney Dis. 2001;37(6):1267–76.
42. Rogers NM, Teubner DJ, Coates PT. Calcemic uremic arteriolopathy: advances in pathogenesis and treatment. Semin Dial. 2007;20(2):150–7.
43. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome, and therapy. Kidney Int. 2002;61:2210–7.
44. Kuchle C, Fricke H, Held E, Schiffl H. High-flux hemodialysis postpones clinical manifestation of dialysis related amyloidosis. Am J Nephrol. 1996;16(6):484–8.
45. Ayli M, Ayli D, Azak A, Yuksel C, Atilgan G, Dede F, Akalin T, Abayli E, Camlibel M. The effect of high-flux hemodialysis on dialysis-associated amyloidosis. Ren Fail. 2005;27(1):31–4.
46. Yamamoto S, Kazama JJ, Narita I, Naiki H, Gejyo F. Recent progress in understanding dialysis-related amyloidosis. Bone. 2009;45 Suppl 1:S39–42.
47. Moe SM, Drüeke TB. Controversies in bone and mineral metabolism in CKD. a bridge to improving healthcare outcomes and quality of life. Am J Kidney Dis. 2004;43(3):552–7.
48. Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. Curr Osteoporos Rep. 2005;3(1):5–12.
49. Toffaletti JG. Calcium: is ionized calcium always right and total calcium always wrong? Clin Lab News. 2011;37(9):8–10.
50. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine; Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press, Washington, DC; 2011.
51. Martin KJ, González EA. Prevention and control of phosphate retention/hyperphosphatemia in CKD-MBD: what is normal, when to start, and how to treat? Clin J Am Soc Nephrol. 2011;6(2):440–6.
52. Qi Q, Monier-Faugere MC, Geng Z, Malluche HH. Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. Am J Kidney Dis. 1995;26(4):622–31.

53. Martin KJ, Hruska KA, Lewis J, Anderson C, Slatopolsky E. The renal handling of parathyroid hormone. Role of peritubular uptake and glomerular filtration. J Clin Invest. 1977;60:808–14.
54. Martin KJ, Akhtar I, Gonzalez EA. Parathyroid hormone: new assays, new receptors. Semin Nephrol. 2004;24:3–9.
55. Goodman WG, Salusky IS, Jūppner H. New lessons from old assays: parathyroid hormone (PTH), its receptors, and the potential biological relevance of PTH fragments. Nephrol Dial Transplant. 2002;17(10):1731–6.
56. Joly D, Drueke TB, Alberti C, Houillier P, Lawson-Body E, Martin KJ, Massart C, Moe SM, Monge M, Souberb JC. Variation in serum and plasma PTH levels in second-generation assays in hemodialysis patients: a cross-sectional study. Am J Kidney Dis. 2008;51(6):987–95.
57. Canavese C, Barolo S, Gurioli L, Cadario A, Portigliatti M, Isaia G, Thea A, Marangella M, Bongiorno P, Cavagnino A, Peona C, Boero R, D'Amicone M, Cardelli R, Rossi P, Piccoli G. Correlations between bone histopathology and serum biochemistry in uremic patients on chronic hemodialysis. Int J Artif Organs. 1998;21:443–50.
58. Moe SM, Drueke T. Improving global outcomes in mineral and bone disorders. Clin J Am Soc Nephrol. 2008;3 Suppl 3:S127–30.
59. Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. Semin Dial. 2007;20(4):295–301.
60. Sullivan CM, Leon JB, Sehgal AR. Phosphorus-containing food additives and the accuracy of nutrient databases: implications for renal patients. J Ren Nutr. 2007;17(5):350–4.
61. Carnovale E, Lugaro E, Lombardi-Boccia G. Phytic acid in faba bean and pea: effect on protein availability. Cereal Chem. 1988;65(2):114–7.
62. Vikas Kumar V, Sinha AK, Hariner PS, Becker K. Dietary roles of phytate and phytase in human nutrition: a review. Food Chem. 2010;120(4):945–59.
63. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson AR, Kopple JD. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(3):519–30.
64. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(2):257–64.
65. Oenning LL, Vogel J, Calvo MS. Accuracy of methods estimating calcium and phosphorus intake in daily diets. J Am Diet Assoc. 1988;88(9):1076–80.
66. Zhang ZW, Shimbo S, Miyake K, et al. Estimates of mineral intakes using food composition tables vs measures by inductively-coupled plasma mass spectrometry: Part 1. Calcium, phosphorus and iron. Eur J Clin Nutr. 1999;53(3): 226–32.
67. Moreno-Torres R, Ruiz-Lopez MD, Artacho R, et al. Dietary intake of calcium, magnesium and phosphorus in an elderly population using duplicate diet sampling vs food composition tables. J Nutr Health Aging. 2001;5(4):253–5.
68. US National Academy of Sciences; Institute of Medicine; Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. 1997. http://www.nal.usda.gov/fnic/DRI//DRI_Calcium/146-189.pdf. Accessed 22 Feb 2012.
69. Langman CB, Cannata-Andia JB. Calcium in chronic kidney disease: myths and realities. Clin J Am Soc Nephrol. 2010;5 Suppl 1:S1–2.
70. Moe SM. Confusion on the complexity of calcium balance. Semin Dial. 2010;23(5):492–7.
71. Goodman WG. Medical management of secondary hyperparathyroidism in chronic renal failure. Nephrol Dial Transplant. 2003;18(3):iii2–8.
72. Gutzwiller JP, Schneditz D, Huber AR, Schindler C, Gutzwiller CE. Estimating phosphate removal in haemodialysis: an additional tool to quantify dialysis dose. Nephrol Dial Transplant. 2002;17:1037–44.
73. Malberti F, Ravani P. The choice of dialysate calcium concentration in the management of patients on haemodialysis and haemodiafiltration. Nephrol Dial Transplant. 2003;18 Suppl 7:vii37–40.
74. Brown AJ. Vitamin D analogues. Am J Kidney Dis. 1998;32(4 Suppl 2):S25–39.
75. Llach F, Keshav G, Goldblat MV, Lindberg JS, Sadler R, Delmez J, Arruda J, Lau A, Slatopolsky E. Suppression of parathyroid hormone secretion in hemodialysis patients by a novel vitamin D analog: 19-Nor-1,25-dihydroxyvitamin D_2. Am J Kidney Dis. 1998;32(4 Suppl 2):S48–54.
76. Teng M, Wolf M, Lowrie E, Ofstun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349:446–56.
77. Frazzo JM, Elangovan L, Maung HM, Chesney RW, Acchiardo SR, Bower JD, Kelly BJ, Rodriguez HJ, Norris KC, Robertson JA, Levine BS, Goodman WG, Gentile D, Mazess RB, Kylklo DM, Douglass LL, Bishop CW, Coburn JW. Intermittent doxercalciferol (1α hydroxyvitamin D2) therapy for secondary hyperparathyroidism. Am J Kidney Dis. 2000;36:550–61.
78. Morii H, Ishimura E, Inoue T, Tabata T, Morita A, Nishii Y, Fukushima M. History of vitamin D treatment of renal osteodystrophy. Am J Nephrol. 1997;17:382–6.

79. Kandula P, Dobre M, Schold JD, Schreiber Jr MJ, Mehrotra R, Naveethan SD. Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials. Clin J Am Soc Nephrol. 2011;6(1):50–62.
80. Monk RD, Bushinsky DA. Making sense of the latest advice on vitamin D therapy. J Am Soc Nephrol. 2011;22:994–8.
81. Block GA, Martin KJ, de Francisco ALM, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350:1516–25.
82. Nemeth EF, Heaton WH, Miller M, Fox J, Balandrin MF, Van Wagenen BC, Colloton M, Karbon WE, Scherrer J, Shatzen E, Rishton G, Scully S, Qi M, Harris R, Lacey D, Martin D. Pharmacodynamics of Type II calcimimetic compound cinacalcet HCL. J Pharmacol Exp Ther. 2004;308:627–35.
83. Goodman WG. Calcimimetics: a remedy for all problems of excess parathyroid hormone activity in chronic kidney disease? Curr Opin Nephrol Hypertens. 2005;14(4):355–60.
84. Daugirdas JT, Chertow GM, Larive B, Pierratos A, Greene T, Ayus JC, Kendrick CA, James SH, Miller BW, Schulman G, Salusky IB, Kliger AS. Frequent Hemodialysis Network (FHN) Trial Group. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. J Am Soc Nephrol. 2012;23(4):727–38.
85. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. Am Surg. 2004;70(2):114–9.
86. Richards ML, Wormuth J, Bingener J, Sirinek K. Parathyroidectomy in secondary hyperparathyroidism: is there an optimal operative management? Surgery. 2006;139(2):174–80.

Chapter 16
Physical Activity and Exercise

Kirsten L. Johansen and Patricia Painter

Key Points

- An overview of the role of physical activity and exercise to minimize health compromise in patients diagnosed with chronic kidney disease.
- Review of approaches to integrate more physical activity and exercise into regular routines among patients diagnosed with chronic kidney disease.

Keywords Physical activity • Exercise • Chronic kidney disease • Reconditioning • Walking • End-stage renal disease • Dialysis

Introduction

Physical activity, or bodily movement that is produced by the contraction of skeletal muscles, is a key modifiable determinant of energy expenditure. In recognition of the important relationship between physical activity and nutrition (energy intake), recent nutrition guidelines from the US Department of Health and Human Services now include recommendations about physical activity [6]. Diet and physical activity should be considered together in order to determine calorie requirements and healthy intake to achieve the desired energy balance, whether it is neutral in order to avoid weight gain, negative to achieve weight loss, or positive to reverse malnutrition through weight gain and accretion of muscle.

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Physical Activity, Exercise, and Their Classification

Physical activity encompasses activities of daily living, recreational activities, and home maintenance and occupational activities. Exercise is a subset of physical activity that is planned, structured, repetitive, and usually done with the intention to improve or maintain fitness or strength. Intensity of exercise or physical activity is generally described as light, moderate, or vigorous, and these can be quantified subjectively or objectively. In healthy individuals, the level of perceived exertion correlates with the heart rate, and therefore subjective designation can be helpful. Subjectively, light activity feels easy. Generally, the breathing pattern does not change noticeably and perspiration is not generated. In moderate activity, the breathing rate increases, and there is often a light sweat after several minutes of activity. Individuals perceive moderate exertion as "somewhat hard" [7] or as a 5 or a 6 on a 0–10-point scale [8]. During vigorous activity, breathing is often deep and rapid, and sweating occurs relatively quickly, and the activity is perceived as hard or very hard or as a 7 or 8 on a 10-point scale.

In objective terms, physical activity is classified as a function of energy expenditure, in units of metabolic equivalents (METs), where one MET is the energy expended at rest. By this metric, activity that requires less than 3 METs is considered light activity, activity that requires 3–5.9 METs is considered moderate, and activity that requires ≥6 METs is considered vigorous. Ainsworth and colleagues have developed a comprehensive list of categories and types of physical activities and their respective MET values and energy cost, and their compendium has received widespread acceptance as a resource for exercise and weight management programs [9].

Exercise is also classified by type as endurance (or aerobic) or resistance (or strengthening) exercise. Endurance exercise involves repetitive, dynamic, and rhythmic use of large muscles and is the form of exercise that is most useful for improving cardiorespiratory fitness or maximal oxygen consumption (VO_{2max}). Resistance exercise generally involves lifting weights (sometimes including the weight of the body) or moving the body against an externally imposed resistance (such as using a strength training machine or stretching elastic bands).

Benefits of Exercise in the General Population

Both endurance and resistance exercise are associated with health benefits in the general population. Specifically, endurance exercise has been linked to lower risk of overall and cardiovascular mortality as well as to reduced risk of outcomes including cardiovascular events and development of diabetes mellitus, hypertension, colon cancer, and depression [10]. Regular physical activity can also improve the control of hypertension and diabetes among those with established disease, increase bone density, improve symptoms of arthritis, and improve physical functioning among those with limitations. In addition, resistance exercise increases muscle size and strength, improves functioning, and can help older individuals remain independent in their activities of daily living. Balance exercises can prevent falls, and flexibility activities such as stretching can help maintain freedom of movement [11].

In light of all of the evidence of the benefit of exercise and of a physically active lifestyle, the US Surgeon General developed a report on physical activity and health in 1996 [10], and more recently the US Department of Health and Human Services [8] and the American College of Sports Medicine together with the American Heart Association have issued updated guidelines and recommendations [12]. There is general consensus that people of all ages benefit from regular physical activity [8, 10]. To promote and maintain health, all healthy adults need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on 3 days each week [12]. Combinations of moderate- and vigorous-intensity activities can be performed to meet this recommendation, and additional benefits can be obtained by exceeding the minimum amounts of physical activity. In addition, adults will benefit by performing muscle-strengthening activities at least twice each week.

Although the Surgeon General's recommendations were meant to apply to adults of all ages, the American College of Sports Medicine and the American Heart Association developed a set of physical activity guidelines specifically addressing older adults (>65 years) and individuals with chronic conditions [13]. These guidelines recognized that the goals of exercise might differ in these populations, shifting from prevention of disease and increasing life expectancy toward controlling chronic diseases, minimizing the biological changes of aging, reversing disuse syndromes, increasing mobility and function, assisting with rehabilitation from acute and chronic diseases, and maximizing psychological health. These guidelines also highlighted the importance of considering the intensity of physical activity on a relative rather than an absolute scale since elderly individuals or those with "clinically significant chronic conditions and/or functional limitations" [13] (such as chronic kidney disease) may perceive activities as moderate or vigorous even if they would be light activity for a younger, healthier individual. The recommendations to maintain an active lifestyle with at least 30 min of moderate endurance activity on 5 or more days per week plus strengthening activities on 2 or more days were identical to those for younger adults with the aforementioned caveat about relative intensity. In addition, the guidelines for older adults and adults with chronic disease include a recommendation that older adults should perform activities that maintain or increase flexibility on at least 2 days each week for at least 10 min/day and that those at substantial risk of falls should perform exercises designed to maintain or improve balance to reduce the risk of injury from falls [13]. Finally, the guidelines specifically address the need to increase activity gradually among those who are not initially active at recommended levels and state that for some older adults with low fitness, gradual and safe increase in activity may necessitate several months of activity at less than target levels.

Potential Benefits of Increased Physical Activity Among Patients with CKD

Patients with end-stage renal disease are extremely inactive as a group, and inactivity is associated with lower survival in this population. In a study that enrolled 286 patients receiving maintenance hemodialysis, 59 % reported that they were not doing any physical activity beyond that needed for activities of daily living [14]. Only 12 % reported meeting recommended physical activity targets (30 min of physical activity on 3 or more days of the week). A recent US Renal Data System special study, the Comprehensive Dialysis Study, used the Human Activity Profile [15] to assess physical activity among 1,642 patients newly initiated on dialysis [16]. Among the 1,547 patients who were ambulatory, Adjusted Activity Score (AAS), which is reflective of usual daily activity, was remarkably low when compared to normative data from subjects, even within groups separated by age and sex (Fig. 16.1) [17]. Among men, the 75th percentile of activity for each age group was below the 25th percentile among healthy men of the same age. Women were even less active, with the 75th percentile for women on dialysis consistently below the 1st percentile for healthy women.

The low level of physical activity among patients with ESRD is associated with low muscle mass, poor physical functioning, and higher mortality [18, 19]. Also associated with physical inactivity, patients with advanced CKD have low cardiorespiratory fitness as measured by peak oxygen consumption. A number of studies have reported on peak oxygen consumption among CKD patients, consistently demonstrating limitations, with maintenance dialysis patients usually approximately 50–60 % of age-predicted norms [20–25], patients with stage 3–4 CKD similarly low [26], and patients who have received kidney transplants at approximately 70 % of age-predicted values [20]. Like sedentary behavior, low cardiorespiratory fitness has been associated with higher mortality among ESRD patients [27]. Several studies have shown that exercise training can improve peak oxygen consumption among patients with ESRD [28–32] and with advanced CKD not requiring renal replacement therapy [26, 33, 34]. However, patients with CKD do not generally achieve normal levels of exercise capacity even after exercise training, suggesting that inactivity is not the only cause of low fitness in this population.

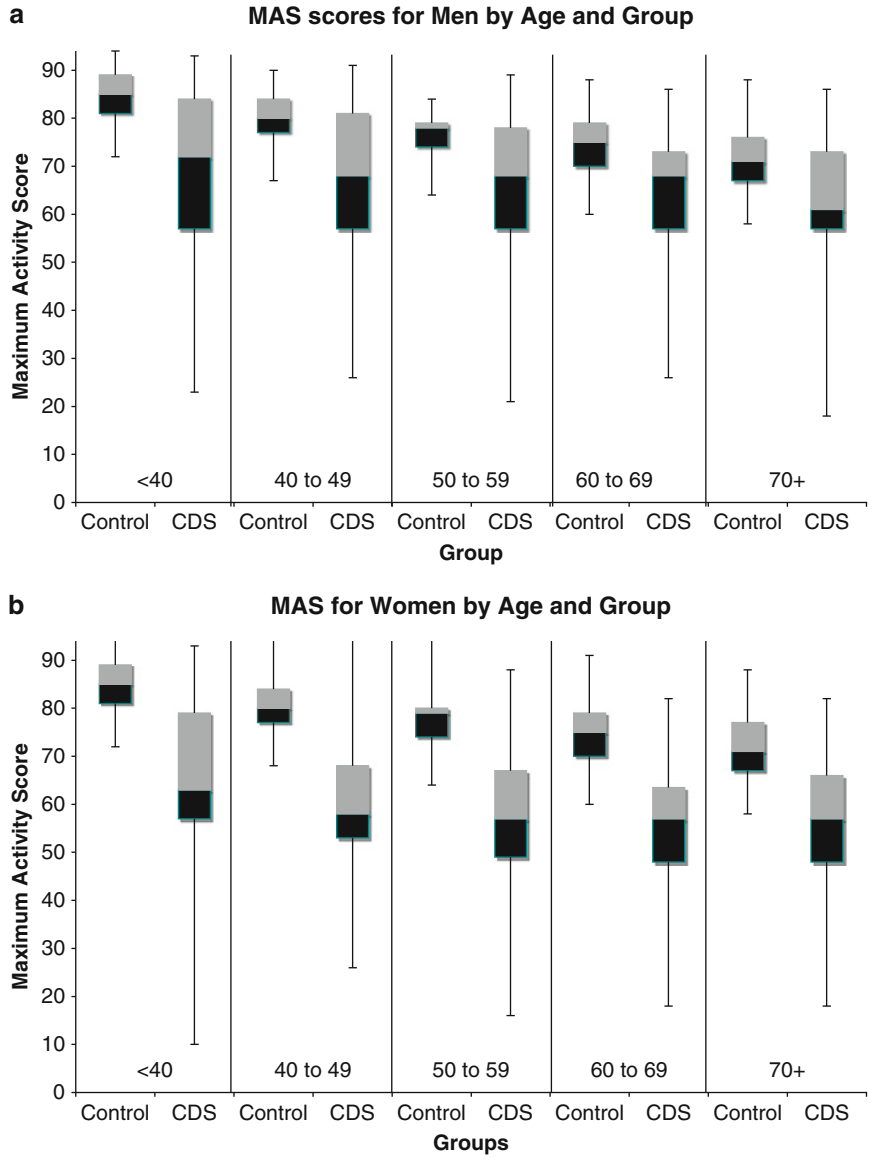

Fig. 16.1 Human Activity Profile scores among men and women in the Comprehensive Dialysis Study compared to norms for healthy individuals. Black boxes represent the 25th to 50th percentile; *gray boxes* represent the 50th to 75th percentile; lines above and below extend to the 9th and 1st percentile, respectively. In each figure, scores are shown by age group, beginning with age <40 and progressing by decade to age 70+. Within each age group, normative data is represented on the *left* and CDS participants' data are plotted on the *right*. Panels (**a**, **b**) show Maximum Activity Score (MAS) for men and women; panels (**c**, **d**) show Adjusted Activity Score (AAS) for men and women. From Johansen KL, Chertow GM, Kutner NG, Dalrymple L, Grimes B, Kaysen GA. Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int*, 2010;78(11):1164–1170. Reprinted with permission from Nature Publishing Group

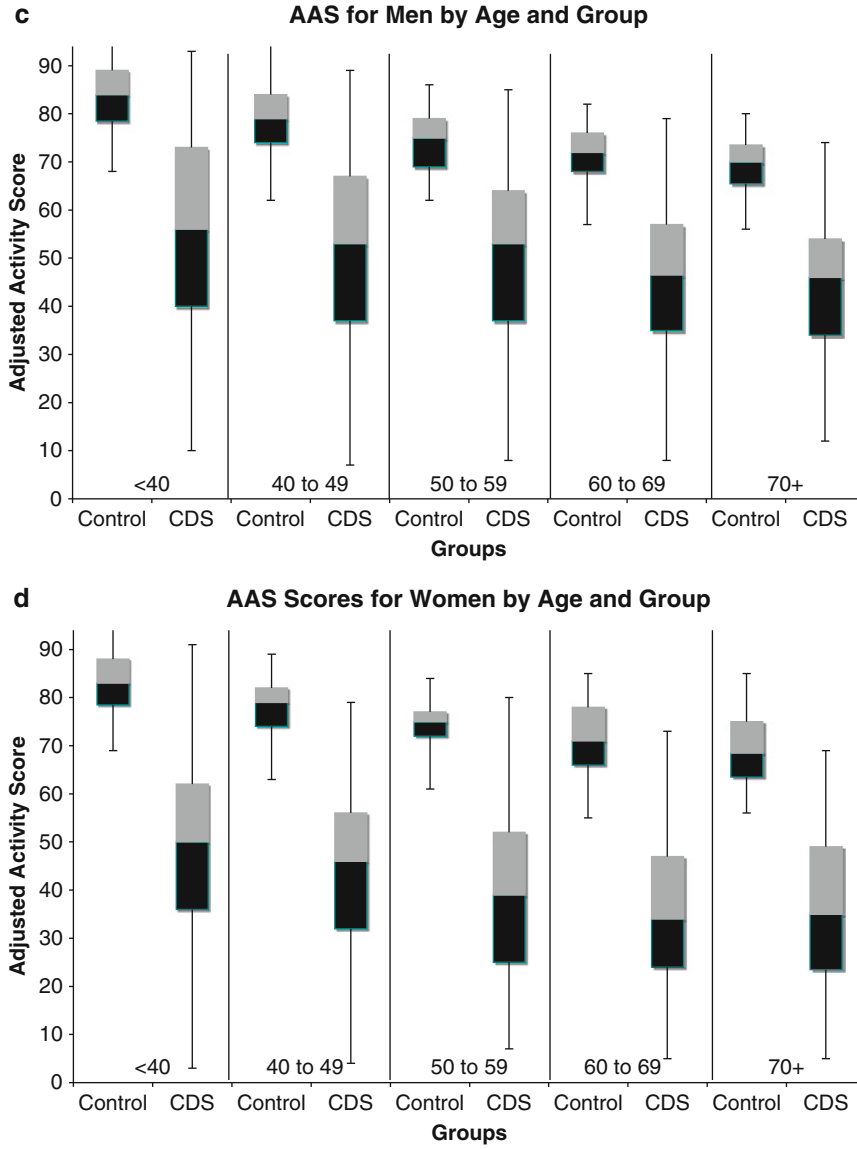

Fig. 16.1 (continued)

Peak oxygen consumption is closely linked to fitness and has been widely studied in the general population and among individuals with CKD, but it has limitations. First, many patients with ESRD cannot perform the maximal treadmill testing or bicycle ergometry needed to measure exercise capacity. Therefore, peak oxygen consumption may overestimate fitness since only those who are healthy and active enough to perform the testing are measured. Second, it is difficult to quantify the impact of improvements in peak oxygen consumption of patients' functioning. Other aspects of physical functioning such as self-reported functioning, physical performance, and physical frailty may be more closely related to quality of life.

Muscle atrophy and muscle weakness are commonly associated with inactivity and have been observed among patients with CKD [35] (Fig. 16.2). Weakness and deconditioning in turn can lead to

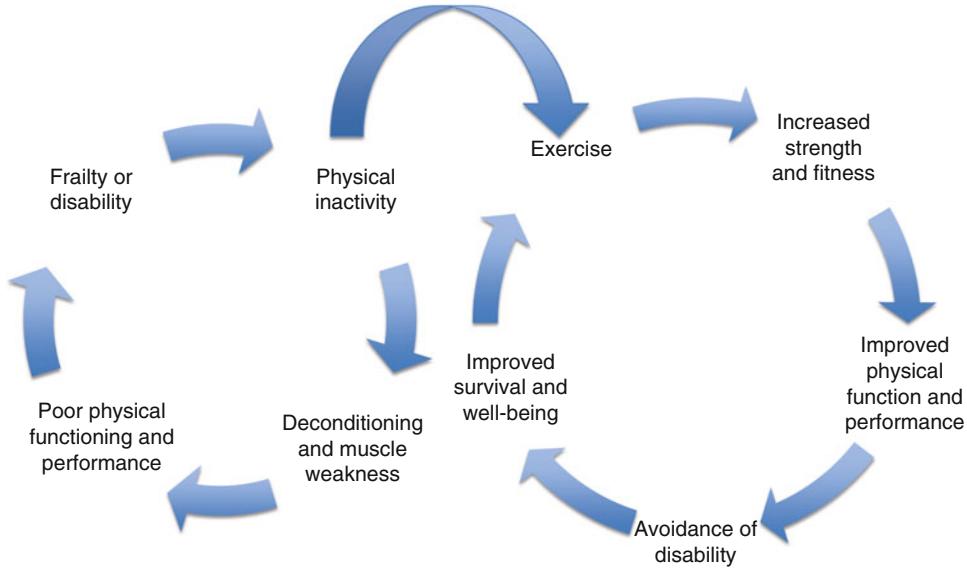

Fig. 16.2 The cycle of physical inactivity and the potential of exercise to reverse it

poor self-reported physical functioning and poor performance on physical tasks. Indeed, when asked about their difficulty in performing various tasks, maintenance dialysis patients report poor physical functioning [36–38], and they perform poorly when asked to do tasks such as walking, rising repeatedly from a chair, or climbing a flight of stairs [39]. Poor physical functioning has in turn been associated with higher mortality in the dialysis population and with worse outcomes following kidney transplantation [36, 40]. Both physical performance and self-reported functioning are correlated with physical activity among patients with ESRD based on questionnaire measures or direct measurement using accelerometry [18], supporting the possibility that physical inactivity is in part responsible for these impairments and raising the possibility that increasing activity could have beneficial effects.

Recently, the concept of physical frailty has been operationalized for study of outcomes among elderly community-dwelling individuals, and frailty has been shown to be associated with increased risk of disability, hospitalization, institutionalization, and death [41]. Low physical activity is one of the five components of this definition of frailty, along with slow gait speed, weak grip strength, exhaustion, and weight loss. Meeting three or more of these criteria marks an individual as frail. Frailty itself and many of its components have been associated with kidney function. In the Cardiovascular Health Study, the cohort in which this frailty phenotype was first developed, individuals with CKD were almost three times as likely to be frail as those with normal kidney function (OR 2.85) [42], and this association persisted after adjustment for demographic characteristics, comorbidity, and laboratory parameters such as hemoglobin and C-reactive protein (CRP; OR 1.5). In addition, some components of the frailty phenotype, such as tests of physical performance, correlate with GFR estimated using cystatin C, even at levels of eGFR above 60 m/min/1.73 m^2, with worse physical performance associated with worse kidney function. Definitions of frailty based on self-reported functioning rather than physical performance, which have also been shown to be associated with outcomes such as mortality and loss of independence [43] but may not identify the same individuals, have been applied in the setting of ESRD as well [44, 45]. Using these definitions of frailty, the majority of new dialysis patients are frail (67–73 %) even when the cohorts are not restricted to older individuals [44, 45]. Frailty was associated with hospitalization and mortality among patients with ESRD to a similar extent as in cohorts of healthy community-dwelling elderly individuals. Moreover, frailty was associated with earlier initiation of dialysis [45], raising the possibility that the clinical presentation of frailty is interpreted as manifestations of uremia.

Table 16.1 KDOQI guidelines about physical activity [62]

14.2	All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity
14.2a	Unique challenges to exercise in dialysis patients need to be identified in order to refer patients appropriately (e.g., to physical therapy or cardiac rehabilitation) and to enable the patients to follow regimens successfully. Such challenges include orthopedic/musculoskeletal limitations, cardiovascular concerns, and motivational issues
14.3	Measurement of physical functioning:
14.3a	Evaluation of physical functioning and reevaluation of the physical activity program should be done at least every 6 months
14.3b	Physical functioning can be measured using physical performance testing or questionnaires (e.g., SF-36)
14.3c	Potential barriers to participation in physical activity should be assessed in every patient
14.4	Physical activity recommendations:
14.4a	Many dialysis patients are severely deconditioned and therefore may need a referral for physical therapy to increase strength and endurance to the point where they are able to adopt the recommended levels of physical activity
14.4ai	Patients who qualify for cardiac rehabilitation should be referred to a specialist
14.4aii	The goal for activity should be for cardiovascular exercise at a moderate intensity for 30 min most, if not all, days per week. Patients who are not currently physically active should start at very low levels and durations and gradually progress to this recommended level
14.4b	Follow-up:
14.4bi	Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. Regular review should include assessment of changes in activity and physical functioning

Although intervention studies in the CKD population have not yet addressed the potential reversibility of frailty, they have demonstrated improvements in muscle strength and improved physical functioning. There have been at least 9 uncontrolled (time series) trials, 7 nonrandomized controlled trials, and 13 randomized controlled trials demonstrating that aerobic exercise training improves peak oxygen consumption among patients with ESRD by approximately 20 % on average [46]. Several studies have also documented improvements in physical performance measures such as gait speed, 6-min walk, and sit-to-stand time [47] as well as self-reported physical functioning, usually based on Physical Component Summary score or Physical Function score of the SF-36 [47–50]. Although the evidence is less robust, several small studies in patients with nondialysis-dependent CKD have also shown improvements in VO_{2peak} or maximal treadmill performance [33, 34, 51–55], physical performance [56], and self-reported physical function [54]. These outcomes are beneficial to patients in and of themselves, but it is possible that there could be additional benefits such as decreased hospitalizations, institutionalization, and mortality. Unfortunately, we are aware of no long-term physical activity interventions among patients with CKD targeting or documenting these outcomes.

In addition to the physical sequelae of inactivity, patients with all stages of CKD including those on dialysis and with transplanted kidneys suffer from a substantial burden of other chronic conditions that are potentially modifiable by participation in physical activity, such as hypertension, dyslipidemia, coronary artery disease, diabetes, and depression. Although the data to suggest that exercise improves these conditions comes mainly from studies in the general population, more and more evidence is accumulating in the CKD population [57]. For example, exercise improved blood pressure control and symptoms of depression among patients on maintenance dialysis [58, 59] and ameliorated endothelial dysfunction [54], inflammation [60], and oxidative stress [61] among patients with earlier stages of CKD. However, the benefits of exercise on outcomes such as cardiovascular events and mortality must still be extrapolated from the studies in healthy individuals. Nevertheless, the KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients include a set of guidelines related to physical activity (Table 16.1) and specifically state that "all dialysis patients should be encouraged by nephrology and dialysis staff to increase their level of physical activity" [62].

Risks of Physical Activity

Of course, increasing physical activity is accompanied by potential risks, particularly among individuals whose functioning is poor and fitness is low as is the case for many patients with CKD in whom risk of cardiovascular events is also high. The two major types of risk are musculoskeletal injury and cardiovascular events. There are no large studies on which to base estimates of risk among patients with CKD. In the general population, regular physical activity, particularly participation in vigorous exercise and sports activities, is associated with an increased incidence of activity-related injury. However, moderate physical activity also appears to confer some protection against injuries, likely through gains in neuromuscular control, balance, and muscle strength. Data from the 2000 to 2002 National Health Interview Survey were used to address this question. Respondents were asked about injuries that occurred in the last 3 months and about their level of physical activity, which investigators then classified as inactive, insufficiently active, or active. Greater leisure-time physical activity participation was associated with higher incidence of injuries related to sports or leisure-time activities. However, the incidence of non-sport and non-leisure-time activity injury episodes was greater among inactive individuals. The increase in injuries related to leisure-time activity as offset by a reduction in non-leisure-time activity-related injuries so that there was no significant association of activity with overall (activity- and non-activity-related) injury [63].

Similar to musculoskeletal injuries, risk of cardiovascular events such as myocardial infarction and cardiac arrest is greater during vigorous physical exertion. This is especially true among persons who are sedentary or who have coronary artery disease, which may be undiagnosed. The degree of increase in risk of an event during exercise is greater with higher intensity exercise and with lower habitual physical activity level. Individuals who exercise regularly do have a transient elevation in risk during and immediately after vigorous exercise, but they have a lower risk of exercise-related cardiac events and sudden death compared with sedentary people who suddenly begin exercising vigorously. Furthermore, it should be noted that physically active and physically fit individuals have a 25–50 % lower overall risk of developing cardiovascular disease.

Patients with CKD are potentially at higher risk for both musculoskeletal and cardiovascular complications of exercise than individuals without kidney disease. Muscle weakness, hyperparathyroidism, and CKD-MBD in general may place patients at greater risk of fracture and spontaneous tendon ruptures. Nevertheless, most musculoskeletal injuries related to physical activity are preventable by gradually working up to a desired level of activity and by avoiding excessive amounts of activity. Similarly, it is possible that the risk of exercise-related cardiovascular events is higher among patients with CKD than among those with normal kidney function because of the high prevalence of known cardiac disease and risk factors for cardiac disease. However, the Surgeon General's report emphasizes that the net effect of regular physical activity is a lower risk of mortality from cardiovascular disease [10].

There are some steps that can be taken to minimize the risks of exercise and thereby maximize the net benefit. The first step is assessment. Patients should be screened for contraindications to exercise participation, which include a history of recent myocardial infarction or recent electrocardiogram changes suggestive of myocardial infarction, uncontrolled arrhythmia, unstable angina, third-degree heart block, severe symptomatic aortic stenosis, suspected or known aortic dissection, or acute progressive heart failure. Exercise should be deferred in patients with any of these conditions until they have resolved or until formal cardiac evaluations have been completed. Exercise is also not recommended in the setting of uncontrolled hypertension with a systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg. The second step, after contraindications have been excluded, is for sedentary individuals to begin exercising at moderate intensity and for short intervals.

Approach to Prescribing and Promoting Physical Activity in the CKD Population

The KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients included a series of recommendations about physical activity (Table 16.1) [62]. A key element is the recommendation that assessment and counseling about physical activity should be done by nephrologists or dialysis unit staff. The recommended target level of physical activity is 30 min of moderate activity on most days, in accord with the Surgeon General and American College of Sports Medicine/American Heart Association recommendations [10, 12]. Similar to the recommendations for older individuals and persons with chronic conditions, the KDOQI guidelines stress that patients should be started at low levels and gradually progressed to recommended levels. Unfortunately, however, a survey of nephrologists showed that most nephrologists do not counsel patients about physical activity [64]. Nephrologists cited lack of confidence in their ability to discuss the topic as a major reason for not doing so. A follow-up survey after the publication of the KDOQI guidelines revealed very similar low rates of counseling [65], suggesting that the guidelines may not have been successful in increasing counseling by nephrologists. One possible reason is that although the guidelines provide specific physical activity targets, they do not address implementation, something nephrologists are reporting that they need.

The guidelines likely did not provide more specific information about exercise prescription because data specific to the dialysis or overall CKD population are limited. In particular there are few studies addressing how to increase physical activity levels, although one recent uncontrolled study demonstrated that providing patients with pedometers to record their daily step counts may have led to an increase in steps per day over the 4-month intervention [66]. This is encouraging and suggests that making patients aware of their limited activity may be one strategy that can lead to increase. It is tempting to speculate that combining this approach with basic counseling about the target levels of activity and the benefits of increased activity might produce even better results, but the small study of pedometers has not been replicated, and more comprehensive interventions would need to be prospectively tested.

Extrapolating from information available in persons without kidney disease, there are a number of options available to increase physical activity participation among patients with CKD. These include asking patients about their level of physical activity and about potential barriers to being physically active, educating them about the benefits of increasing physical activity, referring them for physical therapy or cardiac rehabilitation, and, for patients on dialysis, providing opportunities to participate in physical activity during dialysis (Fig. 16.3).

First, being asked about physical activity by a healthcare provider provides an indication to patients that this is an important aspect of their medical care. Furthermore, if providers get in the habit of asking about activity on a regular basis, patients' responses particularly about changes in activity can be useful information for clinicians, with a reduction in physical activity potentially signaling a worsening in health status or the onset of depression, for example. Second, nephrologists can educate patients about the potential benefits of exercise, which will further reinforce its role in their care. A detailed exercise guide specifically designed for patients on dialysis is available at no cost online through Life Options, a program of research-based education and outreach that aims to improve quality of life among patients with kidney disease [67]. The booklet contains information about the benefits of regular exercise but also includes specific information about how to get started on an exercise program. Nephrologists can refer patients to the Life Options website, or they can download the booklet at no charge and provide it to patients directly. Of note, the website also provides exercise reference material targeted toward nephrologists, including *Exercise for the Dialysis Patient*: *A Guide for the Nephrologist* and *Exercise for the Dialysis Patient*: *A Prescribing Guide*. In addition, there are a multitude of Internet-based sources of exercise information directed at the general public or at older individuals, which are provided by such organizations as the Centers for Disease Control and

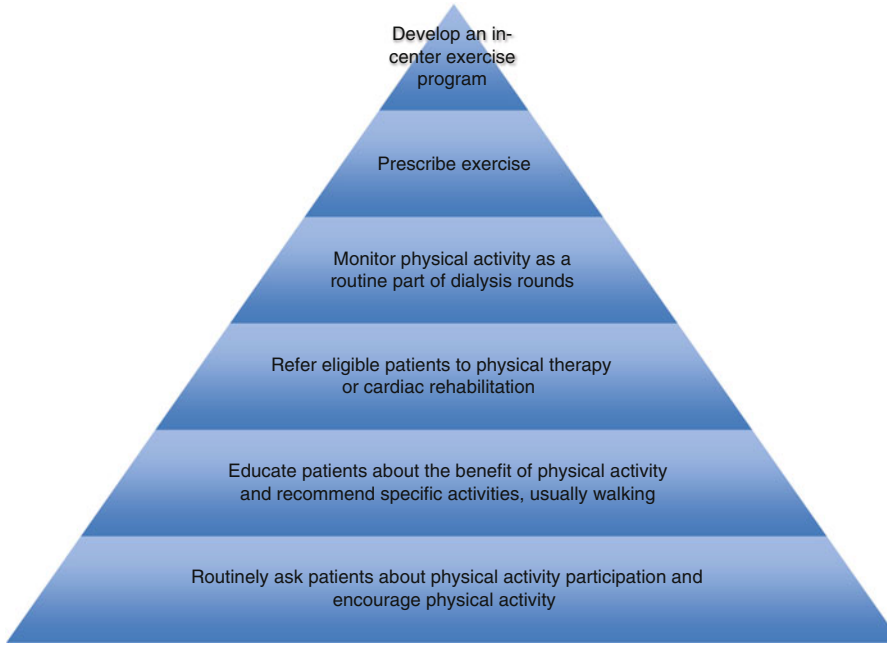

Fig. 16.3 The pyramid of provider intervention to increase physical activity among patients with CKD

Prevention (www.cdc.gov/physicalactivity/), the United States Department of Agriculture (www.cnpp.usda.gov/dgas2010-policydocument.htm), the American College of Sports Medicine (www acsm.org/access-public-information/brochures-fact-sheets-brochures., www.acsm.org/access-public-information/brochures-fact-sheets/fact-sheets), and Harvard School of Public Health (www.hsph.harvard.edu/nutritionsource/staying-active/staying-active-full-story/). These resources are ideal for patients who are healthy except for kidney disease, but some patients may need additional help or support. Patients who are unable to walk, have difficulty walking, or are weak can be referred to physical therapists for evaluation and for recommendations on how to increase strength and physical activity safely, and these services should be covered by Medicare or other insurance providers. Patients who have known or suspected heart disease or congestive heart failure can be referred for cardiac rehabilitation, an underutilized but clearly beneficial option among patients with CKD [68], a large component of which is geared toward beginning an exercise program.

Finally, nephrologists can discuss the specifics of exercise with patients or can provide opportunities for physical activity participation during dialysis sessions for patients receiving in-center hemodialysis. In-center exercise has been shown to be beneficial and in some cases to improve the efficiency of dialysis and reduce adverse effects such as hypotensive episodes and cramping [69]. Several authors have advocated exercise during dialysis because of the possibility of better adherence since it does not require additional time commitment from the patients and because it could reverse the forced inactivity inherent in dialysis that does not include exercise. However, although there are many programs outside of the United States that have successfully incorporated in-center exercise, the dialysis provider system in the United States does not lend itself easily to incorporating such activity during the dialysis treatment. Dialysis staff are often not enthusiastic about supporting dialysis-unit-based exercise programs, citing concerns about lack of time and patient safety issues, including the difficulty of maneuvering around exercise equipment in the event of a dialysis-related emergency [70, 71]. Staff safety is sometimes raised as a concern as well since there is a possibility of injury when moving bulky or heavy exercise equipment to facilitate patient participation while on dialysis. These barriers

are effectively insurmountable in the absence of strong physician and unit leadership support of exercise and a designated staff member or members to manage the prescription and monitoring of exercise. Although very few dialysis facilities in the United States currently have the resources to provide an on-site exercise program, this should not preclude encouragement of exercise outside of the dialysis setting. In addition, because patients on home dialysis, those with CKD not requiring dialysis, and those who have received kidney transplants are also in need of exercise counseling, nephrologists should develop mechanisms to provide information to patients about how to become more physically active as part of their lifestyle.

The most important principle when recommending that patients increase their level of physical activity is to encourage them to start slowly and to increase the intensity and duration of their activity gradually. A major potential impediment to exercise counseling by physicians and to beginning an exercise program for patients is the idea that exercise must be vigorous to be beneficial. Recent evidence is accumulating that although more may be better, even a little is good, and this concept should be heavily emphasized when discussing physical activity with patients with CKD. The old idea of "no pain, no gain" should be abandoned, and patients should be specifically advised to start at a level that can be accomplished without pain. It is also important to recognize that many patients will need to start with a shorter duration of activity and build up to 30 min/day and that moderate exercise should be defined relative to an individual's level of fitness rather than in absolute terms. Thus, patients should be advised to walk at a speed that they perceive as "somewhat hard" to "hard" but not "very hard" for as long as they can manage rather than told to walk at a particular speed or for a specific distance (recommendations that are difficult to follow in any case). Similar principles apply to other types of physical activity such as bicycling, but walking is the most easily prescribed activity because it is generally safe, there is no need for special equipment, it can be done anywhere, intensity can be varied, and it can be monitored by time, distance, or number of steps. In addition, there is specific evidence for the benefit of walking based on several long-term cohort studies, such as the Nurses' Health Study [72], the Harvard Alumni Health Study [73], the National Health Interview Survey [74], and the Women's Health Initiative [75].

A key component of any successful exercise program is monitoring. Nephrologists or dialysis facility staff could help patients monitor their activity even without instituting a unit-based exercise program by routinely asking patients about the time spent in physical activity and the intensity of the activity. Progression to recommended levels could be facilitated in this way, with the first goal to increase the duration of exercise to at least 20 min per session and preferably 30 min. This should be done gradually, with an increase of 1–2 min per session per week as tolerated. After a 20–30-min duration has been achieved, patients can be encouraged to increase the intensity of the activity. In the case of walking, this can be accomplished by increasing speed, adding uphill segments to the route, or by carrying weights or wearing ankle weights, although weights should not be added until and unless patients have first increased their speed to a brisk pace. Most patients should not be encouraged to increase their speed to the point of jogging because jogging may increase the chances of injury. In addition to advising patients to target a level of exertion that they perceive as somewhat hard or hard, they should be told that exertion should not be so strenuous that it is very hard or that they cannot talk during exercise.

In addition to aerobic activity, physical activity guidelines also recommend that older adults perform activities that maintain or increase muscular strength and endurance on at least 2 days/week in order to promote and maintain their health and physical independence. This can be accomplished through progressive weight training, weight-bearing calisthenics, or similar resistance exercises that use major muscle groups. The general principle of starting small and increasing gradually applies to strength training as well as to aerobic exercise. The starting weight should be one that can be lifted at least 10–15 times at a level of exertion that is moderate, and the weight may be different for different muscle groups. Because it may be more difficult for nephrologists to discuss and monitor the specifics of resistance training than walking exercise, the option of a physical therapy referral for detailed instructions should be strongly considered. Physicians can then reinforce progress by asking periodically and by re-referring if needed for progress assessments and updated recommendations.

Physical activity guidelines also recommend that older adults also perform balance and flexibility exercises to maintain mobility and prevent falls. Information about these exercises can be obtained from the Internet resources already mentioned, and a physical therapy referral is also a good way to assist patients in starting such exercises.

Unfortunately, physical activity participation is often interrupted because patients with CKD suffer from many comorbid conditions and become ill or require hospitalization frequently. Fitness declines rapidly during periods of bed rest, and patients can become discouraged by health-related setbacks. Physicians can help by acknowledging that these events are likely to occur and to be associated with losses in ability to exercise. Patients should be encouraged to repeat the process of initiating physical activity during recovery. They should find a new comfortable level of exertion and duration of exercise, which may well be lower than previously tolerated activity, and should build gradually from there.

In summary, physician involvement increases the likelihood that patients will increase and sustain their level of physical activity. A study of patients on dialysis found that lack of encouragement from healthcare providers was a barrier to exercise participation [76]. Unfortunately, patients often receive overt or subtle messages from their physicians that they are not capable or interested in being active. Asking about and encouraging physical activity as part of our routine care for these patients sends an active message.

Case Study

A 67-year-old Caucasian female with ESRD secondary to diabetes who had been treated with hemodialysis for 2 years was complaining of general fatigue and weakness. She had retired from office work upon starting dialysis treatments, which were 3.5 h/session, 3 days/week. She tolerated dialysis well and had good adherence to her dialysis treatments and associated dietary recommendations. She had an AV fistula in her left upper arm. She had history of shortness of breath with exertion before starting dialysis.

Symptoms: "I have been feeling really weak and tired recently. My leg muscles are weak and there are times when I am afraid of falling. I have difficulty climbing stairs and lifting things. I would like to get stronger, since my husband's health is not good, and we want to stay in our home as long as possible."

Height: 139 cm	Weight: 79.4 kg	BMI: 29.1 kg/m^2
Pulse: 85 beats/min	Blood pressure: 158/92	

Medications: Darbepoetin, diltiazem, cinacalcet, multivitamins.

Laboratory values: Albumin, 3.8 mg/dL; hematocrit, 33.5 %; hemoglobin, 11.1 g/dL; kT/V, 1.8.

Physical Function Evaluation (Fig. 16.4) [1]

Physical activity history: The patient walks for normal daily needs but does nothing specific for exercise. She has never been involved in any structured exercise program, never done any strengthening exercises (was given exercises by a physical therapist following ankle injury—10 years ago). She lives in a place where she can walk safely (sidewalks, minimal traffic) and prefers walking exercise and is not interested in going to a gym or other location for her exercise. Her daughter has a stationary exercise bike she can use during inclement weather.

Katz activities of daily living [2]: Scored 4 out of 6 (difficulty with carrying groceries and climbing one flight of stairs).

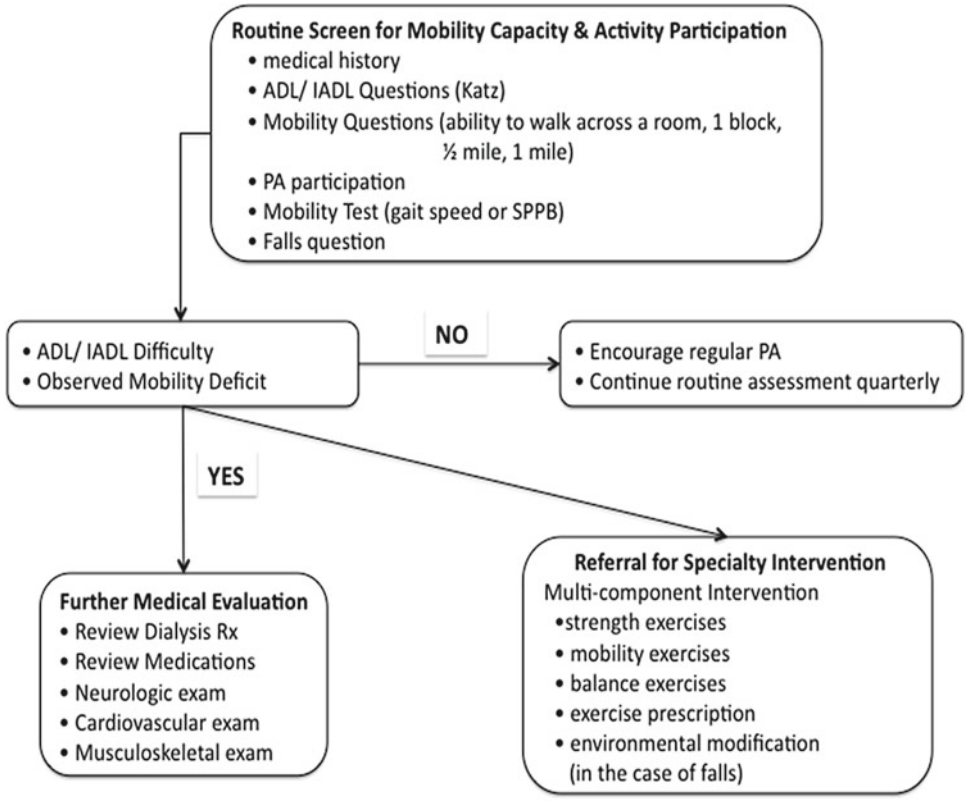

Fig. 16.4 Algorithm for routine evaluation and management of mobility limitation in CKD

Short physical performance battery (SPPB) [3]: total score = 8 (scored from 1 to 12; <7 increases risk of disability in older individuals >70).

Four-meter gait speed: 0.8 m/s (<1.1 m/s indicates impaired mobility [1]; 1.29 is the average age/gender comfortable gait speed [4]; thus, she is 62 % of age expected; 0.73 m/s is average in 60–69-year-old hemodialysis patients [1]).

Chair stands (5 repetitions): 13.5 s (>13.7 s indicates impaired function [3]).

Six-minute walk distance: 451 m (<460 m indicates impaired mobility [1]; 505 m is average age-gender reported distance; thus, she is 89 % of expected).

Comments: Patient tolerated all testing well.

Physical activity goals: Improved muscle strength and endurance.

1. Short-term goals (1 month):
   - Walk around block three times continuously without stopping.
   - Climb one flight of stairs without stopping.
2. Long-term goals (6 months):
   - Walk up to 2 miles continuously.
   - Climb one flight of stairs three times without stopping.

Table 16.2 Recommended activity

Mode	Frequency	Duration[a]	Intensity[a]	Progression
Walking (or cycling)	4–6 days/week	Start with tolerated duration (i.e., 1 block)—work up to 40–60 min/session	Rating of perceived exertion between 10 and 12 (on a 6–20 scale)	Walk 1 block in first week, increase by 1/2 block/week as tolerated
Strengthening exercises	3 days/week	1 set of 10–12 repetitions for each exercise (focusing on lower extremity)	Initially using body weight as resistance for lower extremity (stepping, leg raises, progressing to use of resistance bands); upper extremity use resistance bands or hand weights	Start with as many repetitions as tolerated, then increase each session by 1–2 repetitions until 10–12 repetitions is tolerated, then increase the weight (resistance) and/or increase the number of sets
Flexibility (all major muscle groups)	4–6 days/week	5–10 min	As instructed for each exercise	

[a]Duration and intensity for cardiovascular exercise should include information on warm-up and cool down

Recommended Activity

Patient is given the book: *Exercise*: *A Guide for People on Dialysis* available free from http://lifeoptions.org/catalog/. This book has sample cardiovascular and strengthening exercises with complete illustrations and descriptions for progression and performing the exercises (Table 16.2).

Follow-Up Evaluation (6 Months)

Activity participation: The patient reports regular walking 40–45 min for her exercise session, and she uses soup cans for weights for her arms and a resistance band for her leg exercises. She does her strengthening exercises 3 days/week. She purchased a step counter and has worked up to 7,500 steps/day usually on her nondialysis days. She walks minimally on her dialysis days, although reports less fatigue if she walks instead of lying down when she gets home. She stopped her exercise for about 2 weeks after a brief illness and was unsure when she should restart, but she started back gradually and has continued to progress. She reports increased strength in her legs and is able to climb stairs with minimal difficulty. She still reports some difficulty in lifting and carrying objects such as groceries.

Physical Function Testing

Katz activities of daily living score: *5/6* (still reports difficulty lifting/carrying objects).

Short physical performance battery: total score = 10 (substantial change = 1.0 points [5]).

Four-meter gait speed: 0.92 m/s (increase of 0.12; substantial change = 0.10 m/s [5]).

Chair stand (5 repetitions): 12 s (12 % improvement).

Six-minute walk distance: 539 m (change of 88 m: substantial meaningful change = 50 m [5]).

Recommendations: Continue with program progressing in intensity as tolerated. She may choose to work with the dietitian for guidance on reducing caloric intake for weight loss and increasing the distance (duration) of her walking may help with that effort.

References

1. Painter P, Marcus R. Assessing physical function and physical activity in CKD patients: in-depth review. Clin J Am Soc Nephrol. 2013;8(5):861–72.
2. Katz S. Assessing self-maintenance: activities of daily living, mobility and instrumental activities of daily living. J Am Geriatr Soc. 1983;31:721–6.
3. Guralnik J, Ferrucci L, Simonsick E, Salive M, Wallace R. Lower-extremity function in persons over the age of 70 as a predictor of subsequent disability. N Engl J Med. 1995;43:845–54.
4. Bohannon R. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing. 1997;26:15–9.
5. Perera S, Mody S, Woodman R, Studenski S. Meaningful change and responsiveness in common performance measures in older adults. J Am Geriatr Soc. 2006;54:743–9.
6. U.S. Department of Health and Human Services. Dietary guidelines for Americans, 2010. 7th ed. Washington, DC: U.S. Government Printing Office; 2010.
7. Borg G. An Introduction to Borg's RPE scale. Ithaca, NY: Movement Publications; 1985.
8. U.S. Department of Health and Human Services. 2008 physical activity guidelines for Americans. Washington, DC: USDHHS; 2008.
9. Ainsworth B, Haskell W, Herrmann S, Meckes N, Bassett D, Tudor-Locke C, Greer J, Vezina J, Whitt-Glover M, Leon A. 2011 Compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43:1575–81.
10. Office of the U.S. Surgeon General. Physical activity and health: a report of the surgeon general. Washington, DC: US Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion; 1996.
11. National Institute of Aging. Exercise & physical activity: your everyday guide from the National Institute on Aging! Washington, DC: National Institute on Aging, National Institutes of Health; 2009.
12. Haskell W, Lee I, Pate R, Powell K, Blair S, Franklin B, Macera C, Heath G, Thompson R, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116:1081–93.
13. Nelson M, Rejeski W, Blair S, Duncan P, Judge J, King A, Macera C, Castaneda-Sceppa C. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116:1094–105.
14. Painter P, Carlson L, Carey S, Paul S, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis. 2000;35:482–92.
15. Fix A, Daughton D. Human activity profile professional manual. Odessa, FL: Psychological Assessment Resources; 1988.
16. Kutner N, Johansen K, Kaysen G, Pederson S, Chen S, Agodoa L, Eggers P, Chertow G. The comprehensive dialysis study (CDS): a USRDS special study. Clin J Am Soc Nephrol. 2009;4:645–50.
17. Johansen K, Chertow G, Kutner N, Dalrymple L, Grimes B, Kaysen G. Low level of self-reported physical activity in ambulatory patients new to dialysis. Kidney Int. 2010;78:1164–70.
18. Johansen K, Painter P, Kent-Braun J, Ng A, Carey S, Da Silva M, Chertow GM. Validation of questionnaires to estimate physical activity and functioning in ESRD. Kidney Int. 2001;59:1121–7.
19. O'Hare A, Tawney K, Bacchetti P, Johansen K. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. Am J Kidney Dis. 2003;41:447–54.
20. Painter P, Messer-Rehak D, Hanson P, Zimmerman S, Glass N. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron. 1986;42:47–51.
21. Barnea H, Drory Y, Iaina A, Lapidot C, Reisin E, Eliahou H, Kellerman J. Exercise tolerance in patients on chronic hemodialysis. Isr J Med Sci. 1980;16:17–21.
22. Beasley C, Smith D, Neale T. Exercise capacity in chronic renal failure patients managed by continuous ambulatory peritoneal dialysis. Aust N Z J Med. 1986;16:5–10.
23. Moore G, Brinker K, Stray-Gundersen J, Mitchell J. Determinants of VO_{2peak} in patients with end-stage renal disease: on and off dialysis. Med Sci Sports Exerc. 1993;25:18–23.
24. Moore G, Parsons D, Stray-Gundersen J, Painter P, Brinker K, Mitchell J. Uremic myopathy limits aerobic capacity in hemodialysis patients. Am J Kidney Dis. 1993;22:277–87.

25. Violan M, Pomes T, Maldonado S, Roura G, Fuente I, Verdaguer T, Lloret R, Torregrosa J, Campistol J. Exercise capacity in hemodialysis and renal transplant patients. Transplant Proc. 2002;34:417–8.
26. Padilla J, Krasnoff J, Da Silva M, Hsu CY, Frassetto L, Johansen KL, Painter P. Physical functioning in patients with chronic kidney disease. J Nephrol. 2008;21:550–9.
27. Sietsema K, Amato A, Adler S, Brass E. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int. 2004;65:719–24.
28. Goldberg A, Geltman E, Hagberg J, Gavin J, Delmez J, Carney R, Naumowicz A, Oldfield M, Harter H. Therapeutic benefits of exercise training for hemodialysis patients. Kidney Int. 1983;24:S303–9.
29. Goldberg A, Hagberg J, Delmez J, Haynes M, Harter H. Metabolic effects of exercise training in hemodialysis patients. Kidney Int. 1980;18:754–61.
30. Zabetakis P, Gleim G, Pasternack F, Saraniti A, Nicholas J, Michelis M. Long-duration submaximal exercise conditioning in hemodialysis patients. Clin Nephrol. 1982;18:17–22.
31. Shalom R, Blumenthal J, Williams R, McMurray R, Dennis V. Feasibility and benefits of exercise training in patients on maintenance dialysis. Kidney Int. 1984;25:958–63.
32. Lennon D, Shrago E, Madden M, Nagle F, Hanson P, Zimmerman S. Carnitine status, plasma lipid profiles, and exercise capacity of dialysis patients: effects of a submaximal exercise program. Metabolism. 1986;35:728–35.
33. Boyce M, Robergs R, Avasthi P, Roldan C, Foster A, Montner P, Stark D, Nelson C. Exercise training by individuals with predialysis renal failure: cardiorespiratory endurance, hypertension, and renal function. Am J Kidney Dis. 1997;30:180–92.
34. Clyne N, Ekholm J, Jogestrand T, Lins LE, Pehrsson SK. Effects of exercise training in predialytic uremic patients. Nephron. 1991;59:84–9.
35. Johansen K, Shubert T, Doyle J, Soher B, Sakkas G, Kent-Braun J. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. Kidney Int. 2003;63:201–7.
36. DeOreo P. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. Am J Kidney Dis. 1997;30:204–12.
37. Lowrie E, Curtin R, LePain N, Schatell D. Medical outcomes study short form-36: a consistent and powerful predictor of mortality in dialysis patients. Am J Kidney Dis. 2003;41:1286–92.
38. Wu A, Fink N, Marsh-Manzi J, Meyer K, Finkelstein F, Chapman M, Powe N. Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. J Am Soc Nephrol. 2004;15:743–53.
39. Johansen K, Chertow G, Silva MD, Carey S, Painter P. Determinants of physical performance in ambulatory patients on hemodialysis. Kidney Int. 2001;60:1586–91.
40. Knight E, Oftshun N, Teng M, Lazarus J, Curhan G. The association between mental health, physical function, and hemodialysis mortality. Kidney Int. 2003;63:1843–51.
41. Fried L, Tangen C, Walston J, Newman A, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop W, Burke G, BcBurnie M. Group, ftCHSCR: frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56A:M146–56.
42. Shlipak M, Stehman-Breen C, Fried L, Song X, Siscovick D, Fried L, Psaty B, Newman A. The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis. 2004;43:861–7.
43. Woods N, LaCroix A, Gray S, Aragaki A, Cochrane B, Brunner R, Masaki K, Murray A, Newman A. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005;53:1321–30.
44. Johansen K, Chertow G, Jin C, Kutner N. Significance of frailty among dialysis patients. J Am Soc Nephrol. 2007;18:2960–7.
45. Bao Y, Dalrymple L, Chertow G, Kaysen G, Johansen K. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med. 2012;172(14):1071–7.
46. Johansen KL, Painter P. Exercise in individuals with CKD. Am J Kidney Dis. 2012;59:126–34.
47. Cheema B, Singh M. Exercise training in patients receiving maintenance hemodialysis: a systematic review of clinical trials. Am J Nephrol. 2005;25:352–64.
48. Painter P. Physical functioning in end-stage renal disease patients: update 2005. Hemodial Int. 2005;9:218–35.
49. Johansen K. Exercise in the end-stage renal disease population. J Am Soc Nephrol. 2007;18:1845–54.
50. Parsons T, King-Vanvlack C. Exercise and end-stage kidney disease: functional exercise capacity and cardiovascular outcomes. Adv Chronic Kidney Dis. 2009;16:459–81.
51. Eidemak I, Haaber AB, Feldt-Rasmussen B, Kanstrup IL, Strandgaard S. Exercise training and the progression of chronic renal failure. Nephron. 1997;75:36–40.
52. Pechter U, Maaroos J, Mesikepp S, Veraksits A, Ots M. Regular low-intensity aquatic exercise improves cardiorespiratory functional capacity and reduces proteinuria in chronic renal failure patients. Nephrol Dial Transplant. 2003;18:624–5.

53. Leehey D, Moinuddin I, Bast J, Qureshi S, Jelinek C, Cooper C, Edwards L, Smith B, Collins E. Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. Cardiovasc Diabetol. 2009;8:62.
54. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. Int Urol Nephrol. 2011;43(4):1133–41.
55. Gregory S, Headley S, Germain M, Flyvbjerg A, Coughlin M, Milch C, Sullivan S, Nindl B. Lack of circulating bioactive and immunoreactive IGF-1 changes despite improved fitness in chronic kidney disease patients following 48 weeks of physical training. Growth Horm IGF Res. 2011;21(1):51–6.
56. Heiwe S, Tollback A, Clyne N. Twelve weeks of exercise training increases muscle function and walking capacity in elderly predialysis patients and healthy subjects. Nephron. 2001;88:48–56.
57. Johansen K, Painter P. Exercise in individuals with CKD. Am J Kidney Dis. 2011;59:126–34.
58. Anderson J, Stewart K, Hatchett L. Effect of exercise training on interdialytic ambulatory and treatment-related blood pressure in hemodialysis patients. Ren Fail. 2004;26:539–44.
59. Miller B, Cress C, Johnson M, Nichols D, Schnitzler M. Exercise during hemodialysis decreases the use of antihypertensive medications. Am J Kidney Dis. 2002;39:826–33.
60. Castaneda C, Gordon PL, Parker R, Uhlin K, Roubenoff R, Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. Am J Kidney Dis. 2004;43:607–16.
61. Pechter U, Ots M, Mesikepp S, Zilmer K, Kullissaar T, Vihalemm T, Zilmer M, Maaroos J. Beneficial effects of water-based exercise in patients with chronic kidney disease. Int J Rehabil Res. 2003;26:153–6.
62. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45:S1–154.
63. Carlson S, Hootman J, Powell K, Macera C, Heath G, Gilchrist J, Kimsey C, Kohl H. Self-reported injury and physical activity levels: United States 2000 to 2002. Ann Epidemiol. 2006;16:712–9.
64. Johansen K, Sakkas G, Doyle J, Shubert T, Dudley R. Exercise counseling practices among nephrologists caring for patients on dialysis. Am J Kidney Dis. 2003;41:171–8.
65. Delgado C, Johansen KL. Deficient counseling on physical activity among nephrologists. Nephron Clin Pract. 2010;116:c330–6.
66. Nowicki M, Murlikiewicz K, Jagodzinska M. Pedometers as a means to increase spontaneous physical activity in chronic hemodialysis patients. J Nephrol. 2010;23:297–305.
67. Medical Education Institute, ME: Life Options. http://lifeoptions.org/catalog/
68. Huang Y, Zhang R, Culler S, Kutner N. Costs and effectiveness of cardiac rehabilitation for dialysis patients following coronary bypass. Kidney Int. 2008;74:1079–84.
69. Parsons T, Toffelmire E, King-VanVlack C. Exercise training during hemodialysis improves dialysis efficacy and physical performance. Arch Phys Med Rehabil. 2006;87:680–7.
70. Painter P. Implementing exercise: what do we know? Where do we go? Adv Chronic Kidney Dis. 2009;16:536–44.
71. Painter P, Carlson L, Carey S, Myll J, Paul S. Determinants of exercise encouragement practices in hemodialysis staff. Nephrol Nurs J. 2004;31:67–74.
72. Weuve J, Kang J, Manson J, Breteler M, Ware J, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA. 2004;292:1454–61.
73. Lee I, Paffenbarger Jr R. Physical activity and stroke incidence: the Harvard Alumni Health Study. Stroke. 1998;29:2049–54.
74. Gregg E, Gerzoff R, Caspersen C, Williamson D, Narayan K. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med. 2003;163:1440–7.
75. Manson J, Greenland P, LaCroix A, Stefanick M, Mouton C, Oberman A, Perri M, Sheps D, Pettinger M, Siscovick D. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med. 2002;347:716–25.
76. Goodman E, Ballou M. Perceived barriers and motivators to exercise in hemodialysis patients. Nephrol Nurs J. 2004;31:23–9.

Part IV
Nutrition in Chronic Kidney Disease Among Special Needs Populations

Chapter 17
Pregnancy

Jean Stover

Key Points

- Identify modifications in dialysis therapy and management for the pregnant CKD patient.
- Describe nutritional concerns related to protein, energy, and micronutrients.
- Discuss medical and nutritional management of pregnant CKD patients.

Keywords Pregnancy • Intensive dialysis • Medications • Vitamins • Minerals • Nutrition • CKD

Background

Women with chronic kidney disease (CKD) who become pregnant during the early stages of the disease while undergoing chronic dialysis or after renal transplantation are all considered to be at high risk for complications. Hypertension is the most prevalent life-threatening maternal complication during pregnancy in all stages of CKD. There is also a greater risk for more rapid decline in kidney function for women who become pregnant with a serum creatinine greater than or equal to 1.4 mg/dL, and especially for those who have levels >2.0 mg/dL [1]. Women who become pregnant after a kidney transplant do not have an increased risk for loss of kidney function if the function includes a creatinine <1.5 mg/dL and <500 mg/24 h protein excretion [1, 2]. Immunosuppressive medications (especially cyclosporine), however, have been known to contribute to infants born small for gestational age. These medications have not been shown to increase abnormalities in the fetus, except for mycophenolate mofetil, which is now believed to be teratogenic [3]. The incidence of premature birth also remains high for women during all stages of CKD [1].

Fertility generally returns for women who have a good functioning kidney transplant, but otherwise women with CKD tend to become pregnant less frequently than those with normal kidney function. There is also found to be a significant decrease in conception for women undergoing dialysis [1, 2]. Although it has been reported that the occurrence of pregnancy in the dialysis population has increased, pregnancy is still considered relatively uncommon [4].

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When pregnancy does occur, only about 59 % of pregnancies that reach the second trimester result in positive outcomes [1]. This does represent improvement, however, and in efforts to continue these advances in pregnancy outcome, many challenges are presented to the team of nephrology professionals. The following discussion will focus primarily on the care of this specific population, including changes in the dialysis regimen, medications, and nutrition management, as they all impact on each other as well as on pregnancy outcome.

Confirmation of Pregnancy

The confirmation of pregnancy in women undergoing dialysis generally requires a pelvic ultrasound in addition to the blood test that measures levels of the β subunit of human gonadotropin (hCG). The rationale for the additional testing is that the kidney excretes small amounts of hCG produced by somatic cells, and in renal failure, this test can appear positive by usual standards [5]. Once pregnancy is confirmed, and the woman wishes to proceed, she should be referred to a high-risk obstetrics practice.

Dialysis Regimen

Intensive dialysis is a key component to successful pregnancy outcome for women undergoing dialysis. The amount of dialysis is increased in efforts to mimic more normal kidney function during fetal development. It has been shown that at least 20 h of hemodialysis per week is associated with improved infant survival [1]. A minimum dialysis prescription of 24 h/week has recently been recommended [5, 6]. The greater time commitment for the intensive dialysis is an important message to convey to women in this population as soon as a pregnancy is confirmed, as it involves an alteration in lifestyle. It is also important to inform the patient at this time that she will be transferred to a hospital-based dialysis setting for fetal monitoring during the treatment once she reaches approximately 24 weeks' gestation.

Recently, it has been observed that nocturnal hemodialysis (NHD) performed at home, in which individuals receive 3–4 times as much dialysis as conventional in-center HD (hemodialysis), may be the ideal modality for pregnant dialysis patients. This dialysis regimen has been associated with increased fertility, longer gestation periods with higher birth weights, and fewer complications for the mother and fetus [7]. Thus, women with advanced CKD contemplating pregnancy may be encouraged to seek a program offering this modality, if feasible.

As previously mentioned, hypertension can be a serious complication of pregnancy for women with CKD. Severe hypotension, on the other hand, may promote fetal distress [8]. More frequent dialysis will improve efforts to avoid potential hypertension due to volume overload and potential hypotension with the need to remove large volumes of fluid during the treatment.

The content of the dialysate used for hemodialysis during pregnancy will vary depending on the amount of dialysis given as well as the mother's dietary intake and levels of serum electrolytes, calcium, and bicarbonate. It is recommended that frequent monitoring of all of these levels be done during the pregnancy. With more dialysis, a higher potassium dialysate concentration (generally 3.0 mEq/L) may be required to maintain normal serum potassium levels. The bicarbonate concentration of the dialysate may also need to be decreased due to the higher bicarbonate concentrations currently used. With more frequent dialysis and/or nausea and vomiting during pregnancy, the possibility of developing metabolic alkalosis exists [1].

Even though the fetus requires 25–30 g of calcium for proper skeletal development, it is usually not necessary to increase the dialysate calcium content when calcium-containing medications are taken

Table 17.1 Nutrient recommendations for the pregnant dialysis patient [1, 6, 11–14, 18]

Energy	35 kcal/kg pregravida SBW + 300/day in second and third trimesters; may need a nutritional supplement to meet needs
Protein	1.2 g/kg pregravida SBW (and maybe more with intensive HD) + 10–25 g/day (HD)
	1.2–1.3 g/kg pregravida SBW + 10–25 g/day (PD)
	May need a nutritional supplement to meet needs
Vitamins	*Folic acid*—at least 2 mg/day; even 3–4 mg/day has been recommended—doubling a standard renal vitamin is generally advised
	Vitamin D—analogs have been given, but not enough information on safety during pregnancy; 25(OH)D may be beneficial
	Vitamin A—not usually given, thus renal vitamins are generally given instead of prenatal vitamins
Minerals	*Iron*—usually given IV during dialysis (generally iron sucrose or gluconate) to achieve iron studies in goal range for general dialysis population; oral iron has been used, but not as well absorbed
	Calcium—given as calcium acetate or carbonate to bind phosphorus or as calcium carbonate for a calcium supplement; keep in mind that there is increased absorption of calcium from dialysate with more frequent dialysis
	Sodium, potassium, and phosphorus—can often be liberalized in the diet with more dialysis; phosphate binders may not be needed
	Zinc—at least 15 mg/day recommended

SBW standard body weight, *HD* hemodialysis, *PD* peritoneal dialysis, *IV* intravenously

and more frequent dialysis is given [9]. A standard 2.5 mEq/L calcium dialysate concentration is frequently used. There is also some production of calcitriol by the placenta, which makes it important to frequently monitor serum calcium levels to avoid hypercalcemia [8].

There are case reports in the literature that discuss successful pregnancy outcomes for women undergoing peritoneal dialysis. More frequent exchanges with lesser volumes of instilled peritoneal fluid are necessary as the pregnancy progresses to allow more intense dialysis with less abdominal discomfort [9]. One report utilizes tidal dialysis with the automated cycler machine to promote both comfort and increased dialysis clearance [10].

Energy and Protein Needs

Initial and ongoing nutrition assessment and counseling of the pregnant dialysis patient is very important due to increased energy, protein, vitamin, and mineral needs for this population. It is recommended that the dietitian meet with the patient to discuss an overview of nutritional needs as soon as possible after the pregnancy is confirmed and she has agreed to follow through with it. Weekly follow-up using dietary recalls and/or food intake records to evaluate nutrition adequacy is suggested as well [11]. Also, collaboration with the dietitian at the hospital-based center where the patient will dialyze for the last few months of her pregnancy is recommended.

Generally, 35 kcal/kg/day of pregravida standard body weight (SBW) or adjusted SBW is prescribed in the first trimester, and 300 kcal/day is added to this value for the second and third trimesters (Table 17.1). Daily protein needs are generally at least 1.2 g/kg SBW plus 10–25 g/day for women undergoing hemodialysis and 1.2–1.3 g/kg SBW plus 10–25 g/day for those receiving peritoneal dialysis [12, 13]. It may be easier to meet these needs with liberalization of sodium, potassium, and phosphorus content due to the increased amount of solute removal with more dialysis. At times though, the mother may even require protein or calorie/protein supplements to attain her estimated energy and protein requirements. Generally, a regular commercial supplement may be used with increased dialysis time and more solute removal.

Vitamins and Minerals

Water-soluble vitamins are usually preferred over prenatal vitamins due to the need to avoid excess vitamin A for all individuals with CKD undergoing dialysis. With increased requirements for water-soluble vitamins during pregnancy, as well as increased losses anticipated with more intensive dialysis, a standard renal vitamin containing 1 mg folic acid is often doubled. Folate deficiency has been linked to neural tube defects in infants born to women without CKD; therefore, at least 2–4 mg of folic acid per day is recommended for pregnant women undergoing dialysis [1, 2, 14, 15]. Presently, there are renal vitamin preparations already containing greater than 1 mg folic acid and even added zinc, and these may also be used as long as they contain recommended amounts of other water-soluble vitamins during pregnancy.

Vitamin D analogs have been given intravenously during dialysis to pregnant women needing suppression of the parathyroid hormone (PTH) and to maintain normal serum levels of calcium. There still does not seem to be definitive information available concerning whether these forms of vitamin D cross the placental barrier and, if so, whether they are safe relative to fetal development [2]. It may be beneficial to provide supplements of 25(OH)D, as it does cross the placental barrier and can be utilized by the fetus [16]. Low levels of 25(OH)D have been associated with preeclampsia for pregnant women without CKD [17]. And, although not a vitamin, cinacalcet, a calcimimetic medication used for PTH suppression, is generally avoided due to lack of knowledge about its safety during pregnancy.

There are increased iron needs due to worsening anemia for all women during pregnancy. Intravenous iron in the form of iron sucrose has been given safely and effectively to pregnant patients during hemodialysis [18], based on goal ranges for serum levels of transferrin saturation and ferritin used in the general dialysis population. Ferric gluconate is also considered a category B drug in pregnancy which means that animal studies have not shown adverse effects when this drug is given during pregnancy and there are no adequate human studies available [1, 19]. It is important to mention, however, that in the later stages of pregnancy when anemia is worse, that 80–90 % of intravenous iron may be deposited in the fetus. Therefore, no more than 62.5–100 mg (depending on the iron preparation used) should be given at one time [5]. Although not as well absorbed, oral iron preparations have also been used instead of intravenous iron, either alone or in combination with a vitamin.

Zinc supplements are prescribed in the amount of at least 15 mg/day to prevent increased risks of fetal malformation, preterm delivery, low birth weight, and pregnancy-induced hypertension [11, 20]. Zinc may be included in some renal vitamins or provided as an added supplement.

Calcium-containing phosphate binders are generally given to the pregnant dialysis patient due to increased calcium needs of the fetus. There are no studies to evaluate the safety of using calcium acetate or calcium carbonate during pregnancy; however, these preparations have been utilized during this time [18–20]. They may be given with meals for phosphate binding (though serum phosphorus levels are often low due to intensive dialysis) or apart from meals primarily for calcium supplementation and if the serum phosphorus level is below goal range.

Weight Gain and Serum Albumin

Due to fluid retention with CKD, it is difficult to determine actual solid body weight gain during pregnancy for women undergoing dialysis. It has been suggested that the pregnant dialysis patient's estimated dry weight (EDW) be increased by 0.5 kg/week during the second and third trimesters, when most weight gain occurs [1]. More frequent treatments with gentle fluid removal may help with this assessment, but a team approach involving regular collaboration with the dialysis technicians, nurses, physicians, dietitian, and patient is very important when determining true weight gain.

The evaluation of adequate protein intake is also difficult, as the expected decrease of serum albumin during pregnancy is about 1 g/dL for women without CKD [21]. Recommendations are to continue weekly dietary recalls or records to assess daily protein intake.

Medications

Since blood pressure control is very important for the pregnant dialysis patient, goals are to keep measurements less than or equal to 140/90 mmHg. If there is no apparent fluid overload but hypertension exists, medications are utilized. There are several antihypertensive agents considered safe during pregnancy including methyldopa, β-blockers, and labetalol. There is less experience using calcium channel blockers and clonidine, but these are likely to be safe as well. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), on the other hand, are contraindicated during pregnancy. When given late in the second trimester and during the third trimester, they have been linked to oligohydramnios, an ossification defect in the fetal skull, dysplastic kidneys, neonatal anuria, and death from hypoplastic lungs [1, 9, 15].

As mentioned previously, anemia is another complication during pregnancy, especially for women with CKD undergoing dialysis treatment. Epoetin alfa (Epogen, Amgen, Inc., Thousand Oaks, CA) given during dialysis has been used safely for this population, with no known congenital anomalies reported [5]. The dose frequently needs to be increased by 50–100 % as the pregnancy progresses to maintain a hemoglobin greater than or equal to 10–11 g/dL [1, 5, 9]. It has also been noted in the literature that darbepoetin alfa (Aranesp, Amgen, Inc., Thousand Oaks, CA) has been given successfully during pregnancy to women with CKD prior to initiating dialysis, when undergoing dialysis and following kidney transplantation [22, 23]. The need for blood transfusions during pregnancy for women undergoing dialysis has significantly declined with the use of these medications [7].

Breastfeeding

There is not much in the literature regarding the safety or efficacy of breastfeeding an infant born to a mother with CKD. The theoretical question is always whether the content of the breast milk will be high in urea and cause a diuresis in the infant that must be supplemented with extra water. Most women who plan to breastfeed decide not to once the infant is born, as the pregnancy has been so difficult. Also, transplant patients have generally been advised against breastfeeding due to the antirejection medications they are taking. Some have elected to do so anyway, without noted problems (Susan Hou, MD, personal communication, 2/25/12).

Summary

Pregnancy for women who have CKD, especially for those undergoing dialysis, is a complex medical condition. The dietitian must realize the importance of ensuring that the patient is counseled and evaluated regularly to increase energy and protein in her diet to meet the needs of the developing fetus. The patient must also be guided to change her usual renal vitamin regimen to include adequate amounts of folate and other water-soluble vitamins that have significance during pregnancy. The management of calcium, phosphorus, and vitamin D required may need to be modified for the patient's safety, and zinc will need to be supplemented as well.

As mentioned previously, the management of a pregnant patient with CKD, especially if she is undergoing dialysis, requires a team approach involving nephrology and high-risk obstetrics healthcare professionals. Regular follow-up and communication are important to promote positive outcomes.

Case Study

CD is a 25-year-old African-American female with ESRD due to glomerulonephritis. She initiated hemodialysis with a regimen of 3½ h, three times per week, as she did have a daily urine output of approximately 700 cc at that time. Eight months later, she reported that her last menses was more than 2 months prior. A pregnancy test, beta-human chorionic globulin (hCG) was done and appeared to be positive. To confirm the pregnancy, a pelvic ultrasound was done and showed a live intrauterine gestation corresponding to 10 weeks, 4 days. CD was then counseled about her need for 5–6 days of dialysis if she decided to proceed with the pregnancy. When she agreed to proceed, she was referred to the high-risk obstetrics department at a university hospital associated with the dialysis facility.

CD is 64 in. tall with a medium frame and a SBW of 62 kg based on the NHANES II data. Her EDW at the approximate time of conception was 73 kg which was 117 % of her SBW. Her body mass index (BMI) was calculated to be 28.5. Her estimated kcal/protein needs were 2,500/day (35/kg SBW + 300 kcal/day since she was nearing her second trimester) and 90–105 g/day (1.3 g/kg SBW [for more intensive dialysis with greater protein losses] + 10–25 g/day). Intakes were evaluated by frequent 24-h recalls, and she was eating fairly well, but with frequent dialysis and commuting time when meals were missed at times, a commercial nutritional supplement (Boost High Protein, Nestle USA, Inc., Norwalk, CT) was recommended.

CD's EDW was increased from 73.5 kg when her pregnancy was confirmed to 74 kg at the end of her first trimester to 76 kg at the end of her second trimester when she had reached 24 weeks' gestation. Her serum albumin did decrease from 4.0 to 3.5 g/dL just before she was transferred to the inpatient hospital dialysis unit. CD's diet was not restricted in potassium after she began more intensive dialysis and K^+ levels were initially in goal range, but began to decrease. A 3.0 K^+ dialysate concentration was then needed.

CD's phosphate binders were changed from sevelamer carbonate (Renvela, Sanofi-Aventis, Bridgewater, NJ 08807) to calcium carbonate (500 mg), 2 tid w/ meals. Renvela is considered category C in pregnancy as animal studies have shown some harm to the fetus. No controlled human studies have been done [20]. Phosphorus levels began to decrease, so the calcium carbonate was reduced by 50 % and moved to between meals. Calcium/phosphorus levels then remained acceptable. No active vitamin D was given, as CD's intact PTH was less than 150 pg/mL at the time of confirmation of her pregnancy and the safety of giving it was uncertain. Even when the intact PTH rose to 628 pg/mL, none was given until after her delivery.

Other vitamins, minerals, and medications prescribed for CD during her pregnancy were two renal vitamins (Dialyvite 800 w/ Zinc 15, Hillestad Pharmaceuticals USA Inc., Woodruff, WI) plus 2 mg folic acid daily, increased amounts of epoetin alfa (Epogen, Amgen, Inc., Thousand Oaks, CA) due to decreasing hemoglobin, and intravenous iron sucrose (Venofer, Fresenius medical Care, Waltham, MA) to normalize iron studies and aid in erythropoiesis. Also, for safety, her antihypertensive medication was changed from amlodipine to methyldopa when the pregnancy was confirmed.

CD was transferred to the hospital-based dialysis unit at 24 weeks' gestation for fetal monitoring during dialysis. She remained on hemodialysis for 3½ h, six times per week.

She was admitted to the university hospital at approximately 30 weeks' gestation due to preterm labor and discharged at 34 weeks' gestation. She was then readmitted when she went into labor at 34½ weeks. She delivered a 4 lb 2 oz baby girl at that time. CD decided not to breastfeed due to her dialysis schedule (although now back to three times per week) and other commitments in her life. Presently, both mother and daughter are doing well.

Questions

1. What lifestyle changes must be considered when counseling women with CKD undergoing dialysis once pregnancy is confirmed?
   Answer: Commitment to increased and more frequent dialysis time, and transfer to hospital unit for fetal monitoring during HD at approximately 24 weeks' gestation.
2. How are estimated energy needs calculated for the pregnant dialysis patient?
   Answer: 35 kcal/kg pregravida SBW + 300/day in second and third trimesters.
3. How are protein needs calculated for the pregnant hemodialysis patient?
   Answer: 1.2 g/kg pregravida SBW + 10–25 g/day, and even higher with more intensive dialysis.
4. Which vitamin is supplemented in the diet of pregnant dialysis patients to prevent neural tube defects?
   Answer: Folic acid.
5. Why is the dialysis regimen for a pregnant dialysis patient intensified?
   Answer: To create a less uremic environment for the fetus and allow the patient more liberal dietary intakes to meet nutrient needs of pregnancy.
6. How is anemia treated for pregnant women undergoing dialysis?
   Answer: Intravenous epoetin alfa and iron given during dialysis.

References

1. Hou S. Pregnancy and renal disease. In: Educational review manual in nephrology. 2nd ed. Castle Connolly Graduate Medical Publishing; 2008. p. 251–78.
2. McKay DB, Josephson MA. Pregnancy after kidney transplantation. Clin J Am Soc Nephrol. 2008;3:S117–25.
3. Anderka MT, Lin AE, Abuelo DN, Mitchell AA, Rasmussen SA. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. Am J Med Genet A. 2009;149A(6):1241–8.
4. Furaz-Czerpak KR, et al. Pregnancy in women on chronic dialysis: a review. Nefrologia. 2012;32(3):287–94.
5. Reddy SS, Holley J. Management of the pregnant dialysis patient. Adv Chronic Kidney Dis. 2007;14(2):146–55.
6. Hou S. Pregnancy in women treated with dialysis: lessons from a large series over 20 years. Am J Kidney Dis. 2010;56(1):5–6.
7. Craig KL, Podymow T, Pauly RP. Intensifying renal replacement therapy during pregnancy: the role for nocturnal home hemodialysis. Int Urol Nephrol. 2010;42(1):137–9.
8. Haase M, et al. A systematic approach to managing pregnant dialysis patients—the importance of an intensified haemodiafiltration protocol. Nephrol Dial Transplant. 2005;20(11):2537–42.
9. Grossman S, Hou S. Obstetrics and gynecology. In: Daugirdas JT, Blake PG, Ing TS, editors. Handbook of dialysis. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 624–36.
10. Chang H, Miller MA, Bruns FJ. Tidal peritoneal dialysis during pregnancy improves clearance and abdominal symptoms. Perit Dial Int. 2002;22(2):272–4.
11. Wiggins KL. Nutrition care of adult pregnant ESRD patients. In: Burrowes J, editor. Nutrition care of renal patients. 3rd ed. Chicago, IL: The American Dietetic Association; 2002. p. 105.
12. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35(Suppl 2):S1–140.
13. Institute of Medicine. Dietary reference intake tables. www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx. Accessed 15 Nov 2012.
14. Stover J. Nutritional management of pregnancy in chronic kidney disease. Adv Chronic Kidney Dis. 2007;14(2):212–4.
15. Shemin D. Dialysis in pregnant women with chronic kidney disease. Semin Dial. 2003;16(5):379–83.
16. Hollis BW, Wagner CL. Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcif Tissue Int. 2013;92(2):128–39.
17. Baker AM, Haeri S, Camargo Jr CA, Espinola JA, Stuebe AM. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J Clin Endocrinol Metab. 2010;95(11):5105–9.
18. Vidal LV, et al. Nutritional control of pregnant women on chronic hemodialysis. J Ren Nutr. 1998;8(3):150–6.
19. Drugs.com. http://www.drugs.com. Accessed 5 Feb 2012.

20. Molaison EF, Baker K, Bordelon MA, Brodie P, Powell K. Successful management of pregnancy in a patient receiving hemodialysis. J Ren Nutr. 2003;13(3):229–32.
21. Hyten FE. Nutrition and metabolism. In: Hyten F, editor. Clinical physiology in obstetrics. Oxford, England: Blackwell Scientific Publications; 1988. p. 177.
22. Sobiło-Jarek L, Popowska-Drojecka J, Muszytowski M, Wanic-Kossowska M, Kobelski M, Czekalski S. Anemia treatment with darbepoetin alpha in pregnant female with chronic renal failure: report of two cases. Adv Med Sci. 2006;51:309–11.
23. Goshorn J, Youell TD. Darbepoetin alfa treatment for post-renal transplantation anemia during pregnancy. Am J Kidney Dis. 2005;46(5):e81–6.

Chapter 18
Infancy, Childhood, and Adolescence

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Key Points

- Children typically have different causes of renal failure than adults.
- Treatment of pediatric renal failure focuses on transplant and utilizes PD more commonly.
- Adequacy of linear growth is a unique challenge with pediatric chronic kidney disease (CKD).
- Growth and weight gain are expected for children with CKD and can make adequacy of intake and prevention of protein energy wasting (PEW) more critical.
- Multiple tools are needed for an accurate nutritional assessment picture and include assessment of growth chart curves.
- Energy and individual macronutrient needs are assessed using the 2008 KDOQI Nutrition update.
- The aim for intake of individual micronutrients should be 100 % of the Dietary Reference Intake (DRI) for age, accounting for dialysis losses and possibility of inadequate intake.
- Sodium and potassium intake should be assessed carefully, keeping in mind that young children may have sodium wasting disorders that cause potassium retention.
- Phosphorus management is important for prevention of cardiovascular disease (CVD); however, it should be balanced with adequacy of intake. Calcium intake should be between 100 and 200 % of the DRI for age.
- Fluid needs vary greatly in pediatric patients and depend on primary kidney function and remaining renal function.
- Infants and young children on dialysis require much individual attention as growth is essential for long-term cognition.
- Children and adolescents may have unique challenges related to family dynamics and social-emotional development and need individualization of nutrition instruction.
- Enteral nutrition should focus on oral intake, followed by tube feeding supplementation if further intervention is needed. If enteral nutrition does not meet intake and growth needs, parenteral nutrition may need to be considered.

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- Transplant is the optimal treatment for pediatric CKD but comes with adherence challenges as well as the need for very different nutritional counseling than pre-dialysis and dialysis CKD.
- Transition of the emerging adult from a pediatric-focused care to adult-focused care is an important process to prevent negative health outcomes in the CKD population.

Keywords Children • Pediatric • Chronic kidney disease • Nutritional management • Growth • Dietary modification • Enteral nutrition • Parenteral nutrition

Introduction

Nutritional intervention for infants, children, and adolescents with chronic kidney disease (CKD) is a multifaceted process, as this population not only demands attention to traditional CKD-related dietary issues such as phosphorus, potassium, and sodium, but a heavy emphasis must be placed on the adequacy of growth as well. *Infants and young children withstand nutritional deprivation less well than adults because they have low nutritional stores and high nutritional demands to meet the needs for rapid physical and brain growth. Likewise, adolescents have substantial nutritional needs because of the high demands for growth during puberty. The prevention of uremic toxicity and metabolic abnormalities are additional key treatment goals which nutritional management may influence in the pediatric patient with CKD.

Etiology of CKD*

CKD in children can be caused by congenital, hereditary, acquired, or metabolic disorders. Congenital causes are the most common and include abnormally developed kidneys (e.g., aplastic, hypoplastic, dysplastic) and obstructive uropathy (e.g., posterior urethral valves (PUV)) [1, 2]. The second most common cause is acquired conditions, such as focal segmental glomerulosclerosis (FSGS). In contrast to adults, diabetic kidney disease and hypertensive nephrosclerosis are uncommon disorders in children.

Treatment Modalities*

Traditionally, 60–65 % of pediatric patients have been treated with chronic peritoneal dialysis (PD) once end-stage kidney disease (ESKD) has occurred; however, a recent increase in the proportion of children receiving hemodialysis (HD) has taken place in North America. Virtually all infants receive PD as their initial dialysis therapy, whereas there is a near equal distribution of PD and HD in the adolescent population [1]. *Automated PD is used more often than continuous ambulatory peritoneal dialysis (CAPD) in children cared for in North America, with prescribed dialysate dwell volumes of approximately 1.1 L/m^2 body surface area characteristically provided for 10 h nightly. Whereas most children receive HD three times weekly, the use of daily in-center or out-of-center HD or daily nocturnal home HD in children is a relatively new practice in children and preliminary results have been favorable [3–6].*

Transplantation is the preferred treatment option for children with Stage 5 CKD as it offers the best opportunities for rehabilitation in terms of educational and psychosocial functioning. *Although not common, and depending on the experience of the treatment center, transplantation may occur as early as 1 year of age or when an infant has reached a weight of around 10 kg. Waiting times for transplantation are typically shorter for children than adults; approximately 65–70 % of all children receive a transplant within 18 months of initiating dialysis if they are eligible and a substantial percentage of children receive a preemptive transplant [1].

Linear Growth

Growth in children with CKD is often poor and there are multiple factors that may contribute to this outcome. *In general, observed genetic differences in birth weight among various populations of all children are small, and racial/ethnic differences in growth are primarily the result of health and environmental influences (e.g., poor nutrition, infectious disease, low socioeconomic status), rather than ethnic differences in growth potential [7–9]. This has most recently been demonstrated by the World Health Organization's (WHO) study of the growth of young children from a variety of different countries [10]. In the CKD population, age at onset of disease, etiology, and severity of the primary renal disorder, renal bone disease, fluid and electrolyte balance, metabolic acidosis, inflammation, anemia, abnormalities of the growth hormone-insulin growth factor (IGF) axis, and suboptimal levels of sex hormones are additional factors which influence growth and impact final adult height [11, 12]. Children with CKD are, on average, 1.6 standard deviations below healthy age and gender controls upon initiation of dialysis and tend to decline further while on dialysis [1]. Linear growth is important in this population not only because of quality-of-life issues that may develop during childhood or young adulthood but also because severely reduced height has been associated with increased morbidity and mortality in children with CKD and ESKD [13, 14].

The impact of nutritional intake on growth is most important in the first 2 years of life, during which time half of the final adult height is typically achieved. In a recent global assessment [15] of children less than 2 years of age and undergoing ongoing PD, the use of gastrostomy feedings, as opposed to nasogastric or solely oral feedings, was associated with improved growth. Gastrostomy feedings may be associated with less frequent emesis which may, in turn, improve total caloric intake. Despite these results and as suggested above, recent research indicates that the achievement of standard nutritional goals for energy and protein may not be enough to ensure adequacy of growth in the pediatric CKD population [16]. Since many children have CKD disorders that are characterized by polyuria and salt depletion, care should be taken to ensure an adequate sodium and fluid intake. Failure to meet the often substantial quantity of sodium needs can compromise linear growth [17]. Serum bicarbonate may provide a portion of the sodium as the serum CO_2 level should be corrected to at least 22 mmol/dL in CKD stages 2–5, also important for adequacy of growth [11]. Appropriate management of anemia and renal osteodystrophy is also mandatory. One of the most important interventions is often the provision of recombinant human growth hormone (rGH) because of the resistance to growth hormone that exists as a result of the presence of an increased concentration of IGF-binding proteins [18]. Recent evidence lends support to an early initiation of rGH therapy to avoid growth delay if metabolic and nutritional issues have been addressed and poor height velocity persists [11, 15, 19, 20]. Currently, rGHs recommended when the height standard deviation score (SDS) or height velocity SDS is <1.88 (<3 percentile) [11, 13]. Finally, a study by Tom et al. [16], supported by work from Fischbach et al. [21], would also seem to indicate that increased dialysis may be necessary to overcome growth delays, even when nutritional factors have been addressed and growth hormone is utilized [22, 23].

Adequacy of Weight Gain and Nutritional Intake

The term "malnutrition" is frequently used when referencing the CKD populations, as inadequate dietary intake is common. However, use of the terms "cachexia" or "protein-energy wasting" (PEW) may be more accurate as true malnutrition typically includes adaptive factors such as an increase in appetite and a decrease in metabolic rate [24, 25]. Unfortunately, poor intake and subsequent growth failure, as seen in children with CKD, is often characterized by maladaptive responses such as a decline in appetite and an increase in energy needs. Additionally, these patients may experience muscle wasting of lean body mass without fat decrease. This wasting-type process most often manifests

as inadequate weight gain and crossing percentiles downward in BMI and weight on the growth curve. A number of adverse outcomes may result. It is somewhat difficult to specifically characterize the influence of nutritional wasting on height gain since many factors, as noted above, can influence this outcome [24, 26]. However, as mentioned above, the negative impact on growth during the initial 2 years of life can be substantial. Neurodevelopmental delay in the youngest patients can also occur. In addition, children with chronically inadequate intake display behavioral changes such as irritability, apathy, and attention deficits, and, as suggested above, those that are stunted may experience social disadvantages that adversely affect development and quality of life [27].

In adult and pediatric patients, new evidence is providing some answers as to why poor dietary intake and negative energy balance are frequently seen in the CKD population. Proinflammatory, anti-appetite cytokines, such as TNF-alpha and IL-6, are elevated in this population. Specific appetite modulators are altered as well. Leptin, known to suppress appetite and originating from adipose tissue, has been found to be elevated in the setting of a decreased glomerular filtration rate (GFR) [28]. Although total ghrelin, which typically increases appetite, is normal in the CKD population, the majority of circulating ghrelin is desacyl ghrelin, which is associated with decreased appetite [28]. A study looking at pediatric non-dialysis CKD and HD patients compared to healthy controls found a similar association that although levels of total ghrelin were elevated, it was in the desacyl form, thus likely suppressing appetite [29]. In the young PD patient, the increased intraperitoneal pressure that results from the presence of dialysate can also have a negative influence on appetite.

Although treating nutritional inadequacy in this population is difficult as many factors that are not fully defined or understood likely influence the outcome [24], several small studies have suggested possible intervention strategies. Options to increase calorie and protein intake include tube feedings, supplemental feedings, intradialytic parenteral nutrition (IDPN), or other routes of parenteral nutrition [26]. One study looking at 25 pediatric dialysis patients with poor weight gain reported on the use of megestrol acetate as an appetite stimulant, used at a dose of 7 mg/kg/day [30]. This study showed success over a limited period of time with evidence of increasing weight with minimal side effects. However, more data is needed before megestrol acetate or any other appetite stimulant is recommended for routine use in children with CKD. Increased dialysis time is another strategy that may not only increase linear gain as previously mentioned but may improve overall weight gain as well. It is speculated that reduced diet restrictions and reduced inflammation, made possible by improved clearance, may be the cause of the improved dietary intake and weight gain [22, 31].

In years past, most pediatric CKD patients were underweight or at risk for being underweight. Although much of the focus of care in pediatric CKD continues to be directed to adequate intake and prevention of PEW, the clinician must also be aware of overweight and obesity. With the great increases in rates of childhood and adolescent overweight and obesity in recent decades, this trend is impacting the pediatric CKD population as well [32]. A large, multicenter study of non-dialysis children with CKD recently reported 15 % of the children were obese [33]. Dietary and lifestyle changes may need to be considered for this population. Overweight children suffer from more chronic conditions and have poorer health than healthy-weighted children [34]. In fact, the Chronic Kidney Disease in Children (CKiD) study has found an increased prevalence of dyslipidemia, abnormal glucose synthesis, and hypertension in pediatric patients with CKD who are obese as well [33]. If the patient is very overweight or the patient has reached final adult height, a slow loss of weight is recommended. If the patient is still growing linearly, weight maintenance may be beneficial, allowing the gradual increase in height to reduce BMI. To prevent excessive, rapid weight loss or inadequate nutrition, adequate protein and other nutrients are essential. A focus on increased physical activity and limiting simple carbohydrates is an appropriate and moderate approach to slow weight loss or to achieve weight maintenance and minimize risk.

Table 18.1 Recommended parameters and frequency of nutritional assessment for children with CKD stages 2–5 and 5D

Minimum interval (months)										
	Age 0–1 years			Age 1–3 years			Age 3 years			
Measure	CKD 2–3	CKD 4–5	CKD 5D	CKD 2–3	CKD 4–5	CKD 5D	CKD 2	CKD 3	CKD 4–5	CKD 5D
Dietary intake	0.5–3	0.5–3	0.5–2	1–3	1–3	1–3	6–12	6	3–4	3–4
Height or length-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Height or length velocity-for-age percentile or SDS	0.5–2	0.5–2	0.5–1	1–6	1–3	1–2	6	6	6	6
Estimated dry weight and weight-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.25–1	1–3	1–2	0.5–1	3–6	3–6	1–3	1–3
BMI-for-height-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Head circumference-forage percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1–2	N/A	N/A	N/A	N/A
nPCR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1[a]

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N/A not applicable

[a]Only applies to adolescents receiving HD

Assessment

The assessment of nutritional status of children with CKD is complicated by the myriad of factors that may influence stature, body weight, and intake. Consequently, a variety of assessment tools are recommended to provide a more complete picture than any single measure. The frequency of the assessment is recommended to be at least twice as often as the assessment of healthy children. An even more frequent assessment may be necessary in the setting of comorbid conditions, increasing disease severity, changes in residual renal function or dialysis modality, and for younger ages [11, 35]. The *KDOQI Clinical Practice Guideline for Nutrition in Children with CKD*: *2008 Update* outlines the recommendations for assessment in this population. *A dietitian/clinician should also consider medical history, biochemical parameters, medications, bowel habits, urine output, fluid balance, and activity level when assessing the patient. Refer to the KDOQI guidelines for details on the frequency of assessment in a given patient age group [11] and Table 18.1. Key aspects of the recommended assessment include the following:

- Length or height for age: Length is the preferred measurement in children younger than 2 years of age, while height, which is measured standing, should be used in children aged 2 and older. Length should be measured with a length board to ensure accuracy while height should be measured with a stadiometer. Measurements for children younger than age 2 should be compared to the WHO growth charts or assessed as a SDS. Poor or declining linear growth as a SDS may be one measure of inadequate nutrition; however, and as noted previously, growth is influenced by many factors in this population. Parental height should be compared with the child's placement on the growth chart. Predicted adult height can be calculated for boys as the mother's height plus 5 in. (34 cm) averaged with the father's height and for girls as the father's height minus 5 in. (34 cm) averaged with the mother's height [11].
- Length or height velocity for age: Assessment of height velocity can also be judged as a percentile or SDS score. Reference data from the Fels Longitudinal Study [36] provides data on expected height velocity for age. Serial measurements provide for the best assessment and data can be compared every 6 months. Shorter intervals may not provide accurate velocity readings [11].

Although many of the same factors that influence height in this population affect height velocity as an assessment metric, trending may provide greater insight regarding the influence of the nutritional status.

- Dry weight: Weight can also be assessed as a percentile compared to a standard growth chart or as a SDS. Again, the WHO growth charts should be used in children younger than 2. It is important that the weight assessed is a euvolemic weight as oliguria and associated fluid retention may increase weight and not give an accurate picture of the actual lean body mass. The use of noninvasive blood volume monitoring which measures hematocrit determines the capacity to refill the vascular space when fluid is removed by HD. This tool may aid in determining if a patient has reached their dry weight. Signs of edema, blood pressure control, and biochemical markers such as albumin or serum sodium may also help determine a patient's dry weight.

  When characterized by a percentile, dry weight may need to be compared to a patients "height age" or the age that aligns with the 50th percentile based on their current height. This is important when a patient is very small or short to give a more accurate assessment of the appropriateness of the weight for size. While weight trends may provide important information about adequacy of the nutritional status, a single weight is of limited value without taking other indices (e.g., BMI) into consideration.

  Ideal body weight (IBW) is another clinical tool that can help assess nutrition status. Dry weight can be compared to IBW. IBW is the weight needed to be at the 50th percentile for BMI for age or height age. This can be calculated by taking the 50th percentile BMI or height age BMI × height in meters × height in meters again. Percent IBW can be assessed by dividing the actual dry weight by the IBW and converting to a percentage. The percentage can then help determine if a patient is overweight or underweight, and by what degree.
- BMI for height age: Growth standards based on growth charts should also be used for the assessment of BMI, with a target range of 3–85th percentile (with a BMI of >85th percentile defined as overweight and >95th percentile as obese) [11]. This is supported by an international survey defining thinness in pediatric patients. Grades 1, 2, and 3 thinness are similar in assessment to grades of malnutrition, with grade 2 thinness corresponding with the 3rd percentile BMI [37]. The closer a patient is to the 3rd percentile, the more at risk he/she is of an acute illness or decline in appetite could quickly move them below the 3rd percentile. In older children and adolescents, BMI should be compared to height age as physical and sexual development is more likely to be consistent with the height age as opposed to chronological age [11]. Using chronological age to calculate BMI may overestimate appropriate BMI [38]. A landmark study by Wong et al. has indicated that mortality risk increases in a U-shaped curve for BMIs that are very low or high for age in pediatric CKD patients [14]. Since BMI is not an appropriate measure in children under the age of 2, weight for length percentile is the comparable metric in this age group.
- Head circumference: Head circumference should be measured and compared to normative curves as provided by the WHO standards in children aged 3 and younger [11]. A small head, with absence of comorbidities, may indicate nutritional insufficiency. Prematurity may also affect this measurement.
- Normalized protein catabolic rate (nPCR): nPCR also known as protein-nitrogen appearance (nPNA) indirectly assesses dietary protein intake in dialysis patients with less measurement error than dietary diaries or 24 h recalls. A child who has a desirably low pre-dialysis urea may be a well-nourished patient who is adequately dialyzed or an individual with an inadequate dietary protein intake. Normalized PCR can help differentiate between the two possibilities.

  Recent research indicates that nPCR is a more valid marker of nutritional status than serum albumin in adolescents receiving HD, the latter being influenced by inflammation and fluid status [11]. The nPCR is measured in grams of protein per weight in kilograms per day. For adolescents, nPCR values between 1.0 and 1.2 g/kg/day have been associated with positive outcomes for

appropriate growth and overall nutritional status [39]. Target values for children and infants have not yet been clearly delineated, but theoretically, they would be higher than for adolescents as greater rates of weight gain are expected at younger ages. Because nPCR fluctuates on a daily basis depending on what is eaten, a single value does not provide an optimal picture of usual or average protein intake; therefore, monthly measurements are more informative. The nPCR can be calculated as part of the monthly assessment of clearance for the adolescent HD patient in the following manner:

The *G* must be calculated first:

$$G\,mg\,/\,\min\left(urea\ generation\ rate\right)=\left\{\left(C2\times V2\right)-\left(C1\times V1\right)\right\}/t$$

*C*2 is pre-dialysis blood urea nitrogen (BUN) mg/dL.
*C*1 is post-dialysis BUN.
*V*2 is pre-dialysis total body water (dL; *V*2 = 5.8 dL × pre-dialysis weight in kg).
*V*1 is post-dialysis total body water (dL; *V*1 = 5.8 dL × post-dialysis weight in kg).
T is time (minutes) from the end of the dialysis treatment to the beginning of the next treatment.

The modified Borah equation is then used to calculate nPCR:

$$nPCR\left(\mathrm{g}\,/\,kg\,/\,day\right)=5.43\times est\ \ G\,/\,V1+0.17$$

*V*1 is post-dialysis total body water (L; *V*1 = 0.58 × post-dialysis weight in kg).

A goal of at least 1 g/kg/day is expected for weight maintenance in adolescents and those who have values lower than this may be experiencing weight loss and inadequate nutritional intake. Additionally very high values could indicate catabolism. Values in the 1–1.2 g/kg/day range are ideal for those expected to gain weight [11, 39]. Although PNA has been used to estimate dietary protein intake in children on PD [40–42], outcome measures for interpreting PNA measurements as well as targets of therapy are not well established, and thus monitoring of PNA is not currently recommended as part of routine practice for PD [43].

- Dietary intake: Assessment of intake as it relates to nutrition status is best done via a 3-day food record or three 24-h recalls. A single 24-h recall may be inadequate to account for day-to-day variance, but the 24-h recall may be preferable for some patients or families in whom keeping written dietary records is burdensome. A skilled pediatric dietitian should assess dietary intake with these methods for the determination of the adequacy of intake for energy, protein, and other macro- and micronutrients [11].

In addition to the recommendations pertaining to assessment contained in the KDOQI guidelines, other possible assessment tools have been or are currently being studied in pediatric populations and may be added to the assessment regimen in the future. Subjective global assessment (SGA) has been validated for use in adult renal populations and has now been validated for use in pediatric populations [44]. Further study of the SGA in the pediatric CKD population is forthcoming. Additionally, bioelectrical impedance (BIA) may have a role in better defining dry weight and assist in the assessment of cardiovascular dynamics in pediatric patients on dialysis [25, 45]. BIA has been reported to be noninvasive, simple, and inexpensive to use [25, 46]. Other measures such as dual-energy X-ray absorptiometry (DEXA) and midarm anthropometry have been used in a limited manner in the pediatric CKD population because of expense and/or poor predictive value, respectively [11]. Figure 18.1 represents a sample initial assessment form, as many programs have requirements for initial and annual assessments. (Refer to Chap. 4 for further details on anthropometric assessment in the general renal population.)

Nutrient Requirements

The KDOQI guidelines provide recommendations by age group for macro- and micronutrient intake. These recommendations should be used as an initial starting point with subsequent individualization to the patient's needs [11]. Many variables affect these needs, including periods of catabolic stress, comorbid conditions, and genetic variation. Children who are significantly above or below their IBW may need adjustment as well. A child may need to have their nutrient needs calculated based on height age when he or she has failed to meet goals for weight gain with nutrient needs based on chronological age, especially if height age and chronological age are very different. Adjustment for prematurity may also need to be considered, using adjusted age for calculated needs.

Growth:
Age: Gestational Age: or N/A
Weight: kg Length or Height: cm BMI: kg/m2 Head Circumference cm or N/A
Weight %ile: Length or Height %ile: BMI or Weight/Length %ile: HC %ile:
Weight SDS: Length or Height SDS: Height Velocity SDS:
Previous Weight SDS: Date: % change in SDS:
Previous Length or Height SDS: Date: % change in SDS:
Previous Height Velocity SDS: Date: % change in SDS:
Previous weight: Date: Weight gain: g/day or kg/month
Laboratory Values: (Range for age and clinical status)

Calcium	Date:	Appropriate? Yes/No	Reference Range:
Phosphorus	Date:	Appropriate? Yes/No	Reference Range:
PTH	Date:	Appropriate? Yes/No	Reference Range:
Albumin	Date:	Appropriate? Yes/No	Reference Range:
BUN	Date:	Appropriate? Yes/No	Reference Range:
nPCR (HD only)	Date:	Appropriate? Yes/No	Reference Range:
Potassium:	Date:	Appropriate? Yes/No	Reference Range:
Sodium:	Date:	Appropriate? Yes/No	Reference Range:
Zinc:	Date:	Appropriate? Yes/No	Reference Range:
Aluminum:	Date:	Appropriate? Yes/No	Reference Range:
Cholesterol:	Date:	Appropriate? Yes/No	Reference Range:
LDL:	Date:	Appropriate? Yes/No	Reference Range:
Triglycerides:	Date:	Appropriate? Yes/No	Reference Range:
HDL:	Date:	Appropriate? Yes/No	Reference Range:

Medications:
Phosphorus Binders: _____
Iron/Erythropoietin therapy: _____
Vitamins/Supplements: _____
Stool Softeners/GI Medications: _____
Other pertinent medications: _____
Diet/Intake:
Diet Order: _____

Tube Feeding Prescription: (N/A) _____

Infant Formula Order: (N/A) _____

Bolus Feeding Regimen: Continuous Feeding Rate:
IDPN: (N/A) _____

Subjective Assessment:
Oral intake reported (specify meals, snacks, amounts):

Fig. 18.1 Sample pediatric renal nutrition initial or annual assessment form

Primary food preparer:
Primary food purchaser:
Additional food resources (WIC, SNAP, etc): _____

Other persons present at meal and/or snack times: _____

Physical appearance:
Evidence of muscle wasting: None Mild Moderate Severe
Evidence of fat wasting: None Mild Moderate Severe
Oral cavity concerns (note issues with teeth, sores or marks on the tongue, etc)

Reported Physical Activity:

Appetite Description:

Questions Patient/Family has at this time:

Original Figure, C.L. Nelms

Fig. 18.1 (continued)

Energy

*Adequate intake of calories is important not only for weight gain and growth but also to avoid using protein as an energy source through gluconeogenesis. Energy needs for children with CKD are likely similar to those of healthy children [11]. In 2002, new guidelines for calculating energy needs in pediatric patients were published by the Food and Nutrition Board (see Tables 18.2 and 18.3). Body size and response to these recommendations must be considered for CKD patients when adjusting the recommendations to meet the individual patient [11]. Children with PEW/cachexia may have higher kcal needs [24, 47]. Research indicates that although children with CKD may initially show lower resting energy expenditure (EER) than healthy children, after adjusting for lean body mass, caloric needs are the same for both groups. Many of the children assessed in the study that had lower EER values also had significant fat and muscle losses and caloric and protein deficits [47].

Glucose absorption from peritoneal dialysis solutions provides approximately 9 kcal/kg daily [48] for children on PD. However, the quantity of glucose that is absorbed varies between children and may be influenced by factors such as the number of cycles for patients receiving automated PD, dwell time, body surface area, and peritoneal membrane transport capacity. Although these calories are typically not considered in the calculation of energy recommendations, high or high-average transporters may gain significantly more glucose calories than low or low-average transporters [11]. It is for this reason that KDOQI does not recommend the regular inclusion of this parameter into the determination of energy intake. However, since oral caloric intake may be quite low for the PD patient [49], calories from dextrose may be considered as "bonus" calories. In contrast, if a child is gaining significant weight while receiving PD, calories received from glucose should be considered as a possible source of energy and the dietary intake may require modification.

Table 18.2 Estimated energy requirement calculations

0–3 months: [89 × weight in kg − 100] + 175
4–6 months: [89 × weight in kg − 100] + 56
7–12 months: [89 × weight in kg − 100] + 22
13–35 months: [89 × weight in kg − 100] + 20
3–8-year-old male: 88.5 − 61.9 × age in years + PA × [26.7 × weight in kg = 903 × height in meters] + 20
3–8-year-old female: 135.3 − 30.8 × age in years + PA × [10 × weight in kg = 934 × height in meters] + 20
9–18-year-old male: 88.5 − 61.9 × age in years + PA × [26.7 × weight in kg = 903 × height in meters] + 25
9–18-year-old female: 135.3 − 30.8 × age in years + PA × [10 × weight in kg = 934 × height in meters] + 25

Data from: Institute of Medicine. Dietary References Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients). Washington, DC: National Academy of Sciences; 2002
PA is physical activity factor—see Table 18.3

Table 18.3 Physical activity factors

	Sedentary	Low active	Active	Very active
	Typical activities of daily living only	30–60 min of daily moderate activity	≥60 min of daily moderate activity	≥60 min of daily moderate activity + additional 60 of vigorous or 120 min of moderate activity
Males	1.0	1.13	1.26	1.42
Females	1.0	1.16	1.31	1.56

Data from: Institute of Medicine. Dietary References Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients). Washington, DC: National Academy of Sciences; 2002
*For use in estimated energy equations

Protein

A positive nitrogen balance is important to support growth and prevent catabolism in pediatric CKD patients. However, free access to dietary protein must be modified because of the phosphorus load that accompanies the protein. *Voluntary protein intake usually exceeds age-based Dietary Reference Intakes (DRIs) for healthy children, and thus attention must be directed at the phosphorus-induced elevated levels of parathyroid hormone (PTH) and possibly fibroblast growth factor-23 (FGF-23) because of the associated morbidity that may occur (e.g., cardiovascular disease (CVD) as part of the so-called chronic kidney disease-mineral bond disorder (CKD-MBD) [11]). At the same time, there is no documented benefit of reducing protein intake on the progression of CKD in children, and low-protein diets may interfere with nutritional status and growth. Therefore, the aim of management is to avoid *excessive* protein intake in order to minimize uremia. Protein of high biological value is encouraged because it minimizes urea production by reusing circulating nonessential amino acids (AA) for protein maintenance.

For pre-dialysis children and adolescents, the KDOQI guidelines recommend limiting dietary protein intake to no more than 140 % of the DRI for age for stage 3 CKD (30–59 mL/min/1.73 m^2) and 120 % of the DRI for stage 4 and 5 CKD (<30 mL/min/1.73 m^2). This may aid in the prevention of uremic symptoms and the provision of excess phosphorus intake. However, to ensure adequacy of growth and palatability of the diet, at least 100 % of the DRI for age should be recommended [11]. Dietary protein recommendations for children on dialysis are 100 % of the age-appropriate DRI plus 0.1 g/kg/day for HD patients and 0.2–0.3 g/kg/day for PD patients to account for dialysis-related losses.

Noteworthy is the fact that the Food and Nutrition Board issued new DRI guidelines for protein intake in 2002. The recommendations are lower than the previous Recommended Dietary Allowances (RDA) guidelines and influenced the 2008 KDOQI nutrition update. However, and as noted above, the KDOQI references (see Table 18.4) should be used as a minimum starting point with individualized recommendations contingent upon patient-specific clinical and biochemical follow-up.

Table 18.4 Recommended dietary protein intake in children with CKD stages 3–5 and 5D

Age	DRI (g/kg/day)	Recommended for CKD stage 3 (g/kg/day) (100–140 % DRI)	Recommended for CKD stages 4–5 (g/kg/day) (100–120 % DRI)	Recommended for HD (g/kg/day)[a]	Recommended for PD (g/kg/day)[b]
0–6 months	1.5	1.5–2.1	1.5–1.8	1.6	1.8
7–12 months	1.2	1.2–1.7	1.2–1.5	1.3	1.5
4–13 years	0.95	1.05–1.5	1.05–1.25	1.15	1.3
14–18 years	0.85	0.85–1.2	0.85–1.05	0.95	1

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[a]DRI 0.1 g/kg/day to compensate for dialytic losses

[b]DRI 0.15–0.3 g/kg/day depending on patient age to compensate for peritoneal losses

A number of issues need to be taken into consideration when addressing the patient-specific protein requirements. Protein needs may be overestimated using the DRI based on weight in obese patients or underestimated in small or malnourished children and adolescents. Obese children have a higher amount of adipose tissue, and thus protein needs based on lean tissue may be less than the patient's actual weight would indicate. Common practice allows for the use of an adjusted body weight, calculated as {[(actual weight − ideal weight) × 25 %] + ideal body weight} to use as a weight-based number to calculate dietary protein needs in the obese pediatric patient.

Likewise, small children may have a higher proportion of lean tissue and clinical judgment should be used in assessing protein needs. Wasted children may need additional protein to account for catabolism [11]. Protein requirements may also be increased in patients with proteinuria, acidosis, peritonitis, high transport status, and longer dialysis times or in those patients who are receiving glucocorticoids. *Losses are similar for CAPD, continuous cyclic peritoneal dialysis (CCPD), and tidal dialysis but vary widely between individuals. Protein requirements are highest on a g/kg basis for infants and toddlers because protein losses are inversely related to body weight and peritoneal surface area [11]. If desired, protein losses can easily be measured in dialysate when clearance (e.g., *Kt*/*V*) is determined. *To assess protein status, Edefonti et al. [48] performed nitrogen balance studies in children on PD and found that in only 50 % of the studies was nitrogen balance adequate to meet estimated nitrogen requirements for growth and the metabolic needs of uremic children. In 36 % of the studies, results were considered relatively satisfactory and in 14 % of the studies, children were in negative nitrogen balance. Children who had been on dialysis longer than 1 year had lower energy and protein intakes and poorer nitrogen balance results.*

*Dietary protein intake may be low because of anorexia, low meat intake, chewing problems, or adherence to a low-phosphorus diet that limits protein-rich dairy foods. *Protein intake can be increased via protein-rich foods or powdered protein modules added to infant formula, beverages, pureed foods, cereals, or other moist foods. Minced or chopped meat, chicken, fish, egg, tofu, or skim milk powder can be added to soups, pasta, or casseroles, although phosphorus intake will typically increase. Egg whites may be encouraged as they are lower in phosphorus content than the egg yolk. Meeting protein requirements may be difficult for children receiving PD and for vegetarians, especially vegans, who may need specific dietary counseling.*

Carbohydrate, Fats, and Lipid Management

The macronutrients that comprise total energy intake should be within the acceptable macronutrient distribution range (AMDR) that is recommended by the Institute of Medicine (IOM) [11]. Additionally, the American Academy of Pediatrics (AAP) recommends that children with dyslipidemia, which is common in CKD, limit total fat to <30 % of calories, saturated fat to 7–10 % of calories, and

cholesterol to <300 mg/day for children aged 4 and older [50]. Glucose calories received from peritoneal dialysis may increase the percentage of caloric intake from carbohydrate sources and should be assessed when counseling patients on total percentage of macronutrient intake. Dyslipidemia is common in pediatric CKD, with 44 % of non-dialysis CKD patients presenting with abnormal lipids [33]. Elevated triglycerides were found to be the most common type of lipid abnormality. In non-malnourished/wasted children, an increase in fiber focusing on complex carbohydrates and limited added sugar intake is recommended [11, 50, 51]. If carbohydrate and fat modulars are used to increase the caloric content of formula or supplements, it should be done so proportionately to maintain an appropriate ratio within the AMDR.

*High-calorie diets or tube feedings rich in fats may influence lipid profiles. The American Heart Association (AHA) and the AAP list children with CKD as being a high-risk population for CVD [50, 51]. As noted above, dyslipidemia characterized by elevated levels of triglycerides, in addition to abnormalities of very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), total cholesterol, and low levels of high-density lipoproteins (HDL), is common and often presents with CKD Stages 3–5 [52, 53] or posttransplantation as an adverse effect of immunosuppressant therapy. *Thus, when additional fats are needed as an important caloric source, "heart-healthy" ones should ideally be used, such as canola, olive, or peanut oils. These oils can be used in food preparation or as a condiment and are in the group of monounsaturated and polyunsaturated fats. Saturated and trans fat intake should be minimized [51, 54].

The KDOQI Cardiovascular Guidelines [55] recommend that management of dyslipidemias for prepubertal children with CKD and CKD Stage 5 (including posttransplantation) should follow recommendations by the National Cholesterol Expert Panel in Children and Adolescents (NCEP-C) [56] and that management of postpubertal children or adolescents with CKD Stages 4 and 5 (including posttransplantation) should follow recommendations provided in the KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in CKD [57]. Key features of the KDOQI Dyslipidemia Guidelines that differ from the NCEP-C are the following: (1) more frequent evaluation of dyslipidemias (i.e., after presentation with CKD, after a change in renal replacement therapy [RRT], and annually); (2) if LDL is 130–159 mg/dL, a therapeutic lifestyle change (TLC) diet should be started (if nutritional status is adequate), followed by a statin drug in 6 months if LDL ≥130 mg/dL; and (3) if LDL is ≥160 mg/dL, both a TLC diet and a statin should be started. Lipid-lowering drugs are also to be used in children over the age of 10 with CKD and hyperlipidemia [11, 50–52]. Physical activity should be encouraged for all types of dyslipidemias [50]. Diet therapy may not be appropriate in malnourished/wasted children [11]. See Table 18.5 for a summary of macronutrient needs for pediatric CKD.

Vitamins and Minerals

Adequacy of vitamin and mineral intake is important for growth and overall health. Vitamin and mineral supplementation recommendations in pediatric CKD patients are, however, complicated by the lack of substantial research on the subject. Although one small study [58] that looked at various B-vitamin intakes in children on dialysis found the majority of children to have adequate intakes and high serum levels, other studies have documented water-soluble vitamin intake below recommendations [59, 60]. *Several studies have shown that the combination of dietary and supplemental vitamin intake is routinely associated with blood concentrations that meet or exceed normal values.

Since the volume or variety of dietary intake may be limited by anorexia or dietary restrictions, the dietitian/clinician must carefully assess a patient's intake for risk of vitamin and mineral deficiencies. *Children receiving dialysis have additional risks of deficiencies because of increased losses through dialysis and increased needs (e.g., iron on erythropoietin therapy). *Both the KDOQI Nutrition and Cardiovascular Guidelines note that current opinion and evidence indicate that it is prudent to

Table 18.5 Macronutrient needs for children with CKD

	EER for age or height age			
Energy	Stage 3 CKD	Stage 4–5 CKD	Hemodialysis	Peritoneal dialysis
Protein	100–140 % of DRI	100–120 % of DRI	g/kg/day 0–6 months: 1.6 7–12 months: 1.3 1–3 years: 1.15 4–13 years: 1.05 4–18 years: 0.95	g/kg/day 0–6 months: 1.8 7–12 months: 1.5 1–3 years: 1.3 4–13 years: 1.1 4–18 years: 1.0
Fat	AMDR: Age 1–3: 30–40 % of calories Age 4–18: 25–35 % of calories	Stage 5: <30 % of calories; <7 % of calories from saturated fat, avoid trans fat	<30 % of calories; <7 % of calories from saturated fat, avoid trans fat	
Carbohydrate	AMDR: 45–65 % of calories			AMDR: 45–65 % of calories, ensure oral calories + calories from PD do not exceed AMDR

Data from: National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Am J Kidney Dis 2009;53(suppl 2):S1–S124

supplement, rather than risk deficiency, especially when supplementation is safe at the recommended levels [11, 55]. These guidelines recommend a daily vitamin supplement for children on dialysis, emphasizing adequacy of water-soluble vitamins. A renal-formulated vitamin most likely meets these needs. Although there are no known marketed pediatric renal vitamins, liquid "adult" renal vitamins can be titrated to more closely meet the DRIs of young children. Adolescents typically have similar water-soluble vitamin needs to adult patients and can take similar vitamin supplements. Providing a vitamin that is at or slightly above the DRI for age should be the aim.

Although KDOQI recommends meeting the DRI for all vitamins and minerals with the exclusion of phosphorus, potassium, and sodium, *supplementation of vitamins A and E is generally avoided because blood levels are usually normal or elevated without supplementation in patients with CKD [59, 61, 62]. Children and adults on dialysis have both been found to exhibit elevated levels of serum retinol, retinol-binding protein, and transthyretin; however, it is unclear what the impact of this is, as the symptoms of uremia and vitamin A toxicity are similar. However, there may be hormone-like actions of excess vitamin A closely related to growth-related hormones, which make excess amounts of vitamin A and its derivatives undesirable within the realm of growth, metabolism, and growth-related hormone actions [63]. There is some question about whether vitamin E may have a role in improving the management of anemia in CKD through a reduction of oxidative stress [64]. However, there is not enough evidence at this time to routinely recommend supplementation, and an excess should likely be avoided. Whereas caution regarding excess vitamin C intake is warranted, vitamin C is frequently lost through dialysis so adequacy of intake should be ensured.

Specific attention should be given to the assessment of the nutritional vitamin D (25(OH)D3) status. Vitamin D insufficiency has recently been recognized to be exceedingly common in the healthy pediatric population [65]. To prevent the risk of rickets and to support the role of vitamin D in a number of physiologic activities, the AAP recommends that all infants, children, and adolescents receive at least 400 IU of vitamin D daily, which is an increase from the previous recommendation of 200 IU daily. *Vitamin D supplementation should be provided for all exclusively breastfed infants, especially those at highest risk for vitamin D-deficiency rickets (i.e., infants born to vitamin D-deficient mothers, those having limited exposure to sunlight, or those who are dark skinned) [65–67]. Importantly, children with all stages of CKD [68–70] are at greater risk than the general population for vitamin D insufficiency (<32 ng/mL) and deficiency (<15 ng/mL) [68], and low levels of 25(OH)3 have been

Table 18.6 Micronutrient needs for children with CKD

	Pre-dialysis CKD	Dialysis
Water-soluble vitamins	Supplement if assessment of intake indicates deficiency	Supplement recommended
Fat-soluble vitamins	Avoid vitamin A supplementation and vitamin E and K at DRI, assess and supplement 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D as needed	
Trace minerals	Assess and supplement copper, selenium, and zinc as needed; limit heavy metals	
Calcium	100–200 % DRI	
Phosphorus	100 % DRI if PTH at target, 80 % DRI if PTH elevated	80 % DRI

Data from: National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Am J Kidney Dis 2009;53(suppl 2):S1–S124. Vannucchi, MTI, Vannucchi H, Humphreys M. Serum levels of vitamin A and retinol binding protein in chronic renal patients treated by continuous ambulatorial peritoneal dialysis. Int J Vitam Nutr Res 1992;62:107–12. National Kidney Foundation. KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease. Am J Kid Dis 2005;46(4, Suppl 1):S1–121

seen in the majority of patients with advanced CKD or on dialysis [68, 70, 71]. It appears that the prevalence of low vitamin D levels has increased in recent years [68, 69].

Children with CKD are frequently prescribed 1,25 dihydroxyvitamin D (calcitriol) because of the reduced capacity of the diseased kidney to convert 25-hydroxyvitamin D (ergocalciferol or cholecalciferol) to the active form and the well-known consequent bone metabolism issues that may arise. However, it is important to recognize that not only is the generation of activated vitamin D a substrate-dependent process in patients with CKD that is dependent upon adequate levels of 25(OH)D3 but that 25(OH)D3 itself likely plays an important role in immune function, prevention of malignancy, and cardiac function in patients with CKD, irrespective of the provision of activated vitamin D [68, 69, 71]. There is now also evidence that maintenance of a 25(OH)D3 replete state may have a role in lowering PTH levels in children with CKD [71]. Accordingly, the KDOQI Clinical Practice Guidelines for Nutrition in Children with CKD recommends monitoring vitamin D levels and supplementing if levels are low, with the size of the repletion course of therapy dependent on the baseline vitamin D level; continued use of maintenance therapy is recommended once the patient is repleted [11].

It is well known that anemia is common in CKD, but the role of iron and other treatment of anemia of CKD is beyond the scope of this chapter. Refer to Chap. 24 for further discussion of micronutrients in the general CKD population. See Table 18.6 for a summary of micronutrient needs for pediatric CKD.

Sodium

The specific approach to be used for sodium management is very much dependent upon the clinical status of the patient. Restriction of dietary sodium is appropriate for children with CKD who experience salt and water retention and associated hypertension. This is particularly important as CVD is the most frequent cause of mortality of children and adults with end-stage renal disease. In contrast, it is not appropriate to restrict salt for children with salt-wasting syndromes such as obstructive uropathy, renal dysplasia, tubular disease, or polycystic kidney disease or for infants receiving PD who may require sodium *supplementation* to prevent sodium depletion, a decrease in extracellular volume, and impaired growth [17, 72]. In fact, failure to provide adequate supplemental salt to young patients receiving on PD has been associated with severe cerebrovascular complications [72]. The need for sodium supplementation for the salt-losing disorders typically decreases with age as the common western high sodium diet provides more than adequate intake, and these children may actually develop hypertension that would benefit from sodium restriction.

The most recent Dietary Guidelines for Americans [73] recommend that hypertensive individuals older than 2 years of age consume no more than 1,500 mg of sodium per day, while KDOQI nutrition guidelines indicate 1,500–2,400 mg/day is allowable, based on the DRI Upper Tolerable Limit (UL) for age. Restaurant meals and salt added by manufacturers provide 75 % of the daily sodium intake of most people living in North America [74]. *To reduce sodium intake, children and caregivers are advised to limit salt used in cooking or added at the table, to rely on fresh rather than processed foods, to eat out less often, and to read ingredient lists and nutrient content tables on food labels to avoid salty foods, defined as having more than 140–200 mg sodium/serving [73]. Significant pressure from social groups, the lack of available lower sodium foods, and palatability may make these goals difficult to achieve, especially for many adolescents. A restriction of 2,000–3,000 mg of sodium per day may be better accepted in some populations and hypertension control must be balanced with adequacy of nutritional intake.

Homemade baby foods prepared from fresh ingredients are lower in sodium, and commercial baby foods also do not contain added salt. Lunch ideas should be discussed, especially for children who eat at school. Salt substitutes are contraindicated in children with hyperkalemia, because manufacturers use potassium chloride to replace some or all of the sodium chloride in some food products.

Potassium

Dietary potassium must be restricted for many children with advanced CKD. The need to restrict potassium often correlates with the progression of CKD, with many children not requiring a restriction of dietary potassium until they are near or reach the need for dialysis [11]. However, infants and toddlers with CKD often have congenital disorders, such as renal dysplasia or obstructive uropathies that cause potassium retention. Thus, this population may need special care in limiting potassium [11]. In addition, the need for restriction may be hastened when certain medications, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), are required [75]. Infants with these disorders should be provided a low-potassium formula. On occasion, persistence of the elevated potassium levels results in the need for infant formulas or enteral feedings to be pretreated with an ion exchange resin (e.g., sodium polystyrene sulfonate, calcium polystyrene sulfonate) to lower their potassium content. Although no official protocol has been recommended, based on the original studies, most centers typically recommend treating formula or other beverages if appropriate for a half hour or an hour. Usually, 1 g of sodium polystyrene sulfonate is added to the formula per mEq of potassium. The formula is shaken, refrigerated, and after the allotted time, formula is decanted and a minimal amount of formula containing bound potassium residue is thrown away [76, 77]. However, the amount of sodium polystyrene sulfonate used may be altered depending on individual lab response. Once the infant starts taking additional oral food, caregivers should be advised to offer low-potassium choices and limit high-potassium foods, including several fruits and vegetables.

Older children with these conditions may not need as tight of a restriction, but children receiving hemodialysis, despite the primary cause of renal failure, will typically need to limit high-potassium foods including milk, yogurt, bananas, cantaloupe, tomato and potato products, and potassium-fortified foods, among others. Children receiving PD may, on the other hand, not need a restriction or as tight of a restriction and, in some instances, may need supplementation. This is largely dependent upon the peritoneal membrane transport status, with high transporters often losing large amounts of potassium across the peritoneal membrane [11].

There are not clear guidelines on how much dietary potassium is appropriate for pediatric CKD patients. The common adult guideline recommendation of 2,400 mg/day may be extrapolated to <30–40 mg/kg/day or 0.8–1 mmol/kg/day. For infants and toddlers, 1–3 mmol/kg/day may be a reasonable starting place [11]. It is important to remember that there may be non-dietary causes of hyperkalemia,

including constipation, acidosis, inflammation, catabolism/starvation, elevated glucose levels, dialysis adequacy and potassium bath, increased activity, and medications [75], and all these issues, including dietary intake, should be considered when addressing/correcting hyperkalemia.

Phosphorus and Calcium

The incidence of renal bone disease is higher in children compared to adults due to high bone turnover in the growing skeleton. To prevent growth failure as well as CVD associated with poor calcium-phosphorus balance (CKD-MBD), the achievement of target values for calcium (Ca^{2+}), phosphorus (PO_4), and PTH is extremely important.

The KDOQI Bone Guidelines for Children with CKD [78] have made recommendations for the strict control of serum PTH levels and the $CaXPO_4$ product. The Kidney Disease Improving Global Outcomes (KDIGO) bone guidelines allow greater variance with PTH targets, recommending 2–9 times normal values in pediatric ESKD [20]. Maximum dietary phosphorus intake and intake of calcium from calcium-containing phosphorus binders and diet are also outlined in the KDOQI bone guidelines. It is recommended to limit phosphorus intake to the DRI if PTH values are elevated and 80 % of the DRI if serum phosphorus levels are additionally elevated in CKD. Eighty percent of the DRI for age is appropriate for all pediatric dialysis patients. Intake below 500 mg of phosphorus in any age group, however, may not be compatible with adequate oral intake for those who consume all calories from food as opposed to tube feedings or formulas. Current recommendations from the KDOQI nutrition guidelines indicate that serum phosphorus levels should ideally be normal for age. However, some evidence [79] discourages over-restriction of dietary phosphorus, given the associated possibility for PEW. This would support the previously published KDOQI bone guidelines allowing for serum phosphorus in the range of 3.5–5.5 mg/dL for adolescents and 4–6 mg/dL for younger children on dialysis, which is slightly higher than normal values. Normal levels for age for CKD stage 1–4 are also supported by the bone guidelines [78]. A lower serum phosphorus level may be more attainable in those with residual renal output as opposed to children who are anuric or severely oliguric.

A plan for *dietary modification must take into consideration foods that are naturally high in phosphorus, as well as foods and drinks in which phosphate salts have been added by the manufacturer for nonnutritive reasons. In a typical mixed-food diet comprised of natural foods, about 60 % of phosphorus is absorbed. However, nearly 100 % of phosphorus is absorbed from processed foods in which phosphate additives have been used in the manufacturing process. Without changing protein or calcium content, it may also be possible to consume an extra 1,000 mg of phosphorus in the adolescent diet, just by the inclusion of more processed versus natural foods [80]. One of the most challenging aspects of phosphorus-related counseling for children and families with CKD is that phosphorus may be difficult to detect. Phosphorus is abbreviated in many different additive forms, and many standard nutrient data bases underestimate the phosphorus content of food due to an increased use of these additives in the last decade [81]. This is of particular concern as the typical adolescent diet may be comprised of many of these items such as colas, fast food, and convenience quick-cooking products.

Excretion of endogenous phosphorus is mainly through the kidneys with a smaller amount being excreted in the stool. The amounts of phosphorus removed by thrice weekly HD (~800 mg/treatment or 2,400 mg/week) or daily PD (300–400 mg/treatment or 2,100–2,800 mg/week) is far less than that ingested by most children. The inefficiency of phosphate removal by standard HD and PD can, however, be rectified in children by the use of frequent HD. Patients who have received this therapy have often not required diet restrictions and have required fewer or no phosphate binders [6, 16, 21]. Patients with residual kidney function and patients on PD who are high transporters also tend to have lower serum phosphorus levels [82].

*Non-breastfed infants with CKD who are hyperphosphatemic require a low-phosphorus formula. Similac PM 60/40® (Abbott Nutrition, Columbus, Ohio) is the only infant formula designed specifically for pediatric CKD patients that is currently available in the United States. However, if electrolyte balance allows, a general infant formula that has lower phosphorus content may work as well. Other formulas designed for older children may also be an option (see discussion in "Infants" section). Typically, the low-phosphorus formula choice is continued beyond 1 year of age to delay introducing phosphorus-rich cow's milk.

Phosphorus restriction may complicate efforts to achieve adequate protein intake because protein and phosphorus are often found in the same foods. The lowest quantity of phosphorus in proportion to the quantity and quality of protein comes from animal flesh proteins (average: 11 mg phosphorus/g protein), whereas eggs, dairy products, legumes, and lentils have higher phosphorus to protein ratios (average: 20 mg phosphorus/g protein). In the case of a non-dialysis patient with CKD, who may not need as large a quantity of high-biological value protein to cover dialysis losses, there is new evidence [83] that a vegetarian diet may be appropriate. Because of the increased use of phosphate additives, especially in many animal products, the "typical American" diet is higher in phosphorus than it was even in past decades. On the contrary, because of the phytate content of legumes and nuts, which binds some phosphorus, a well-planned, natural-foods-based vegetarian diet may actually be lower in phosphorus than the traditionally prescribed diet that limits high-phosphorus legumes and nuts. Additionally, a natural-based vegetarian diet may provide other benefits such as increased fiber and reduced saturated fat that may be important in modifying the cardiovascular milieu associated with CKD.

Education of the pediatric patient and his/her family about the reasons and methods for dietary phosphorus restriction and the impact on patient outcome is important. The "renal diet" is not easy to comply with and may be particularly challenging for the pediatric patient whose normal diet is exceedingly high in phosphorus. Often patients' families may have social or cultural barriers that also influence the ability to achieve the necessary dietary management. The experiences of one center indicate that intensified diet education using many different learning styles and tools may be important for diet understanding and improved phosphorus levels [84].

Individualization of the low-phosphorus diet also requires attention to adherence. Preferences of the child should be considered, including as many favorite foods as possible, within nutrition and electrolyte limitations, to increase intake. There is evidence that self-monitoring in the pediatric population is beneficial to phosphorus control. Teaching patients to adjust the phosphorus binder dose to the amount of phosphorus consumed at a meal or snack has been shown to not only be effective in empowering the pediatric patient, but it has also led to improved phosphorus levels [85]. Additionally, calorie to phosphorus ratio should be considered to maximize total nutrient intake, especially for those who struggle with adequacy of weight gain. Timing of meals and amount eaten at meals should be assessed, especially when prescribing a binder regimen. Popular phosphorus binders available include calcium carbonate, calcium acetate (Phoslo®), sevelamer carbonate (Renvela®), and acetate (Renagel®). Sevelamer carbonate and acetate are noncalcium options for pediatric patients, and recent evidence highlights the possibility of their use to pretreat beverages (such as formula) to lower phosphorus content [86]. The KDOQI guidelines [11] indicate that calcium-based binders should be the first choice for infant and young children, but noncalcium-based binders may be used if hypercalcemia is a concern [78].

When considering calcium needs, a clinician must balance the need for adequacy of intake for bone mineralization and growth versus the concern for excess intake and the subsequent development of adynamic bone disease or cardiac calcification. High doses of active vitamin D may contribute to increased intestinal calcium absorption as well [11]. The KDOQI guidelines recommend that the calcium intake for children and adolescents be between 100 and 200 % of the DRI for age from dietary intake and calcium binders or supplements combined [11]. However, calcium intake may need to be further adjusted if the patient is hypocalcemic or hypercalcemic, per the normal ranges for age or additionally defined as >10.2 mg/dL for hypercalcemia. A calcium supplement, given away from meals

and not more than 500 mg at a time for best absorption, may be appropriate if the patient is not meeting the DRI for age or is hypocalcemic [78]. Calcium intake may also be low due to dietary restrictions, reduced intestinal absorption due to low levels of 1,25-(OH)2D, or poor appetite and intake [11].

Fluid

Children with polyuria need extra fluid intake to prevent chronic dehydration and poor growth. Fluid supplementation may be needed in children who cannot meet their oral fluid needs, and clinical signs of dehydration should be regularly assessed to ensure adequate fluid intake. On the other hand, children who have edema and possibly hypertension require fluid restriction with calculation of output based on a combination of insensible fluid losses, measured 24-h urine output, dialysis ultrafiltration capacity, and other losses (diarrhea, gastric). Families should be taught that food that is liquid at room temperature contains water and must be counted as part of their daily fluid allotment. *Many fruits and vegetables contain significant amounts of water and can inconspicuously add to a child's fluid intake. Children struggling with fluid restrictions should be advised to drink from smaller cups or glasses; quench their thirst by sucking on crushed ice, chew gum, gargle, or use breath sprays/sheets; and more importantly, limit their sodium intake. Excess sodium intake can increase thirst and make it nearly impossible to control fluid intake. Additional dialysis is warranted if fluid restrictions make it impossible to meet nutritional goals. Nutrition should *not* be compromised in a growing child as a result of fluid-related issues, if at all possible.* See Table 18.7 for a summary of fluid and electrolyte needs in pediatric CKD.

Age-Related Intervention and Monitoring

Infants and Toddlers (Ages 0–3)

Infants and toddlers with CKD may demand much of the clinicians' time and resources. Growth and associated cognitive development are most active during the first few years of life. Consequently, growth, biochemical profiles, and adequacy of intake must be monitored closely. One dialysis center

Table 18.7 Electrolyte and fluid needs for children with CKD

	Pre-dialysis CKD	Hemodialysis	Peritoneal dialysis
Sodium	Limit to DRI (upper tolerable limit) if hypertensive; if polyuric, consider supplementation		Supplementation to be considered for all infants Limit to DRI (upper tolerable limit) if hypertensive; if polyuric, consider supplementation
Potassium	If at risk for hyperkalemia: Infants and young children: 1–3 mmol/kg/day Older children: 0.8–1 mmol/kg/day		High transporters may need supplement; low transporters' needs similar to HD patients
Fluid	Typically unrestricted unless edematous; supplement if polyuric	Supplement if polyuric If oliguric: fluid restriction = Insensible fluid losses + urine output + additional losses (i.e., vomiting, diarrhea)—amount to be deficited	

Data from: National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Am J Kidney Dis 2009;53(suppl 2):S1–S124

reports that dietetic contacts were needed twice as much for optimal care in children younger than age 5 compared to those children older than age 5, indicating that younger children require more close monitoring, intervention, and clinician time than older children [87].

Most infants with CKD are satisfied with small volumes of oral feedings and often have slow or no progression through normal stages of acquired oral feeding skills, thus often having inadequate intake or intake that is not age appropriate. Advanced stages of CKD are commonly associated with feeding problems. *One particular problem, e.g., *post-traumatic feeding disorder*, is an oral hypersensitivity and aversion to fluids and/or foods that typically occur in infants and toddlers with a history of previous invasive medical procedures around their oral-nasal cavities. Such procedures include intubation, oral or nasal suctioning, or the placement of nasogastric (NG) or orogastric tubes [88, 89]. Unfortunately, many young children with CK have such a history. Memories of these unpleasant procedures lead the child to perceive that anything approaching their mouth is potentially painful. Other children may be able to swallow but are *unwilling* to eat. They may turn their head away and refuse to open their mouth when food is offered, they may spit out the food or they may store it in their cheeks for long periods of time. Nausea and vomiting are common and contribute to feeding dysfunction, undernutrition, and growth failure. Caregivers of infants and young children should be questioned regularly about age-appropriate eating/feeding skills (e.g., sucking, chewing, swallowing, self-feeding) and related problems (e.g., storing food in cheeks, inability to advance textures, food refusal).*

Delayed gastric emptying and gastric dysrhythmias alone or with gastroesophageal reflux disease (GERD) [90–92] may also have a negative impact on the provision of adequate nutrition. Delayed gastric emptying causes sustained gastric distension and an early sense of satiety. GERD has been found in over 70 % of infants and children with CKD who are experiencing vomiting and feeding problems [90–92]. Symptoms may diminish with time or persist until transplantation. Common empirical therapies for GERD include maintaining the infant in an upright position during and after feedings, use of whey-predominant infant formula to improve gastric emptying and prokinetic medications, H_2-antagonists, or proton pump inhibitors to prevent reflux esophagitis. When changes to feeding content and/or administration fail to improve symptoms and medical therapy for GERD is unsuccessful, continuous tube feedings, jejunal feeding, or fundoplication is indicated [92]. Tube feeding will be discussed in a later section.

*With its low mineral and electrolyte content, human milk is the ideal source of nutrition for infants with CKD. Aluminum toxicity is of particular concern for persons with CKD. Breast milk is naturally low in aluminum with serum levels reduced in breastfed infants [93]. Breastfeeding should be supported; however, for a variety of reasons, infants with Stage 5 CKD are often unable to meet their nutritional requirements by exclusive feeding at the breast. Motivated mothers should be supported to pump breast milk for supplemental feeding. Unfortunately, medical stressors and social or environmental factors may be barriers to a mother being willing or able to produce enough breast milk for the child to meet all of their needs.

Infant formulas containing lower amounts of phosphorus and potassium are indicated when relevant biochemical abnormalities begin to appear in the infant with CKD who is formula fed [94]. The aforementioned Similac PM 60/40 is often prescribed for such a need. Sodium and phosphate supplementation may be needed in some cases to prevent the development of hyponatremia and hypophosphatemia. A new pediatric renal product, Renastart®, currently used in Europe, may soon be available in North America for ages 1 and older. Renastart is lower in potassium and higher in sodium than Similac PM 60/40 which may be beneficial for children whose primary kidney disorder is complicated by sodium wasting. Renastart may also be used as a supplement or in combination with Similac PM 60/40 or another infant formula to achieve a desired, individualized micronutrient profile. One center has successfully used diluted "adult" renal products, such as Suplena (Abbott Nutrition, Columbus, OH) [95] in infants to control potassium levels. However, some components of the micronutrient profile may be undesirable for the pediatric populations' needs. Adding fat and carbohydrate modulars to formula or breast milk to increase calorie content with minimal increase in renal solute

and mineral load may be more desirable. The use of protein modulars may also help reach protein needs, especially in the infant on peritoneal dialysis. Although formulas not designed for renal needs may be considered depending on the patients' biochemical profile and stage of CKD, the long-term effects of the increased aluminum, vitamin A, and other mineral loads inherent to these formulas generally make their selection less desirable of an option. For example, soy and elemental formulas are high in phosphorus, potassium, and aluminum. Soy formula should be avoided and elemental formulas should only be used when absolutely medically necessary. *Due to its high renal solute load in addition to the phosphorus content, cow's milk is not suitable before 1 year of age and is often avoided or limited well into the second year of life and beyond for infants with CKD.

*Unless severe development delay or medical contraindications suggest otherwise, solids should be introduced and textures advanced in young patients with CKD at the same ages as for healthy infants [11]. However, since infants and toddlers with CKD often have difficulty with textures and food advancement, appropriate intervention (e.g., referral to speech or occupational therapy) should be considered, if deemed necessary, without delay. Encouraging good feeding practices, including food exploration, positive reinforcement of desired eating behaviors, family meal time, adequate oral stimulation, and a wide variety of foods, is important. Nevertheless, in the case of the infant or toddler on dialysis, feeding success may be slow or not achieved until the posttransplant period [96].

Children (Ages 4–12)

Children with CKD may suffer from poor appetite for multiple reasons including uremia, dietary restrictions, and developmental feeding-related delays that persist from infancy. Processed foods, fast food, and other foods with high phosphorus and sodium content are commonly preferred by children, but they are often restricted because of the child's CKD status. In turn, children may learn to self-induce vomiting through vigorous crying, coughing, or retching to avoid eating food selected and offered by caregivers. The patient with a poor appetite may respond favorably to small, frequent but scheduled meals and snacks.

Regular, structured times for meals and snacks are important to encourage developmentally appropriate eating behaviors and prevent further suppression of appetite by "grazing." Parents may be tempted to only give favorite foods or allow eating on demand to indulge the child with a chronic illness. This can limit nutrient dense intake, exacerbate electrolyte problems, and discourage advancement in the acceptance of a varied diet. The primary caregivers need guidelines for setting limits around food and eating behavior, and they require support from the healthcare team, especially dietitians, to consistently enforce them. *Other caregivers (e.g., grandparents, childcare workers, and teachers) need to be made aware of appropriate foods, fluids, and the limits that have been established with respect to the child's diet and should be asked to be consistent in providing care. Some children may remain on supplemental tube feeding for an extended period of time. It is important to encourage hunger by providing tube or other supplemental formula feedings after meals and snacks or overnight to promote transition to a normal oral regimen [11]. As children become older, they ideally should be granted some autonomy in making appropriate food choices but also need to be counseled about their diets so they can recognize and refuse restricted foods offered by others. *Important topics to be discussed with the children (and their caregivers) include meals and snacks at school or after-school programs that may include undesirable food choices. Communication with school or daycare providers by the dietitian, nurse, or physician may sometimes be necessary to emphasize the importance of the dietary restrictions without making the child feel uneasy.

Pica and the use of herbal supplements and alternative medications may be additional topics that need to be addressed. Children, especially those on hemodialysis, appear to be at high risk for pica with 46 % of children on dialysis at one center reporting pica [97]. Although the majority of these

patients were found to exhibit "ice" pica (compulsive consumption of ice), 12.6 % of patients ingested items such as chalk or soap, indicative of "hard" pica. Pica is a concern not only for the common comorbidity of iron deficiency anemia but also because of the potential for the ingestion of harmful, toxic substances.

Adolescents (Ages 13 and Older)*

Teenagers, who often eat independently of their families, regularly require dietary information, preferably from their renal dietitian. As commonly seen in the general adolescent population, poor eating habits, such as skipped meals (in particular breakfast and/or lunch), high fluid intake (especially milk and sodas), and preference for salty, processed/convenience and fast foods are common issues in the adolescent renal population. Dietary instruction that addresses food provided at school and activities, eating out, snacks, and acceptable drink choices supports the teenager's ability to make relatively safe selections when eating on their own or with friends. An educational approach used is the provision of a menu of the patients' 10–15 favorite foods with the often difficult to find phosphorus content listed, along with the daily phosphorus allotment, to assist in the process. Relating nutritional status to physical appearance (e.g., healthy hair and skin), school or athletic performance (e.g., energy, alertness, muscle mass), and/or preparation for transplantation may motivate individual adolescents to improve dietary adherence. Undernourished females may, on the other hand, be pleased with their thin appearance and be refractory to efforts to promote weight gain. High energy needs may be particularly difficult to achieve in the setting of dietary restrictions and poor appetite. Finally, regular assessment of biochemical indices and electrolyte status, success toward the achievement of the overall nutritional needs, and the risk for PEW should be carefully evaluated in this population.

Enteral Nutrition

Oral Supplementation

The KDOQI guidelines recommend supplemental nutritional support when growth is poor or calorie or protein intake is less than requirements. Oral supplementation should be considered as the preferred form of nutrition support [11]. The use of high-calorie agents in existing foods, such as powders or added fats, is an option, as well as homemade high-calorie drink recipes or commercial beverages. Manipulations to liquid feedings often require minimizing volume to maintain fluid balance, optimizing tolerance, and keeping the total hours of feeding manageable for the family.

Infants and toddlers frequently need supplementation with tube feedings of expressed breast milk or infant formula in addition to their oral intake. Often, fortification to a higher energy density is necessary as well with breast milk and formula both having a base caloric content of 0.67 kcal/mL or 20 kcal/oz [98, 99]. Gradual, stepwise increases of 2–4 kcal/oz theoretically improve tolerance. Some children may not tolerate very concentrated formula and tolerance of each stepwise increase must be assessed carefully before consideration is given to concentrating the solution further. Intolerance may present as increased retching or emesis, abdominal pain, or stool changes, usually being diarrhea.

Increasing the energy density by concentrating the base formula is often not possible because of the accompanying increase in sodium, potassium, phosphorus, and other vitamins and minerals. Therefore, fat and/or carbohydrate modules are often used. Protein modulars are typically added and adjusted based on protein needs but may contribute somewhat to the caloric concentration as well.

The choice of which macronutrient to add is based upon the serum glucose and lipid profiles, presence or absence of malabsorption or respiratory disease (carbohydrate metabolism increases CO_2 production), and cost. In addition, lipid modulars may impair gastric emptying while excessive carbohydrate modulars may increase stooling. Lipid modulars often do not mix as well with formula; especially if some or all of the formula is given via tube (see below). *Unless malabsorption is present, "heart-healthy" oils such as corn, canola, or safflower may be preferable because they are readily available and low in cost. However, if to be used in a tube feeding, an emulsified oil (i.e., Microlipid®, Novartis Medical Nutrition, Freemont, MI) can be used to prevent oil from separating out during continuous feedings. Polycose® (Abbott Nutrition, Columbus, OH) is a common carbohydrate modular. *When making a feeding which involves more than three stepwise increases (2–4 kcal/oz per step) in energy density, the distribution of energy from carbohydrate and fat should be kept similar to the base formula. As energy density increases, oral intake may decrease and a tube feeding may be needed.*

Calories can also be added to foods using heart-healthy margarines or oils, cream and other fats, sugars, syrups, or carbohydrate modulars. Commercial energy bars and homemade or commercial milkshakes/energy drinks made from whole milk and cream may be used; however, their phosphorus and potassium content may be too high depending on the severity of the CKD. Milkshakes and desserts made from nondairy products can be used to boost caloric intake for children who are hyperphosphatemic. However, many nondairy products contain phosphate additives which make them inappropriate choices. Low-calorie or calorie-free drinks should be avoided in most patients.

*Nonrenal enteral feedings designed for children older than 1 year have an appreciable amount of calcium and phosphorus to support bone growth as well as a high content of potassium. They may also have higher amounts of other undesirable components such as vitamin A and aluminum. These products are contraindicated in children with hyperphosphatemia and/or hyperkalemia. Unless the aforementioned Renastart® or another commercial product becomes available in the United States, there is currently no pediatric-specific product designed to fit the needs of children ages 1–10. Often infant formula, such as Similac PM 60/40®, is used past 1 year of age. *Adult renal products (e.g., Nepro® (Abbott Nutrition, Columbus, OH), Suplena®, Novasource Renal® (Nestle Nutrition, Florham Park, NJ), Renalcal® (Nestle Nutrition, Florham Park, NJ)) are designed to be calorically dense and low in minerals and electrolytes and are often used for adolescents. However, they have even been used successfully prepared at diluted strength for younger children (personal communication via pediatric listservs, multiple dates), recognizing that the protein content and the micronutrient profile should be carefully assessed in patients using this product. The protein content of Nepro® and Novasource Renal ® is too high for young children and a low-protein product such as Suplena®, should be used instead. Renalcal, which has minimal micronutrient content, is typically used as a supplement to other formulas. *The magnesium content of these products is significantly higher than in breast milk or infant formulas; therefore, serum levels should be monitored closely when transitioning from an infant feeding to one of these products. Table 18.8 summarizes enteral feeding options in pediatric CKD.

Tube Feeding

*Tube feeding is recommended if oral supplementation is unsuccessful in correcting energy and/or protein deficits [11]. Tubes may also provide access for additional fluid and sodium supplementation and are often used for fluid needs and liquid medication administration posttransplant [100]. *Studies have routinely demonstrated the effectiveness of tube feeding in preventing and reversing weight loss and growth retardation in children of all ages and achieving significant catch-up growth in children less than 2 years of age with CKD [101, 102]. In one study, weight and BMI *z*-scores, although not height *z*-scores, were significantly higher in children with gastrostomies versus children who were not tube fed. Fortunately, these children were also not at greater risk for overweight or obesity than non-tube-fed children in the long term [32]. Various routes of tube feeding (i.e., nasogastric (NG),

Table 18.8 Enteral nutrition feeding options for pediatric renal patients

Enteral feeding option	Comments	Age range for use	Pre-dialysis use?	Dialysis use?
Breast milk	Biologically ideal for infant feeding and may be used for toddlers if available	If available, through at least 1 year of age; may continue if available and desired by family	Yes	Yes
Similac PM 60/40®	Only infant formula designed for CKD patients. May need modulars to meet kcal and protein needs	Infancy and through age 3	Yes	Yes. May need protein modulars if patient is receiving PD
Nepro®	High protein "adult" product	Typically ages 10 and older	No	Yes
Suplena®	Low-protein "adult" product. Can be diluted for tolerance in younger ages	Typically ages 10 and older but has been used (often diluted) in younger ages including infants	Yes	Typically only in young children
Novasource Renal®	High protein "adult" product	Typically ages 10 and older	No	Yes
Renalcal®	Liquid modular supplement to other formulas due to minimal vitamin/mineral content. Not a stand-alone formula	Ages 1 and older	Yes	Yes

Original table, C. L. Nelms

gastrostomy tube (GT), gastrojejunostomy (GJ), jejunostomy tube (JT)) have all been used successfully to provide additional breast milk, infant formula, or enteral feedings by intermittent bolus or continuous infusion [100, 103]. Gastrostomies are preferred for long-term use of tube feeding as opposed to NG tubes in many centers because the NG tubes are unsightly, can cause irritation to the nose and throat, and may disrupt oral-feeding behavior [101]. *The choice of formula/feeding is guided by age, biochemistries, fluid allowances, and cost. The method of delivery (e.g., continuous vs. intermittent bolus) is dependent on the age of the patient, the quantity to be delivered, the composition of the formula, gastrointestinal (GI) tolerance (vomiting, delayed gastric emptying, and GERD), and safety factors.

*Intermittent bolus feeds are used for infants to maintain normal blood glucose levels and to pattern the feeding after normal intake schedules. However, many infants need both daytime bolus feeds and nocturnal continuous feedings to meet caloric needs and to allow caregivers the opportunity for overnight rest [11, 96]. After infancy, continuous overnight feedings are preferred so as to offer the child an opportunity for spontaneous oral intake during the day and freedom from being attached to feeding equipment. However, if children are very delayed orally with very minimal oral intake or if the total volume needed is too large for a child to tolerate, daytime bolus feeds may still be needed in addition to the nocturnal feedings.

Feedings are initiated and advanced according to pediatric guidelines and tolerance (see Table 18.9). Reported complications of tube feeding include emesis, exit-site infection, leakage, and displacement [104, 105]. Wherever possible, placement of GT or GJ tubes should occur prior to the initiation of PD to decrease the risk of peritonitis [104–106]. *Oral stimulation and nonnutritive sucking should be provided to infants totally dependent on tube feeding to help smooth their eventual transition to oral feeding, often following successful transplantation. Using a multidisciplinary approach to preventative and behavioral treatment programs, several centers have reported successful transitioning virtually 100 % of their patients from tube feedings to complete oral feedings within 2–6 months after successful transplantation [96, 107–109], illustrating that tube feeding need not preclude development of normal oral feeding skills.*

Table 18.9 Suggested rates for initiating and advancing tube feedings

	Age	Age	Age
Continuous feedings			
0–1 years	10–20 mL/h or 1–2 mL/kg/h	5–10 mL/8 h or 1 mL/kg/h	21–54 mL/h or 6 mL/kg/h
1–6 years	20–30 mL/h or 2–3 mL/kg/h	10–15 mL/8 h or 1 mL/kg/h	71–92 mL/h or 4–5 mL/kg/h
6–14 years	30–40 mL/h or 1 mL/kg/h	15–20 mL/8 h or 0.5 mL/kg/h	108–130 mL/h or 3–4 mL/kg/h
14 years	50 mL/h or 0.5–1 mL/kg/h	25 mL/8 h or 0.4–0.5 mL/kg/h	125 mL/h
Bolus feedings			
0–1 years	60–80 mL q 4 h or 10–15 mL/kg/feed	20–40 mL q 4 h	80–240 mL q 4 h or 20–30 mL/kg/feed
1–6 years	80–120 mL q 4 h or 5–10 mL/kg/feed	40–60 mL q 4 h	280–375 mL q 4 h or 15–20 mL/kg/feed
6–14 years	120–160 mL q 4 h or 3–5 mL/kg/feed	60–80 mL q 4 h	430–520 mL q 4 h or 10–20 mL/kg/feed
14 years	200 mL q 4 h or 3 mL/kg/feed	100 mL q 4 h	500 mL q 4 h or 10 mL/kg/feed

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Note: Calculating rates based on age and per kilogram body weight is useful for small-for-age patients

*Goal is expected maximum that child will tolerate; individual children may tolerate higher rates or volumes. Proceed cautiously for jejunal feedings. Goals for individual children should be based on energy requirements and energy density of feeding and therefore may be lower than expected maximum tolerance

Parenteral Nutrition

*Published guidelines for the use of parenteral nutrition (PN) in children with CKD are limited. There are data that 4.5–7.5 % of pediatric patients on dialysis may need nutritional supplementation to reverse malnutrition or wasting, beyond what enteral interventions can provide [21]. *If no fluid restriction is needed, nutrition-related fluid volumes can be based on daily maintenance fluid requirements. For patients who require a fluid restriction, more concentrated PN solutions of AA, dextrose, and lipids are used. Unless otherwise indicated, goals for PN are 85 % of energy recommendations (because there is no thermal effect of feeding) and 100 % of protein recommendations specific to the child's stage of kidney disease and type of RRT. Mineral and electrolyte content should be adjusted to maintain acceptable serum levels and the acetate and chloride content adjusted to maintain acid/base balance.* Standard trace vitamin and mineral supplements may need to be given every other day to prevent excesses of those that are not cleared well when renal function is impaired. If possible, the provision of water-soluble vitamins daily is optimal as a means of addressing the substantial dialysis-related losses. PN may be required more frequently for neonates with renal disease and for those on continuous renal replacement therapy (CRRT) due to high nutrient needs [98, 110, 111] then for other children with CKD. Protein needs are typically higher in both populations and those on CRRT may need additional vitamin and mineral supplementation [98, 110, 111]. Frequent laboratory monitoring and adjustment of PN is critical in both populations [110–112].

Intradialytic Parenteral Nutrition

*There is limited evidence of the safety and efficacy of IDPN as an intervention to reverse malnutrition and improve weight gain in children receiving maintenance HD [113–115]. Children treated with IDPN have achieved gains in body weight and BMI and/or percent IBW from receiving 100–150 % of the recommended calorie intake from a combination of oral and parenteral AA, dextrose, and lipids delivered at each dialysis session over a period of 6 weeks to 6 months. Reported adverse events have been minor and have included hypophosphatemia, transient hyperglycemia, lipid intolerance, and

mildly elevated liver function tests. Improvements in serum albumin concentrations were not observed as virtually all of the children had albumin levels in the normal range before IDPN was started.* IDPN is typically given as a concentrated amino acid and dextrose solution, with lipid being given separately and based on the patients' tolerance and individual requirements. The primary goal of the therapy is an increase in protein intake with a modest increase in kcal intake [116]. The KDOQI nutrition guidelines recommend the use of IDPN if oral supplementation and subsequent tube feeding do not meet the nutritional needs and goals of children with CKD [11].

*Intraperitoneal Amino Acid Dialysis**

The use of a dialysate-containing mixture of essential and nonessential AA instead of glucose as the osmotic agent has improved protein malnutrition and nitrogen balance in a small number of children receiving PD who are unable to maintain adequate protein intake [117, 118]. In most cases, one exchange per day is replaced with the AA dialysate, with 50–90 % of the infused AA absorbed. To avoid using the AA for energy, the solution is typically given during the day when meals/snacks provide a source of calories; however, giving the AA overnight via the cycler, coupled with the standard glucose dialysate as an energy source, has also been successful [117]. Despite the theoretical benefits of this approach, the routine use of intraperitoneal amino acid dialysis (IPAA) is impractical due to cost and a commercial preparation is not available in the United States.

Transplant

Although there is no cure for CKD, transplant is the desired treatment option for children with ESKD to improve their quality of life and ideally their longevity. Nutritional care may contribute to the expected duration of the functioning transplanted kidney and the overall health of the patient. At the same time, it must be recognized that medications necessary for the maintenance of the functioning allograft may be associated with side effects, such as nausea, diarrhea, mouth sores, and taste changes which can have a negative impact on nutritional management [119]. These side effects may be of greatest concern when medication doses are highest, such as immediately post transplant or when treating a rejection episode. Food safety is also of the utmost importance in this immune-compromised population but is all too often neglected as part of posttransplant education [11]. The clinician must work with the patient and family to optimize good nutrition through these challenges.

Following successful transplantation, immunosuppressive therapy using high-dose prednisone characteristically stimulates appetite, and calorie control is needed to prevent excessive weight gain. This becomes a new issue for children who have previously struggled to consume sufficient calories. Posttransplant weight gain can be particularly upsetting for the adolescent age group. Preparatory education on the benefits of caloric restriction and increased physical activity for weight control should begin well before transplantation occurs. Newer immunosuppressive regimens that are based on a steroid withdrawal or a steroid avoidance protocol may help prevent excessive weight gain and other steroid-related side effects.

In addition to the issue of weight gain, when glucocorticosteroids are used, along with immunosuppressive agents such as tacrolimus, increase insulin secretion, causing impaired glucose tolerance, glycosuria, and a relative resistance to insulin, leads to diabetes in approximately 5–20 % of children [120]. Avoidance of simple carbohydrates, weight control, and physical exercise are prescribed to assist in the management of steroid-induced diabetes. Excess concentrated sweets may also induce hyperglycemia, especially when medication doses are highest [11].

Table 18.10 Nutrition for pediatric renal transplant

Energy	EER for age. Avoid excess weight gain
Protein	Initially 150 % of the DRI for surgical healing, then DRI long-term
Carbohydrates	AMDR, limit simple carbohydrates
Fat	AMDR, limit trans and saturated fat, especially in the presence of dyslipidemia
Sodium	Restrict to UL to prevent HTN except in young children with urinary losses. Young children may need supplementation to perfuse adult-sized kidneys
Potassium	Some may need restriction due to medication-related retention, particularly early posttransplant
Calcium	100–200 % of DRI for age
Phosphorus	May need to supplement during initial posttransplant period
Magnesium	May need to supplement during initial posttransplant period
Vitamins	Supplement only if evidence of deficiency in diet. Some may need additional vitamin D
Other minerals	Supplement only if evidence of deficiency in diet. Some may need additional iron
Fluid	1.5–4 L/day depending on urine output. Young children may need a high amount for their size to perfuse adult-sized kidneys

Data from: National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Am J Kidney Dis 2009;53(suppl 2):S1–S124

Almost 80 % of children are hypertensive 1 month after transplantation due to the effects of many of the immunosuppressive medications, mandating dietary sodium restriction [121]. Risk of hypertension does decrease over time, but many posttransplant patients will continue to have hypertension or need medication to control hypertension. The KDOQI guidelines recommend limiting sodium intake to the DRI for age in hypertensive children [11].

*In the immediate posttransplant period, protein needs are thought to be increased by approximately 50 % in association with surgical stress and the catabolic effects of steroids, decreasing to the normal recommendations for age around 3 months after transplantation. Energy needs are thought to be the same for kidney transplant recipients and healthy children. Of course, adjustment to caloric intake may be needed to address weight loss or gain. Macronutrient distribution should fall in the range of the AMDR, and heart-healthy guidelines, such as limitation of saturated and trans fat, are encouraged [11]. Hyperlipidemia is a common side effect of the medications used and the provision of 3–4 g of omega-3 fatty acids has been shown to be effective in lowering lipids in adolescents [122]. Traditional measures such as statins are typically effective as well.

*Multivitamin therapy is rarely needed after a successful renal transplant because dietary restrictions are not warranted and appetite significantly improves. However, if intake remains poor or the quality of the diet is less than desired, a general, age-appropriate multivitamin may be warranted. It is important to correct any abnormal electrolyte levels. Magnesium and phosphorus wasting and potassium retention commonly occur in the early posttransplant period and supplementation may be required [11, 121]. A liberal dietary intake of phosphorus-rich foods and fluids is also often encouraged in the early transplantation period to help manage hypophosphatemia. *Glucocorticosteroid therapy can induce osteoporosis; therefore, calcium supplementation may be necessary for children unable to meet the DRI for calcium [123]. KDOQI guidelines mirror recommendations for all CKD populations, encouraging 100–200 % of the DRI [11].

*A high fluid intake is required posttransplantation to maintain good perfusion of the transplanted kidney and to prevent toxicity from immunosuppressive agents due to dehydration [121]. Adequacy of hydration is a key education point and its importance should be discussed frequently both pre- and posttransplant. Fluid needs may range from 1.5 to 4 L/day depending on size and activity. Young children with adult-sized transplanted kidneys may need a very high amount of fluid per body surface area to perfuse the large kidney. One protocol recommends 2,500 mL × body surface area (2,500 mL/m^2 BSA) for 6–12 months posttransplant [124]. Young children who receive large kidneys may also require sodium supplementation to enhance renal perfusion. See Table 18.10 for a summary of pediatric renal transplant nutrition guidelines.

Transition

As technology and medical expertise for chronic illnesses such as CKD advances, children affected by it are no longer expected to expire before reaching adulthood. It is estimated that there are nearly 7,000 adolescents on dialysis and 11,000 with kidney transplants in the age range of 15–24, considered the emerging adult phase [125]. This group provides multiple challenges as they prepare to move or "transfer" from pediatric-focused care to adult-focused care. The process of "transition" is defined by Bell et al. [126] as "a deliberate, planned, and focused process, in which adolescents and emerging adults with chronic illness assume progressively increasing responsibility for the management of their health." The AAP [127] recommends that planning for transition start at age 14 and that this plan be reviewed at least annually, with follow-up and review after the actual transfer to adult care has taken place. Gradually shifting responsibility for nutritional and other medical care to the patient and focusing education and intervention toward the patient (vs, the parent) should be done during this time [125].

When considering the emerging adult, it is important to remember that the typical primary cause of renal failure in this patient population is very different than most adult patients. Comorbidities are typically related to urinary or bladder issues, and effects of autoimmune disorders or cognitive delays as opposed to manifestations of diabetes or other common adult causes of renal failure. Nutrition education must be conducted with this in mind.

Issues such as short stature, impaired self-esteem, and delays in sexual and developmental maturation may result in "juvenilization"—or treatment of these young adults as younger than they are. This can lead to healthcare providers and family members not expecting mature decision making and healthcare responsibility, all of which can result in dependence and nonadherence. It is estimated that at least a third of adolescents with a transplant are nonadherent and adolescents and young adults account for the highest rates of acute and chronic rejection and graft loss [126, 128]. Cognitive function, especially that which affects reasoning and decision making, continues to develop well into the 20s. Therefore cognition is an issue that must be accounted for in patient education pertaining to medication and nutritional management [125].

It is also important for the healthcare team to address concerns related to sexuality and reproduction in the context of the chronic medical condition. If reproduction is deemed a possibility, the dietitian should prepare nutritional counseling geared to such [126]. Risky behaviors affecting nutrition and medical care, such as alcohol or drug intake must be addressed as well [129]. Self-identification is peaking at this time. Social issues such as employment, income, and obtaining self-insurance must be addressed and are paramount to adherence to nutritional and health regimens, as affordability of nutritious food, medication, and health care may be affected. Young adults also are more likely to question medical care recommendations and may benefit from interactions with healthcare providers that are frank, allow for questions, respectful of confidentiality, and make the patient feel autonomous. It may take time to build trust and understanding [126, 129]. Pediatric dialysis and transplant centers also typically have a higher staff to patient ratio and emerging adults may need greater individual attention, at least at first, after transition to an adult-focused center [128]. A close working relationship between the transferring pediatric center and the accepting adult center is ideal, with communication between comparable clinicians. An official "transition clinic" reviewing healthcare needs, including nutrition, is recommended in settings that permit its development. In free-standing children's hospitals, occasional interaction between the adult care providers and the emerging adults prior to transfer followed by attendance of a representative from the pediatric facility at the first visit of the patient to the adult center is beneficial [129].

Summary*

Nutritional therapy is vital to the management of children with CKD. Children and adolescents are confronted with frequent dietary modifications that occur concurrently with significant changes in growth, development, and independence [130]. As a result, optimizing nutritional status is a continuing process that requires frequent monitoring and adjustments to the nutritional plan based on changes in age, development, growth, and body composition, laboratory values, residual renal function, RRT, medications, and psychosocial status.

A registered dietitian with pediatric renal experience should be the central individual in nutrition and dietary management [11, 130] in collaboration with the nephrologist, nurse, social worker, and other CKD professionals [131]. Input from the child/adolescent and caregivers is essential as well. Consistent promotion of the benefits of dietary modification and provision of practical information and emotional support to children and their families can positively influence adherence and clinical outcomes and minimize stress around nutritional issues.

Case Study*

AB is a 5-day-old infant who presents with oliguria, BUN 55 mg/dL, Cr. 2.8 mg/dL, K^+ 7.5 mEq/L, Ca^{2+} 8 mg/dL, and PO_4 7.0 mg/dL. Investigations reveal that he has CKD due to PUV and dysplastic kidneys. Following surgical correction of his PUV, BUN, creatinine, and biochemistries improve, but he becomes polyuric and continues to have high urine output long-term.

Questions

1. What infant feeding would you choose for him during the initial presentation? What formula would you choose following surgical correction of his PUV? What will be the most important nutritional management issues if his CKD advances?

   Answer: Breast milk would be the preferred source of nutrition; if not, Similac PM 60/40® infant formula. With normalization of his serum potassium and phosphorus levels, he can continue on breast milk or be switched to a standard infant formula. He will continue to have high urine output, requiring a high fluid intake and sodium supplements for high sodium excretion. He will innately prefer to drink water over formula and his high fluid intake will decrease his appetite for solids. He may need energy supplementation of his feedings or tube feeding to meet both his calorie and fluid requirements.

   Follow-up: By 15 months of age, his GFR has dropped to approximately 35 mL/min/1.73 m^2. His PTH is 350 pg/mL, ionized Ca^{2+} 1.09 mmol/L, K^+ 5.8 mEq/L, and his PO_4 is 6.8 mg/dL. He takes very small amounts of solids and has been resistant to progress beyond jarred baby foods; however, now he is showing some interest in foods his parents eat. He drinks 1.5 L of water daily and receives continuous overnight g-tube feedings. A local pediatrician placed him on a standard pediatric enteral feeding product (e.g., Pediasure) after 1 year of age. His rate of weight gain is slowing and his weight/length curve on the growth chart has decreased from 25 to 50 percentile to ~10 percentile.
2. What specific formula and diet modifications do you need to discuss with his caregivers?

   Answer: The dietitian should review the low-phosphorus diet with his caregivers. Parents need to become knowledgeable about the makeup of a low-phosphorus diet and timing of phosphate

binders, when prescribed. A change of the enteral formula to a renal product, likely fortified Similac PM 60/40®, should be considered so that the phosphorus and potassium load could be reduced. Consideration could also be given to add a daytime feeding to his routine which could be something that the daycare is able to administer.

Follow-up: At age 4 years, AB will be starting preschool and at the same time needs to initiate peritoneal dialysis.

3. What nutritional interventions will you implement?

   Answer: If AB continues to need enteral product supplementation at this age, it may need to be adjusted to provide additional protein to compensate for the peritoneal losses. This can be done with the addition of a protein modular. He should also be on a pediatric or diluted adult renal product if he is not already. AB's serum potassium level should be monitored as potassium needs may vary depending on the dialysis prescription used. His parents should continue to be educated on the phosphorus content of table foods and drinks. As AB eats more solid food, his intake of sodium should be assessed and sodium supplements adjusted if needed.

   Follow-up: After 18 months on PD, AB receives a living-related donor kidney transplant. His urine output increases to 3 L/day. He becomes hypertensive, hyperkalemic, hypophosphatemic, and hypomagnesemic on immunosuppressant therapy.

4. How will you adjust his nutritional regimen?

   Answer: As soon as kidney function is in an appropriate range, if he is not yet on a full solid oral diet, his feeding should be converted back to a standard pediatric product, and any dietary phosphorus restriction should be discontinued. If possible, over the next few months the calories provided by the g-tube should be decreased to stimulate hunger. When AB is able to take approximately 75 % of his calorie requirements orally, hold his g-tube feeds for at least 1 month to be sure he can further increase his intake before removing his g-tube. AB's parents should also be educated about the nutrition-related side effects of his immunosuppressive therapy. Education should be provided about a low-sodium, low-potassium diet as well. Monitoring of AB's weight and serum glucose, cholesterol, and triglyceride levels should also occur. As he begins to gain weight, discussions about nutrition-related issues should address portion sizes, highlighting foods and drinks that are low in simple sugars and contain small amounts of "heart-friendly" fats. The importance of daily physical activity to support weight gain that is a healthy combination of muscle and fat mass should be emphasized. As immunosuppressive therapy decreases, dietary restriction of potassium restrictions and supplementation of phosphorus and magnesium supplementation may be able to be discontinued.

Acknowledgment (*) Indicates sections or sentences that D. Secker Ph.D., M.Sc., R.D. contributed the majority of the sentence or section as the author of the original chapter. Asterisks surrounding text indicate several sentences or a section and a single asterisk indicates an individual sentence.

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References

1. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) Annual Report. 2011. https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf
2. Chan JCM, Williams DM, Roth KS. Kidney failure in infants and children. Pediatr Rev. 2002;23(2):47–60.
3. Simonsen O. Slow nocturnal dialysis as a rescue treatment for children and young patients with end-stage renal failure. J Am Soc Nephrol. 2000;11:327A.
4. Fischbach M, Terzic J, Laugel V, et al. Daily on line hemodiafiltration: a pilot experience in children. Nephrol Dial Transplant. 2004;19:2360–7.
5. Geary DF, Piva E, Gajaria M, Tyrrel J, Picone G, Harvey E. Development of a nocturnal home hemodialysis (NHHD) program for children. Semin Dial. 2004;17(2):115–7.

6. Geary DF, Piva E, Tyrrell J, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147(3):383–7.
7. Habicht JP, Martorell R, Yarbrough C, Malina RM, Klein RE. Height and weight standards for preschool children: how relevant are ethnic differences in growth potential? Lancet. 1974;1:611–5.
8. Martorell R, Medoza FS, Castillo RO. Genetic and environmental determinants of growth in Mexican-Americans. Pediatrics. 1989;85:864–71.
9. Mei Z, Yip R, Trowbridge F. Improving trend of growth of Asian refugee children in the USA: evidence to support the importance of environmental factors on growth. Asia Pacific J Clin Nutr. 1998;7(2):111–6.
10. WHO Multicentre Growth Reference Study Group. Assessment of differences in linear growth among populations in the WHO multicentre growth reference study. Acta Paediatr. 2006;S450:56–65.
11. National Kidney Foundation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53 Suppl 2:S1–124.
12. Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D. Stature in children with chronic kidney disease: analysis of NAPRTCS database. Pediatr Nephrol. 2006;21:793–9.
13. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. Pediatr Nephrol. 2006;21:917–30.
14. Wong CS, Gipson DS, Gillen DL, et al. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis. 2000;36:811–9.
15. Rees L, Azocar M, Borzych D, et al. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22:2303–12.
16. Tom A, McCauley L, Bell L, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134:464–71.
17. Parekh RS, Flynn JT, Smoyer WE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12:2418–26.
18. Tonshoff B, Kiepe D, Ciarmatori S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. Pediatr Nephrol. 2005;20:279–89.
19. Franke D, Zivienjak M, Ehrich JHH. Growth hormone treatment of renal growth failure during infancy and early childhood. Pediatr Nephrol. 2009;24:1093–6.
20. International Society of Nephrology. 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(S113):S1–130.
21. Fischbach M, Terzic J, Menouer S, et al. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21:1746–52.
22. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14(3):297–303.
23. Fischbach M, Fothergill H, Seuge L, Zaloszyc A. Dialysis strategies to improve growth in children with chronic kidney disease. J Ren Nutr. 2011;21(1):43–6.
24. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2012;27:173–81.
25. Edefonti A, Mastrangelo A, Paglialonga F. Assessment and monitoring of nutrition status in pediatric peritoneal dialysis patients. Perit Dial Int. 2009;29(S2):S176–9.
26. Srivaths PR, Wong C, Goldstein SL. Nutrition aspects in children receiving maintenance hemodialysis: impact on outcome. Pediatr Nephrol. 2009;24:951–7.
27. Morel P, Almond PS, Matas AJ, Gillingham KJ, Chau C, Brown A. Long-term quality of life after kidney transplantation in childhood. Transplantation. 1991;52:47–53.
28. Yildiz OI, Gurdol F, Kocak H, et al. Appetite-regulating hormones in chronic kidney disease patients. J Ren Nutr. 2011;21(4):316–21.
29. Naufel MFS, Bordon M, de Aquino TM, Ribeiro EB, de Abreu Carvalhaes JT. Plasma levels of acylated and total ghrelin in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2010;25:2477–82.
30. Hobbs DJ, Bunchman TE, Weismantel DP, et al. Megestrol acetate improves weight gain in pediatric patients with chronic kidney disease. J Ren Nutr. 2010;20(6):408–13.
31. Fischbach M, Dheu C, Seuge L, Orfanos N. Hemodialysis and nutritional status in children: malnutrition and cachexia. J Ren Nutr. 2009;19(1):91–4.
32. Sienna JL, Saqan R, Teh JC, et al. Body size in children with chronic kidney disease after gastrostomy tube feeding. Pediatr Nephrol. 2010;25:2115–21.
33. Wilson AC, Schneider MF, Cox C, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2759–65.
34. Skinner AC, Mayer ML, Flower K, Weinberger M. Health status and health care expenditures in a nationally representative sample: how do overweight and healthy-weight children compare? Pediatrics. 2008;121(2):269–77.
35. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22:1689–702.
36. Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. Am J Clin Nutr. 1986;43:711–22.

37. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ. 2007;335:194–202.
38. Foster BJ, Leonard MB. Measuring nutritional status in children with chronic kidney disease. Am J Clin Nutr. 2004;80:801–14.
39. Juarez-Congelosi M, Orellana P, Goldstein R. nPCR and sAlb as nutrition status markers in pediatric hemodialysis patients. Hemodial Int. 2006;10(1):129.
40. Cano F, Azocar M, Cavada G, Delucchi A, Marin V, Rodriguez E. Kt/V and nPNA in pediatric peritoneal dialysis: a clinical or a mathematical association? Pediatr Nephrol. 2006;21:114–8.
41. Schaefer F, Klaus G, Mehls O. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. J Am Soc Nephrol. 1999;10(8):1786–92.
42. Cano F, Marin V, Azocar M, et al. Adequacy and nutrition in pediatric peritoneal dialysis. Adv Perit Dial. 2003;19:273–8.
43. Mendley SR, Majkowski NL. Urea and nitrogen excretion in pediatric peritoneal dialysis patients. Kidney Int. 2000;58:2564–70.
44. Secker DJ, Jeejeebhoy KN. Subjective global nutritional assessment for children. Am J Clin Nutr. 2007;85:1083–9.
45. Brooks ER, Fatallah-Shaykh SA, Langman CB, Wolf KM, Price HE. Bioelectrical impedance predicts total body water, blood pressure, and heart rate during hemodialysis in children and adolescents. J Ren Nutr. 2008;18(3): 304–11.
46. Juarez M, Goldstein SL. Pediatric renal nutrition symposium II—nutrition assessment in HD: parameters to weigh in [unpublished lecture notes]. In: Annual dialysis conference, San Antonio, TX, 27 Feb 2012.
47. de Aquino TM, Avesani CM, Brasileiro RS, de Abreu Carvalhaes JT. Resting energy expenditure of children and adolescents undergoing hemodialysis. J Ren Nutr. 2008;18(3):312–9.
48. Edefonti A, Picca M, Damiani B, et al. Dietary prescription based on estimated nitrogen balance during peritoneal dialysis. Pediatr Nephrol. 1999;13:253–8.
49. Salusky IB, Fine RN, Nelson P, Blumenkrantz MJ, Kopple JD. Nutritional status of children undergoing continuous ambulatory peritoneal dialysis. Am J Clin Nutr. 1983;38:599–611.
50. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2009;128(5):S213–58.
51. American Academy of Pediatrics Endorsed Policy Statement. Cardiovascular risk reduction in high-risk pediatric populations. J Pediatr. 2007;119:618–21.
52. Querfeld U. Disturbance of lipid metabolism in children with chronic renal failure. Pediatr Nephrol. 1993;7:749–57.
53. Querfeld U, Salusky IB, Nelson P, Foley J, Fine RN. Hyperlipidemia in pediatric patients undergoing peritoneal dialysis. Pediatr Nephrol. 1988;2:447–52.
54. Kavey RW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high blood pressure research, cardiovascular nursing, and the kidney in heart outcomes research: endorsed by the American Academy of Pediatrics. Circulation. 2006;114:2710–38.
55. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(4 Suppl 3):S1–154.
56. National Cholesterol Education Program. Report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics. 1992;89:495–584.
57. National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Dis. 2003;41 Suppl 3:S1–92.
58. Don T, Friedlander S, Wong W. Dietary intakes and biochemical status of B vitamins in a group of children receiving dialysis. J Ren Nutr. 2010;20(1):23–8.
59. Kriley M, Warady BA. Vitamin status of pediatric patients receiving long-term peritoneal dialysis. Am J Clin Nutr. 1991;53:1476–9.
60. Warady BA, Kriley M, Alon U. Vitamin status of infants receiving long-term peritoneal dialysis. Pediatr Nephrol. 1994;8:354–6.
61. Vannucchi MTI, Vannucchi H, Humphreys M. Serum levels of vitamin A and retinol binding protein in chronic renal patients treated by continuous ambulatorial peritoneal dialysis. Int J Vitam Nutr Res. 1992;62:107–12.
62. Blumberg A, Hanck A, Sander G. Vitamin nutrition in patients on continuous ambulatory peritoneal dialysis (CAPD). Clin Nephrol. 1983;38:914–20.
63. Fassinger N, Imam A, Klurfeld DM. Serum retinol, retinol-binding protein and transthyretin in children receiving dialysis. J Ren Nutr. 2010;20(1):17–22.
64. Nemeth I, Turi S, Haszon I, Bereczki C. Vitamin E alleviates the oxidative stress of erythropoietin in uremic children on hemodialysis. Pediatr Nephrol. 2000;14:13–7.

65. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children and adolescents. Pediatrics. 2008;122:1142–52.
66. American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. Policy statement. Pediatrics. 2005;115(2):496–506.
67. Canadian Paediatric Society, Dietitians of Canada, and Health Canada. Nutrition for healthy term infants. Ottawa: Minister of Public Works and Government Services; 1998.
68. Ali FN, Arguelles LM, Langman CB, Price HE. Vitamin D deficiency in children with chronic kidney disease: uncovering an epidemic. Pediatrics. 2009;123(3):791–6.
69. Seeherunvong W, Abitbol CL, Chandar J, Zilleruelo G, Freunduch M. Vitamin D insufficiency and deficiency in children with early chronic kidney disease. J Pediatr. 2009;154(6):906–11.
70. Querfeld U, Mak RH. Vitamin D deficiency and toxicity in chronic kidney disease: in search of the therapeutic window. Pediatr Nephrol. 2010;25:2413–30.
71. Hari P, Gupta N, Hari S, Gulati A, Mahajan P, Bagga A. Vitamin D insufficiency and effect of cholecalciferol in children with chronic kidney disease. Pediatr Nephrol. 2010;25:2483–8.
72. Rodriguez-Soriano J, Arant BS. Fluid and electrolyte imbalances in children with chronic renal failure. Am J Kidney Dis. 1986;7:268–74.
73. United States Department of Health and Human Services (HHS) and the Department of Agriculture (USDA). Dietary guidelines for Americans; 2005.
74. Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr. 1991;10(4):383–93.
75. Beto J, Bansal VK. Hyperkalemia: evaluating dietary and nondietary etiology. J Ren Nutr. 1992;2(1):28–9.
76. Bunchman TE, Wood EG, Schenck MH, Weaver KA, Klein BL, Lynch RE. Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. Pediatr Nephrol. 1991;5:29–32.
77. Rivard AL, Raup SM, Beilman GJ. Sodium polystyrene sulfonate used to reduce the potassium content of a high-protein enteral formula: a quantitative analysis. JPEN J Parenter Enteral Nutr. 2004;28(2):76–8.
78. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis. 2005;46(4 Suppl 1):S1–121.
79. Shinaberger CS, Kopple JD, Van Wyck D, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? Am J Clin Nutr. 2008;88:1511–8.
80. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? Semin Dial. 2003;16(3):186–8.
81. Sullivan CM, Leon JB, Sehgal AR. Phosphorus-containing food additives and the accuracy of nutrient databases: implications for renal patients. J Ren Nutr. 2007;17(5):350–4.
82. Sedlacek M, Dimaano F, Uribarri J. Relationship between phosphorus and creatinine clearance in peritoneal dialysis: clinical implications. Am J Kidney Dis. 2000;36(5):1020–4.
83. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:257–64.
84. Abercrombie EL, Greenbaum LA, Baxter DH, Hopkins B. Effect of intensified diet education on serum phosphorus and knowledge of pediatric peritoneal dialysis patients. J Ren Nutr. 2010;20(3):193–8.
85. Ahlenstiel T, Pape L, Ehrich JHH, Kuhlmann MK. Self-adjustment of phosphate binder dose to meal phosphorus content improves management of hyperphosphatemia in children with chronic kidney disease. Nephrol Dial Transplant. 2010;25:3241–9.
86. Raaijmakers R, Willems J, Houkes B, Heuval CS, Monnens LA. Pretreatment of various dairy products with sevelamer: effective P reduction but also a rise in pH. Perit Dial Int. 2008;29:S15A.
87. Coleman JE, Norman LJ, Watson AR. Provision of dietetic care in children on chronic peritoneal dialysis. J Ren Nutr. 1999;9(3):145–8.
88. Benoit D, Green D, Arts-Rodas D. Posttraumatic feeding disorders. J Am Acad Child Adolesc Psychiatry. 1997;36(5):577–8.
89. Benoit D, Coolbear J. Post-traumatic feeding disorders in infancy: behaviors predicting treatment outcome. Inf Ment Health J. 1998;19(4):409–21.
90. Ravelli AM, Ledermann S, Bissett W, Trompeter R, Barratt T, Milla P. Foregut motor function in chronic renal failure. Arch Dis Child. 1992;67:1343–7.
91. Ravelli AM. Gastrointestinal function in chronic renal failure. Pediatr Nephrol. 1995;9:756–62.
92. Ruley EJ, Bock GH, Kerzner B, Abbott AW, Majd M, Chatoor I. Feeding disorders and gastroesophageal reflux in infants with chronic renal failure. Pediatr Nephrol. 1989;3:424–9.
93. Hawkins NM, Coffey S, Lawson MS, Delves HT. Potential aluminum toxicity in infants fed special infant formulas. J Pediatr Gastroenterol Nutr. 1994;19:377–81.
94. Fried M, Khoshoo V, Secker D, Gilday D, Ash J, Pencharz P. Decrease in gastric emptying time and episodes of regurgitation in children with spastic quadriplegia fed a whey-based formula. J Pediatr. 1992;120(4 Pt 1): 569–72.

95. Hobbs DJ, Gast TR, Ferguson KB, Bunchman TE, Barletta GM. Nutritional management of hyperkalemic infants with chronic kidney disease, using adult renal formulas. J Ren Nutr. 2010;20(2):121–6.
96. Warady BA, Kriley M, Belden B, Hellerstein S, Alon U. Nutritional and behavioural aspects of nasogastric tube feeding in infants receiving chronic peritoneal dialysis. Adv Perit Dial. 1990;6:265–8.
97. Katsoufis CP, Kertis M, McCullough J, et al. Pica: an important and unrecognized problem in pediatric dialysis patients. J Ren Nutr. 2012;22(6):567–71.
98. Spinozzi NS, Nelson PA. Nutrition support in the newborn intensive care unit. J Ren Nutr. 1996;6(4):188–97.
99. Yiu VW, Harmon WE, Spinozzi N, Jonas M, Kim MS. High-calorie nutrition for infants with chronic renal disease. J Ren Nutr. 1996;6(4):203–6.
100. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25:699–704.
101. Ledermann SE, Shaw V, Trompeter RS. Long-term enteral nutrition in infants and young children with chronic renal failure. Pediatr Nephrol. 1999;13(9):870–5.
102. Coleman JE, Watson AR, Rance CH, Moore E. Gastrostomy buttons for nutritional support on chronic dialysis. Nephrol Dial Transplant. 1998;13(8):2041–6.
103. Coleman J, Warady B. Supplemental tube feeding. In: Warady BA, Alexander SR, Fine RN, Schaefer F, editors. Pediatric dialysis. Dordrecht: Kluwer Academic; 2004. p. 243–57.
104. Ramage IJ, Harvey E, Geary DF, Hebert D, Balfe JA, Balfe JW. Complications of gastrostomy feeding in children receiving peritoneal dialysis. Pediatr Nephrol. 1999;13(3):249–52.
105. Ledermann SE, Spitz L, Moloney J. Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol. 2002;17:246–50.
106. Warady BA. Gastrostomy feedings in patients receiving peritoneal dialysis. Perit Dial Int. 1999;19(3):204–6.
107. Dello Strologo L, Principato F, Sinibaldi D, et al. Feeding dysfunction in infants with severe chronic renal failure after long-term nasogastric tube feeding. Pediatr Nephrol. 1997;11(1):84–6.
108. Coleman JE, Watson AR. Growth posttransplantation in children previously treated with chronic dialysis and gastrostomy feeding. Adv Perit Dial. 1998;14:269–73.
109. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7.
110. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: a prospective comparison between classic hemofiltration and hemofiltration with dialysis. Crit Care Med. 2000;28(4):1161–5.
111. Zappitelli M, Goldstein SL, Symons JM, Somers MJ, et al. Protein and calorie prescription for children and young adults receiving continuous renal replacement therapy: a report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. Pediatr Crit Care Med. 2008;36:3239–45.
112. Nakamura AT, Btaiche IF, Pasko DA, Jain JC, Mueller BA. In vitro clearance of trace elements via continuous renal replacement therapy. J Ren Nutr. 2004;14(4):214–9.
113. Krause I, Shamir R, Davidovits M, et al. Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. J Ren Nutr. 2002;12(1):55–9.
114. Goldstein SL, Baronette S, Vital Gambrell T, Currier H, Brewer ED. nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. Pediatr Nephrol. 2002;17:531–4.
115. Orellana P, Juarez-Congelosi M, Goldstein S. Intradialytic parenteral nutrition and biochemical marker assessment for malnutrition in adolescent maintenance hemodialysis patients. J Ren Nutr. 2005;15(3):312–7.
116. Council on Renal Nutrition of New England. Intradialytic parenteral nutrition. In: Renal nutrition handbook for renal dietitians. Massachusetts National Kidney Foundation; 1993. p. 86–98.
117. Canepa A, Verrina E, Perfumo F, et al. Value of intraperitoneal amino acids in children treated with chronic peritoneal dialysis. Perit Dial Int. 1999;18 Suppl 2:S435–40.
118. Qamar I, Secker D, Levin L, Balfe J, Zlotkin S, Balfe J. Effects of amino acid dialysis compared to dextrose dialysis in children on continuous cycling peritoneal dialysis. Perit Dial Int. 1999;19:237–47.
119. McPartland KJ, Pomposelli JJ. Update on immunosuppressive drugs used in solid-organ transplantation and their nutrition implications. Nutr Clin Pract. 2007;22:467–73.
120. Greenspan L, Gitelman S, Leung M, Glidden D, Mathias R. Increased incidence in post-transplant diabetes mellitus in children: a case-control analysis. Pediatr Nephrol. 2002;17:1–5.
121. Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol. 2000;11 Suppl 15:S1–86.
122. Fine RN, Webber SA, Olthoff KM, Kelly DA, Harmon WE, editors. Pediatric solid organ transplantation. 2nd ed. Oxford, UK: Blackwell Publishing; 2007.
123. Institute of Medicine. Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride. Washington, DC: National Academy of Sciences; 1997.
124. Salvatierra Jr O, Singh T, Shifrin R, et al. Successful transplantation of adult-sized kidneys into infants requires maintenance of high aortic blood flow. Transplantation. 1998;66:819–23.

125. Ferris ME, Bell LE. Transitioning the adolescent dialysis patient to adult care. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. 1st ed. The Netherlands: Springer; 2012.
126. Bell LE, Ferris ME, Fenton N, Hooper SR. Health care transition for adolescents with CKD—the journey from pediatric to adult care. Adv Chronic Kidney Dis. 2011;18(5):384–90.
127. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. Pediatrics. 2002;110(6):1304–6.
128. Bell LE, Bartosh SM, Davis CL, et al. Adolescent transition to adult care in solid organ transplantation: a consensus conference report. Am J Transplant. 2008;8(11):2230–42.
129. Bell LE, Sawyer SM. Transition of care to adult services for pediatric solid-organ transplant recipients. Pediatr Clin North Am. 2010;57(2):593–610.
130. Warady BA, Alexander SR, Watkins S, Kohaut E, Harmon WE. Optimal care of the pediatric end-stage renal disease patient on dialysis. Am J Kidney Dis. 1999;33(3):567–83.
131. Harvey E, Secker D, Braj B, Picone G, Balfe JW. The team approach to the management of children on chronic peritoneal dialysis. Adv Ren Replace Ther. 1996;3(1):1–14.

Chapter 19
The Aging Adult

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Key Points

- To describe the population shifts concerning older Americans and profile the psychosocial aspects and comorbid disease states of the aging adult.
- To identify the normal physiological changes of aging and changes associated with chronic kidney disease (CKD).
- To review risk factors associated with coupling of aging and CKD.
- To provide guidelines for nutritional assessment and management utilizing a geriatric focus.

Keywords Geriatrics • Frailty • Older adults • Aging • Chronic kidney disease

Introduction

In 1900, the percent of the population in the United States that was age 65 or older was 4.1 %. The growth of this segment of the population has increased significantly since the turn of the century. The older adult represented 13 % of the population in 2010 and population estimates suggest continued growth as high as 16.2 % in 2020 and 20.2 % in 2050 [1]. Rates of CKD are increasing with a trend towards multiple comorbidities including congestive heart failure (CHF) and diabetes mellitus (DM). Chronic diseases including CKD can leave the individual more frail than their peers and dramatically increase morbidity and mortality risks. Based on these trends, a geriatric approach, meaning a focus on maintaining functional capacity and quality-of-life, may be beneficial for care of the older patient with CKD. This requires collaboration among the healthcare team members and referral to community resources.

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With improvements in medical technology, decreased birth and mortality rates, the number of persons over the age of 65 is increasing [2]. By definition, any person over age 65 is defined as an older adult. An increased understanding of the needs of the older adult is necessary, since this population has increased by 15.3 % or 5.4 million from 2000 to 2010, to a total of 40.4 million people [2]. The 85 and older population is predicted to grow from 5.5 million in 2010 to 6.6 million in 2020. In 2010, 20 % of the 65 years of age and older population were minorities, increasing from 16.4 % in 2000. Growth estimates for 2030 indicated continued increase in the older minority segment of the US population to 26.4 % with women outnumbering men at 21 vs. 14.9 million [2]. The average life expectancy for individuals 65 years of age as of 2010 is an additional 18.8 years [2].

Profile of Older American

Psychosocial factors impact the lives of older adults, since it can directly affect how they handle chronic disease. In 2010, the profile of older Americans revealed the following [2].

Marital Status and Living Arrangements

- 72 % of men are married vs. 42 % of women, and they live with their spouse.
- 29 % of non-institutionalized older persons live alone; 8.1 million women, 3.2 million men.
- 10 % of men have alternative living arrangements vs. 19 % of women.
- 11.3 % of older Medicare enrollees receive formal/informal personal care from others.

Economic Status

- 18.3 % of men are employed vs. 10.7 % of women.
- The median income for men is $25,704 vs. $15,072 for women.
- 9.0 % of elderly live below the poverty level vs. 7.3 % of women.

The major source of income as reported by older adults in 2009 was social security (87 %), income from assets (53 %), private pensions (28 %). The social security benefit accounted for 38 % of the aggregate income of the older population.

Older Americans have at least one chronic disease, with the highest percentages reported for heart disease, HTN, arthritis, cancer, or DM [3]. This has remained unchanged as of data available through 2010 [3]. As the number of chronic diseases increases, the annual number of prescriptions increases by almost twofold. In 2004, average prescription costs were $207 per month [2]. An older American with four or more chronic diseases spent an average of $3,862.00 per year on prescription drugs. It is clear that chronic disease can be deemed costly on many levels.

Normal Physiological Changes

To fully understand the unique challenges of treating the aging adult, it is instructive to review the common physiological changes that occur as a result of the normal aging process. Such information will provide a foundation for later when the aging adult diagnosed with CKD is discussed.

Sensory

Sensory changes can impact activities of daily living (ADL), social interaction, ability to learn, as well as one's eating abilities and food choices. Decreased dentition and increased cavities are associated with aging [4]. Dental care is a high out-of-pocket healthcare expense and is often seen as not necessary or justifiable in the aging population. An increased risk for macular degeneration, a loss of central vision, is the most common cause of legal blindness in the aging adult [4]. This results in increased difficulty reading small print and the need for more lighting. Loss of high-frequency sensitivity, impairment of frequency discrimination, sound localization, and speech discrimination impact hearing [4]. Older adults often do not complain of hearing loss, but of an inability to understand what is said [4].

Skin

Skin changes can result in increased risk exposure to the aging adult. The epidermis, the outer layer, has decreased turnover resulting in poor wound healing, increased drying, decreased photo protection (i.e., the skin burns easier), and decreased vitamin D production [5]. Dermal, the under layer, has a 20 % loss of thickness leading to transparent skin, increased risk of heat stroke and hypothermia due to decreased thermoregulation, and decreased hypersensitivity reactions [5]. The subcutaneous layer atrophies impacting heat, insulation, caloric reserves, and loss of the shock absorber feature. Nail thickening and decreased skin growth rates lead to an increased risk of skin trauma and heightened foot problems [5].

Respiratory

Aging can result in increased susceptibility to pneumonia. There is decreased inflation, secretion expulsion, vital capacity with increased lung volume, and poor ciliary function which leads to decreased cough reflex [6]. There is also decreased oxygen uptake by the cells, largely caused by an anterior-posterior chest wall increase with transverse decrease which leads to kyphosis, calcification of the costal cartilage, and reduced rib motility; equating to less deep breathing [6].

Cardiovascular

Aging-related changes can lead to structural changes in the heart and the risk of systolic hypertension. The heart muscle mass increases with left ventricle wall thickening and deposits of collagen, which alter pumping function; valve leaflets thicken and increase in circumference leading to an increased risk of valvular stenosis and regurgitation; arterial intimal thickening occurs and collagen in vessels leads to narrowing and decreased cardiac perfusion; the left ventricle systolic function is unchanged; there is decreased compliance of left ventricle diastolic function with increased early diastolic left ventricle filling [7]. In the vessels, there is decreased compliance, leading to increased risk of systolic hypertension [7].

Gastrointestinal

Drug breakdown and metabolism can be affected by aging as well as vitamin and mineral metabolism. Decreased saliva flow, some impaired tongue movement during swallowing, decreased acid

production, and increased gastrin production may alter the breakdown of drugs. An increased intestinal transit time and motility leads to a decreased absorption of calcium, vitamin D, B_{12}, folate, and iron. Once the GI (gastrointestinal) mucosa, musculature, and transit time are decreased in colon, there is an increased risk of diverticular disease. In the aging adult, the diminishing size of the liver along with decreased hepatic blood flow can alter drug metabolism [8].

Musculoskeletal

A decrease in lean body mass, total body water, and bone density, increased adipose tissue, and cartilage loss in weight-bearing joints increase the risk of osteoarthritis and significantly decrease in muscle strength and speed of contractility [9].

The Kidneys

There is a spontaneous and regular decrease in renal function with age, starting at age 40 [10]. This results in an estimated renal function at about 70 mL/min or less at age 80, without having developed a specific kidney disease. In addition many antihypertensive medications act on kidney by increasing sodium loss (furosemide) or by reducing glomerular pressure such as angiotensin converting enzyme inhibitors (ACEIs) or anti-angiotensin II blockers. Older adults also have decreased thirst mechanisms, which can lead to dehydration and potential kidney injury [10]. In addition, there is an increase in reduplication and focal thickening of both the glomerular and the tubular basement membrane [11]. There is also decreased renal plasma blood flow and diminished creatinine production; increased sodium conservation along with decreased sensitivity to antidiuretic hormone; diminished plasma renin and aldosterone levels; increased prevalence of hyperkalemia, impaired ammoniagenesis, impaired maximal urinary concentration, and impaired water excretion [11, 12]. Thus if patients also present with hypertension and/or diabetes, there is a high probability that they have actual kidney disease.

Aging and Kidney Function

Aging does not automatically mean progressive CKD. Based on the National Health and Nutrition Examination Survey (NHANES) III data, the mean GFR for individuals 60–69 years of age was 85 mL/min/1.73 m^2 and 75 mL/min/1.73 m^2 for persons 70 years of age, with 25 % of all Americans over the age of 70 noted to have moderate to severe decreases in kidney function [13]. Serum creatinine levels can be inversely impacted by many chronic illnesses, such as cardiovascular disease (CVD), thereby affecting muscle mass, promoting malnutrition, inflammation, frailty, and decreased kidney function, that is not obvious unless the GFR is calculated [14, 15]. Women typically have lower muscle mass and hence lower serum creatinine values than men. All of these factors support the need to use GFR calculations as opposed to relying on the serum creatinine values to define CKD [15, 16].

However, the best method to estimate kidney function in the elderly population is being redefined. The use of a simplified MDRD equation has been recommended since it is less affected by age than other formulas [17].

Aging and CKD Risk Factors

CKD typically arises in the presence of other chronic conditions. Diabetic nephropathy is the most common cause of CKD and accounts for 55 % of all patients initiating renal replacement therapy (RRT) [18]. In the aging population, diabetes is a main contributor as well but a growing number of persons, 17 %, have CKD in the presence of CHF [18]. Twenty-two percent of persons over the age of 65 have all three comorbid conditions (CKD, DM, and CHF), which equates to a "triple threat" [18]. Such multiple risk factors are far less common in those under the age of 65 years; with less than 7 % of the population experiencing these comorbidities [18].

The primary focus of treatment for CKD is reversing or slowing the progression of CKD as well as the management of renal complications. Controlling the risk factors for CVD should be the major area of focus [11, 16]. This should be done using established national guidelines such as The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines for blood pressure control [19, 20]. Treatment for dyslipidemia should be based on the guidelines of KDOQI and the National Cholesterol Education Program Adult Treatment Plan III (NCEP ATP III) [20, 21]. Persons with CKD should be considered in the highest risk category for CVD [21]. Since DM is a risk factor for CVD, establishing glycemic control with glycated hemoglobin (HgbA1C) <7–8 % based on the American Diabetes Association guidelines is essential [22].

The average age of dialysis recipients is increasing, with the median age for the incident population at 64.8 years with the majority choosing in-center hemodialysis. According to the latest United State Renal Data Systems, older persons in the 65–74-year age range have the highest prevalence rates among all other age groups, while the incidence and prevalence rates increase to 47–50 % in those adults 75 years of age and older [18]. Three-fourths of all older persons begin RRT with five or more comorbid disease states. CVD, primarily CHF and ischemic heart disease, occurs 2 years prior to RRT at the alarming rates of 90 % in people with diabetes and nearly 70 % in those without diabetes [18].

It has recently been reported that within each stage of CKD as evaluated by estimated glomerular filtration rate (eGFR) equation that the rates of treated vs. untreated kidney failure were up to more than tenfold higher in younger compared with older individuals [23]. Age groups were divided into groups for analysis and spanned 18 to greater than 85 years of age. This study based in Alberta, Canada suggests that rates of untreated kidney failure are significantly higher in older than younger people. Defining and recognizing progressive kidney disease, how to do so, and what changes in eGFR actually clinically indicate in the elderly population is an area of continued debate.

Heightened Risks in Older Adults with CKD

Older adults with CKD tend to have multiple comorbidities, which coupled with the effect of aging, can leave the individual more frail than their peers [24]. It is important to be aware of the increased risks in order to decrease morbidity and mortality in older persons [25]. Changes in the musculoskeletal system with aging as well as chronic disease can have a negative impact on physiological function and can lead to frailty that is a precursor for disability [16, 25]. Frailty is characterized by self-reported weakness, fatigue, balance or gait disorders, undernutrition, and an impaired ability to recover from insult leading to impaired homeostatic reserve, malnutrition, decreased mobility, or functional loss related to diseases such as cerebrovascular accident (CVA), Parkinson's disease, or arthritis [16]. Shlipak found that elderly persons with CKD were three times more likely to be frail than their counterparts with normal kidney function [25].

As the healthcare team looks at managing the risk factors for CVD, they need to be aware of the following areas: hypotension, increased falls risk, vascular dementia, protein energy wasting, anemia, and bone disease.

Hypotension

There are multiple causes for hypotension including drug effects, aging in the presence of DM or CHF/left ventricular hypertrophy, postprandial effects in the presence of severe autonomic nerve system dysfunction. For those individuals receiving maintenance dialysis, there are added factors such as rapid fluid removal, inappropriate dry weights, and lower pretreatment blood pressures that can lead to persons being under dialyzed [26, 27].

Increased Falls Risk

Falls risk can be related to polypharmacy, impaired mobility, DM with impaired sensory neuropathy, autonomic neuropathy and/or visual impairment, orthostatic hypotension, renal osteodystrophy, and/or the risk of osteoporosis [16, 26–28]. In addition, depression can impact judgment and safety awareness, which can increase falls risk. Falls risk in elderly dialysis patients is high with a 4.4 relative risk of hip fracture and the resultant mortality at 1 year being 2.5 times greater; the fall rates in this group are close to the rates in nursing homes [28, 29]. Falls can also lead to further decreases in mobility, which can directly impact ADLs and instrumental activities of daily living (IADLs) such as shopping and meal preparation.

Vascular Dementia

Vascular dementia increases in CVD with CKD, DM, and increased age [30, 31]. Cognitive impairment with vascular dementia is the leading cause of morbidity and mortality in CKD [16]. The individual with vascular dementia will have areas of intact function contrasted with others of profound impairment and task-specific disabilities based on the location of the vascular event in the brain [16]. The Kidney Disease Quality of Life Cognitive Function (KDQOL-CF) Subscale can be used to screen for cognitive function and help determine who needs further work-up [32]. Individuals on beta-blockers and those with higher educational backgrounds scored higher on the KDQOL-CF [32].

Protein Energy Wasting

Older persons need to be screened and/or treated for wasting in stages 3–5 CKD, since it is strong predictor of morbidity and mortality [11, 16, 33], with survival significantly influenced by age, level of serum albumin and pre-albumin level, body mass index, and presence of DM [34]. Based on validation studies of the KDQOL-CF tool, malnutrition is a strong predictor of cognitive impairment in addition to other factors such as stage 5 CKD, stroke history, presence of peripheral vascular disease (PVD), use of benzodiazepine, higher serum phosphorus levels, and lower serum albumin [32].

Anemia Management

Management of stages 3–5 CKD in older adults includes screening for and/or treating anemia [11]. Functional iron deficiency anemia has been shown to be less common in elderly persons on hemodialysis, though iron is not readily absorbed in the aging gut. It is important that the healthcare team evaluate causes of anemia, since older adults are at increased risk for folate and vitamin B_{12} deficiencies, diverticular disease and cancers, and typically require lower doses of erythropoietin [35]. A supplemental iron treatment is often recommended, being more efficient when given intravenously before starting an erythropoietin stimulating agent (ESA). An ESA may be initiated when indicated by hemoglobin levels; frequently indicated when eGFR decreases below 30 mL/min.

Bone Disease Management

Since screening is occurring at earlier stages of CKD and is included as part of the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), management of bone disease is addressed across the spectrum of kidney disease. Evaluation incorporates screening for and/or treating vitamin D deficiency/insufficiency, calcium and phosphorus metabolism, and hyperparathyroidism. Coupled with the bone health risk factors associated with CKD are the additional risks for osteoporosis, vitamin D deficiency, decreased mobility, and the lack of weight-bearing exercises in the older adult [10, 15, 16]. The most common type of renal osteodystrophy in the geriatric patients with CKD is osteitis fibrosa; with clinical manifestations including proximal muscle weakness in the lower extremities, vascular or soft tissue calcification, fractures or bone pain, and intractable pruritis [36]. The symptoms can have significant impact on the individual's quality-of-life in terms of their ability to perform ADL's and IADL's freedom of movement. A treatment by cholecalciferol may be recommended since CKD patients are often deficient. Supplemental calcium (not to exceed 1,500 mg/day) may be prescribed if nutritional intake of calcium is below 500–800 mg/day.

Geriatric Focus

Because of the increasing age of the CKD population and the multiple comorbidities associated with this cohort, a geriatric approach to care may be beneficial. The goal of the geriatric focus is to maintain functional capacity and quality-of-life [28, 37, 38]. When assessing the nutritional status of older adults, the assessment should be based on their physiological and psychosocial state, keeping this geriatric focus in mind.

Barriers to Care

It is important to assess barriers to care including making observations about sensory deficits in order to maximize the teaching environment and to provide the right instructional medium. If the individual is hard of hearing, ask the person when it is easiest for them to hear. They will often note that it is hard to hear in crowds or with background noises, so choose a teaching site that is away from this environment. For those with visual deficits or of low-literacy levels, the educational materials need to be chosen carefully: the paper should not be glossy to minimize glare, the paragraphs should be double spaced, and the font should be large (16 point) using plain block-type letters in black print [39].

When assessing an individual's nutritional status, it is essential to be mindful of obstacles that may make the typical plan of care impractical. If the older person with CKD is not the primary person doing the shopping or cooking or if the person has cognitive impairment, have the spouse/caregiver present during the education session. There may be limited meal preparation/cooking skills due to role change, lack of caregiver, and change in living situation/economic status that may require the reliance on ready-to-eat, frozen entrees or community-sponsored meals/food banks. Listen for cues that suggest financial difficulties such as food avoidance, reporting medications are expensive, or history of the person not taking the medications as directed to make them last longer. In a caring, compassionate, and non-threatening manner, any healthcare team member can ask about financial concerns or shortfalls, which impact the older adult's ability to appropriately take part in their self-management.

Be aware of an increased risk of depression, since it can also impact functional status. It can result in weight changes, changes in activity and sleep patterns, increased risk of falls, uncontrolled pain, as well as decreased interest in following dietary modifications or taking medications as instructed. All healthcare team members have an obligation to communicate their observations/suspicions to other team members if they suspect the presence of depression.

Geriatric Assessment

Much of the focus when working with the older individual with CKD is on the development of a solid foundation for lifestyle modification to reduce risk factors for CVD. A firm foundation must be laid before it can be built upon, with specific individualized needs arising as a result of CKD progression. Much of this foundation is based on the JNC 7 criteria including: weight management/loss to maintain BMI between 18.5 and 24.9 kg/m^2; assessment of metabolic syndrome/prediabetes based on the NCEP ATP III criteria; reduction in dietary sodium along with reduced total fat and saturated fat; aerobic physical activity for 30 or more minutes, most days of the week; moderate alcohol consumption; and smoking cessation if needed [19].

The changes in the musculoskeletal system, as well as an increased risk of edema due to CKD, heart failure (HF), or PVD, can make the nutrition assessment challenging. With musculoskeletal changes and decreased activity levels, the basal metabolic rate and total energy intake level declines. The total energy intake level appears to be 30–35 kcal/kg of standard body weight/day for the older adult [20]. With the ultimate goal of achieving/maintaining an adequate BMI, laboratory values should be monitored to assess the risk for DM, weight and/or subjective global assessment should be monitored for changes, and nutritional interviews/diaries monitored for signs of deterioration in nutritional status [20]. Daily protein intake is generally less than that consumed by average population at levels of 0.6–0.75 g/kg of standard body weight/day for stages 3–4 CKD [22]. The challenge is to maintain a balance between symptoms of azotemia and protein malnutrition as aversions to protein occurs. Proteinuria also needs to be assessed since it serves many purposes. It substantiates the prognosis for kidney disease progression as well as premature CVD and serves as a guide to therapy, especially concerning the use of ACEIs in patients experiencing profound proteinuria [20].

A complete nutritional assessment involves a review of documented medical problems to determine how to satisfy the individual's nutritional needs and diet modifications. It is important to ask the older adult about any special diets or avoidance of any specific foods in order to get a sense of their understanding of the diet and disease needs. Such gentle probing is imperative because many older persons become overwhelmed as they try to compartmentalize all of the diet information they may have received over the years.

Dietary sodium modification is the cornerstone of managing the risk factors for CVD. Older adults tend to be more sensitive to changes in sodium load. It has a direct impact on blood pressure, fluid status, and medication efficacy. Often times if blood pressure or fluid status are not controlled, the first

line of defense in the healthcare setting is medication adjustment/addition as opposed to an evaluation of dietary intake, cognition and behavior, or financial status. A dietary evaluation of an increased sodium and/or fluid load needs to be addressed; it is often a key contributor to uncontrolled fluid intake and blood pressure. A useful teaching technique that is easier for older persons to grasp is the rule of 200s, which breaks down the daily goal of <2,000 mg of sodium by looking at individual food choices. The individual is taught to focus on two aspects of a food label, the serving size and the amount of sodium (mg). Often, the older adult gets confused by the percent listing next to the sodium on the label, so it is essential to stress amounts in milligrams. Encourage the person to choose food items that have 200 mg of sodium or less per serving. If the individual is willing to live with the allotted serving size or if they can increase serving sizes and maintain an intake less than 200 mg per serving, then it is a good food choice. Typically, patients are advised to choose frozen dinners with <600–700 mg sodium per day, if the use of frozen dinners is necessary. Sometimes when dealing with older adults who are diagnosed multiple chronic diseases later in life, balancing quality-of-life with quantity is important. The practitioner man needs to assist the older individual in locating the lowest sodium version of their favorite foods or advising them when it is most safe to have these types of food.

Healthcare team members must stay abreast of the medications used to manage or treat the risk factors associated with CVD or CKD. It is important to have access to a good drug guide, whether it is an up-to-date book, online drug guide, or a personal data assistant (PDA) smart phone application version. It is also important to be aware of food–drug interactions and adverse drug effects, many of which are gastrointestinal (GI)-related causing increased risk of nausea, vomiting, or constipation or which may impact function by causing somnolence or fatigue.

The assessment of nutritional status in older adults with CKD must include a review of systems such as oral health and its impact on food selections and GI symptoms or food aversions since it can be indicative of uremia. With constipation, be aware of foods or medicinal products used to correct it, since they can have a direct impact on overall health including lab data. Constipation can also decrease oral intake, increase fluid intake, result in use of higher potassium foods such as prune juice, and result in elevated potassium from GI reabsorption.

It is important to encourage strengthening or at least maintenance of large muscle group strength since it can directly impact functional status. Resistance training has a beneficial impact on protein utilization and muscle mass in persons with CKD on low-protein diets (0.6 g/kg/day) by improving muscle mass and nutritional status as denoted by pre-albumin and function [38]. Regular exercise is an integral part of CKD management and quality-of-life. It should be encouraged and matched to the individual's current level of abilities. Some educational tools have been designed for older adults and incorporate seated techniques for maximum safety while working on upper and lower body stretching, strengthening, and balance [39].

Summary

The older population is experiencing growth which will continue through the year 2030. The aging adult has one or more chronic diseases. CKD is occurring in the presence of multiple comorbidities in this population. It is imperative that healthcare team members be aware of changes associated with aging and the increased risks that can occur in the CKD population as well as the psychosocial challenges that this population may experience. Because of the increasing age of the CKD population, a geriatric focus to the care of older patients with CKD may be beneficial. This requires the healthcare team to focus on maintaining functional capacity and quality-of-life. It should incorporate the goals of the older adult as they are guided in self-management and outlined in their coordinated plans of care. A geriatric focus requires a multidisciplinary team approach with knowledge of both geriatrics and the available aging-related community resources.

Case Study

LSK is a 76-year-old Caucasian male with a history of hypertension (HTN), diabetes, osteoarthritis of the hips and spine. He took a number of over-the-counter nonsteroidal anti-inflammatory drugs for 15 years and has been quitting smoking 5 years ago. He presents a mild coronary heart disease under medical treatment only. He lives with a low income in a street level apartment with his wife who takes care of grocery and cooks the meals. He walks his dog around the block every morning and evening. Despite having a good health insurance care plan, he declares not taking all pills that are regularly prescribed by his general practitioner.

His measurements are: height: 5″9, weight: 210 lb with no reported weight changes and no digestive symptoms. He claims having a good appetite. From time to time he describes difficulties in keeping his balance. His blood pressure sitting is 160/85 mmHg. His labs are: HgA1C 8.5 %, BUN 30 mg/dL, Cr 2.4 mg/dL, Na^+ 136 mEq/L, K^+ 4.8 mEq/L, CO_2 22 mEq/L, RBC 3.80, Hgb 11.1 g/dL, Hct 34.4 %, total cholesterol 201 mg/dL, TRG 180 mg/dL, HDL 40 mg/dL, LDL 130 mg/dL, Ca^{2+} 9.0 mg/dL, phosphate 5.0 mg/dL. Serum parathyroid hormone is 100 pg/mL. Urine protein is 2.6 g/day.

His medications include ramipril 5 mg, furosemide 40 mg, atenolol 50 mg, aspirin 75 mg, repaglinide 3 mg, simvastatin 10 mg, calcium carbonate 1 g, Kayexalate® (sodium polystyrene sulfonate) 1 spoon every other day.

Questions

1. What are this patient's cardiovascular (CV) risk factors?
   Answer: CV risk factors are: HTN uncontrolled, uncontrolled hyperlipidemia, uncontrolled DM, obesity with a BMI of 31. Elevated serum phosphate, uncontrolled proteinuria.
2. How much is his estimated glomerular filtration rate (eGFR) and what is his CKD stage?
   Answer: The eGFR (using MDRD formula) is 35 mL/min despite a "moderate" increase in serum Cr, patient has Stage 3B CKD.
3. What are some areas of concern related to this patient psychosocial situation?
   Answer: Psychosocial issues include: modest income, occasions of limited physical activity, which impacts dietary intake, as well as risk of falls from fuzzy balance.
4. What CKD complications are you concerned? What additional information would be useful?
   Answer: CKD issues of concern include uncontrolled cholesterol particularly its LDL fraction, HTN, insufficient glycemic control, hyperphosphatemia, and elevated parathyroid hormone. Additional information which would be beneficial include serum iron and transferrin to check for iron deficiency and to prevent onset of anemia, vitamin D level to help bone disorders to improve and treat potential deficit.
5. What would you check in his treatment and potentially propose to modify?
   Answer: First verify good compliance to treatment and any potential side effects that could be improved; Check for sodium intake which should be reduced to 2 g/day; increase ramipril to 7.5–10 mg daily to improve BP control AND reduce proteinuria as low as possible; increase Kayexalate if serum potassium does rise above 5.3–5.5 mEq/L to 1 or 2 spoons per day, increase statin to improve LDL cholesterol, check vitamin D, and give cholecalciferol if necessary. Introduce a non-calcium phosphate binder to improve phosphate control. Finally check his glycemic control and prescribe additional antidiabetic drug (DPP4 inhibitor) or insulin.

References

1. Administration on Aging, Department of Health and Human Services. Aging statistics. 2010. www.aoa.gov/aoa-root/aging.statistics/future_growth/future_goals. Accessed 1 Aug 2012.
2. Administration on Aging, U.S. Department of Health and Human Services. A profile of older Americans: 2011. www.aoa.dhhs.gov/prof/Statisticstatuspostrofile/profiles.asp. Accessed 1 May 2012.
3. Older Americans 2012: key indicators of well-being. http://agingstats.gov. Accessed 4 Aug 2012.
4. Burke MM, Laramie J. Sensory impairment. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 439–52.
5. Burke MM, Laramie J. Aging skin. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 142–60.
6. Burke MM, Laramie J. Respiratory. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 161–201.
7. Burke MM, Laramie J. The aging cardiovascular system. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 202–53.
8. Burke MM, Laramie J. Gastrointestinal conditions. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 254–68.
9. Burke MM, Laramie J. Musculoskeletal: common injuries. In: A primary care of the older adult: a multidisciplinary approach. St. Louis: Mosby; 2000. p. 302–53.
10. Bevan M. The older person with renal failure. Nurs Stand. 2000;14:48–54.
11. Yuanne FE, Anderson S. Kidney in aging. In: National Kidney Foundation. Primer on kidney diseases. 4th ed. Philadelphia: Saunders; 2005.
12. Hansberry MR, Whittier WL, Krause MW. The elderly patient with chronic kidney disease. Adv Chronic Kidney Dis. 2005;12:71–7.
13. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in adults US population. Third Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41:1–12.
14. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. J Am Soc Nephrol. 2005;16:180–8.
15. Stevens LA, Levey AS. Chronic kidney disease in the elderly—how to assess risk. N Engl J Med. 2005;20: 2122–4.
16. Wiggins J. Core curriculum in nephrology: geriatrics. Am J Kidney Dis. 2005;46:147–54.
17. Froissart M, Rossert J, Pallard JC. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol. 2005;16:763–73.
18. U.S. Renal Data System. USRDS 2005 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2005. www.USRDS.org/adr.htm. Accessed 27 Jan 2006.
19. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Bethesda, MD: National Institutes of Health, National Heart, Lung and Blood Institute; 2003. www.nhlbi.nih.gov/guidelines/hypertension/index.htm. Accessed 27 Jan 2006.
20. K/DOQI clinical practice guidelines. National Kidney Foundation, 2000–2004. www.kidney.org/professional/kdoqi/guidelines.cfm. Accessed 27 Jan 2006.
21. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD. Cholesterol Education Program, National Institutes of Health, National Heart, Lung and Blood Institute. 2002. www.nhlbi.nih.gov/guidelines/cholesterol/atp.3_rpt.htm. Accessed 27 Jan 2006.
22. Clinical Practice Guidelines 2006. American Diabetes Association. 2005. http://care.diabetesjournals.org/content/vol/29/suppl_1/. Accessed 11 Feb 2006.
23. Hemmelgam BR, James MT, Manns BJ, O'Hare AM, Muntner P, Ravani P, Quinn RR, Turin TC, Tan Z, Tonelli M; Alberta Kidney Disease Network. Rates of treated and untreated kidney failure in older vs younger adults. JAMA. 2012;307:2507–15.
24. Letourneau I, Ouimet D, Dumont M, Pichette V, Leblanc M. Renal replacement in endstage renal disease patients over 75 years old. Am J Nephrol. 2003;23:71–7.
25. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis. 2004;43:861–7.
26. Ismail N. Complications of hemodialysis in the elderly. http://uptodateonline.com/application/topic/topic/topicText.asp?file=dialysis/20591. Accessed 25 Feb 2005.
27. Roberts RG, Kenny RA, Brierley EJ. Are elderly haemodialysis patients at risk of falls and postural hypotension? Int Urol Nephrol. 2003;35:415–21.
28. Sims RJ, Cassidy MJ, Masud T. The increasing number of older patients with renal disease. BMJ. 2003;327:463–4.

29. Desmet C, Beguin C, Swine C, Jadoul M. Falls in hemodialysis patients: prospective study of incidence, risk factors and complications. Am J Kidney Dis. 2005;45:148–53.
30. Pereira AA, Weiner DE, Scott T, Sarnack MJ. Cognitive function in dialysis patients. Am J Kidney Dis. 2005;45:448–62.
31. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. J Am Geriatr Soc. 2004;52:1863–9.
32. Kurella M, Luan J, Yaffe K, Chertow GM. Validation of kidney disease quality of life (KDQOL) cognitive function subscale. Kidney Int. 2004;66:2361–7.
33. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;4:391–8.
34. Chauveau P, Combe C, Laville M, et al. Factors influencing survival in hemodialysis patients aged older than 75 years: 2.5 year outcome study. Am J Kidney Dis. 2001;37:997–1003.
35. Nicholas JC. A study of response of elderly patients with end-stage renal disease to epoetin alfa or beta. Drugs Aging. 2004;21:187–201.
36. Char R, Culp K. Renal osteodystrophy in older adults with end-stage renal disease. J Gerontol Nurs. 2001;27: 46–51.
37. McHugh Sanner B. Are your written materials missing the mark? J Active Aging. 2003:19–24.
38. Castaneda C, Gordon P, Uhlin K, et al. Resistance training to counteract the catabolism of low-protein diet in patients with chronic renal insufficiency: a randomized, controlled trial. Ann Intern Med. 2001;135:965–76.
39. Exercise for Life! A physical activity program for older adults. Live well, live long. San Francisco, CA: American Society of Aging; 2004. www.asaging.org/cdc. Accessed 21 Sept 2005.

Chapter 20
Nephrotic Syndrome

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Key Points

- Identify the nephrotic syndrome, its causes, and its complications.
- Describe the pharmacologic management of nephrotic syndrome.
- Discuss the nutritional management of nephrotic syndrome.

Keywords Nephrotic syndrome • Complications • Treatment • Protein restriction • Renin-angiotensin blockade • Dietary treatment

Definition of Nephrotic Syndrome

Nephrotic syndrome results from excessive urinary losses of albumin and other plasma proteins of similar mass and is characterized by edema, hyperlipidemia, and hypoalbuminemia [1, 2]. At least 3.5 g of protein per 1.73 m^2 of body surface area must be present in a 24-h urine collection to make the diagnosis, although most patients have, on average, 6–8 g of proteinuria a day. Over 80 % of the urinary protein is albumin, reflecting plasma protein composition. The remainder of the urinary protein is comprised of other plasma proteins such as immunoglobulins, binding proteins, complements, and coagulation factors [2].

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Manifestations of Nephrotic Syndrome

≥3.5 g proteinuria/1.73 m^2/day
Hypoalbuminemia
Edema
Hyperlipidemia
Lipiduria

Causes of Nephrotic Syndrome

A wide range of glomerular diseases can cause the nephrotic syndrome and may be primary (idiopathic) in nature or secondary to a systemic disease or medication [1–3]. Primary or idiopathic glomerular diseases that result in nephrotic syndrome include minimal change disease (MCD), membranous nephropathy, and focal segmental glomerulosclerosis (FSGS) [1–3] (Table 20.1). The diagnosis is made on the basis of pathologic appearance of the kidney tissue.

Systemic diseases or medications also can cause the nephrotic syndrome (Table 20.1). Of these causes, diabetic nephropathy is the most common. Certain connective tissue diseases, infections, chronic inflammatory states, malignancies, drugs, and plasma cell dyscrasias also can give rise to the nephrotic syndrome [1–3]. Diagnosis is made on the basis of a thorough history, careful physical examination, and selected tests guided by the history and examination. A kidney biopsy is sometimes required for further classification as in the case of lupus nephritis or to exclude other types of glomerular diseases, especially when hematuria is prominent [3]. Whatever the underlying cause, injury to the podocyte is what ultimately alters the permselective properties of the glomerular barrier and results in massive urinary protein loss [4].

Table 20.1 Causes of nephrotic syndrome

Primary or idiopathic	Secondary to systemic diseases	
Membranous nephropathy (33 %)	Diabetes mellitus	Infections
Focal segmental glomerulosclerosis (35 %)	Systemic lupus erythematosus	• HIV
Minimal change disease (15 %)	Amyloidosis	• Hepatitis B
IgA nephropathy (10 %)	Dysproteinemias	• Hepatitis C
Membranoproliferative glomerulonephritis (2–5 %)	• Multiple myeloma	• Syphilis
Other (2–5 %)	• Other light chain-mediated disease	• Malaria
	Malignancy	Drugs
	• Breast, colon, lung	• NSAID
	• Lymphoma	• Gold
		• Penicillamine
		• Captopril

HIV human immunodeficiency virus, *NSAID* nonsteroidal anti-inflammatory drug

Complications of Nephrotic Syndrome

Regardless of the etiology of nephrotic syndrome, the clinical sequelae are identical (Table 20.2). All of the adverse effects discussed below result directly or indirectly (through decreased levels of albumin or of other specific plasma proteins and/or oncotic pressure) from urinary protein losses [1–3]. Therefore, management of nephrotic patients targets reduction of proteinuria to modify the complications of nephrotic syndrome.

Sodium Retention (Edema)

Edema is a common clinical manifestation in nephrotic syndrome and occurs because of accumulation of fluid in the interstitial space. Two mechanisms were thought to be responsible for the edema: (1) avid renal sodium retention due to the loss of tubular response to atrial natriuretic peptide [5], resulting in "overfilling" of the vascular space and consequent edema, and (2) decrease in plasma oncotic pressure when serum albumin levels fall below 1.5–2.0 g/dL, resulting in translocation of fluid into the interstitial space [1–3, 6, 7] (Table 20.2). More recent evidence suggests that plasma serine proteases such as plasminogen appear in nephrotic urine and undergo cleavage to active plasmin.

Table 20.2 Systemic complications and clinical sequelae of nephrotic syndrome

Complication	Mechanism	Clinical sequelae
Sodium retention	Atrial natriuretic peptide resistance	Edema → skin breakdown → cellulitis
	↓ Plasma oncotic pressure	Pleural effusion → shortness of breath
	↑ Urine plasmin → ENaC activation	Ascites → spontaneous bacterial peritonitis
Hypercoagulable state	Loss of antithrombin III	Deep venous thrombosis
	↓ Plasma proteins C and S	Pulmonary embolism
	Thrombocytosis	Renal vein thrombosis
	↑ Plasma fibrinogen	
Infection	Loss of immunoglobulins	Spontaneous bacterial peritonitis
	Loss of complement	Other infections with encapsulated organisms
Hyperlipidemia	Altered lipoprotein metabolism: ↑ Proatherogenic lipoproteins Oxidized high-density lipoprotein ↑ Triglycerides	Accelerated atherosclerosis
Progressive renal injury	Iron-induced oxidative injury	Interstitial fibrosis
	Lipid peroxidation	Chronic kidney disease
	Complement-mediated injury	
Nutritional depletion	Loss of tissue proteins	Tissue proteins → muscle wasting
	Loss of erythropoietin	Anemia
	Loss of plasma binding proteins	Transferrin → iron deficiency anemia
		Thyroglobulin binding protein → hypothyroidism
		Vitamin D binding protein → hypocalcemia, rickets
		Zinc (bound to albumin) → zinc deficiency

ENaC epithelial sodium channel

Plasmin, in turn, activates the epithelial sodium channels (ENaCs) in the cortical collecting tubule, enhancing sodium absorption and resulting in edema [6, 7]. Regardless of the mechanisms, the consequences are edema, pleural effusions, and ascites. Skin breakdown from tense edema and the presence of ascites predispose to infection.

Hypercoagulability (Thrombophilia)

The underlying mechanism for thrombophilia in nephrotic syndrome is poorly understood. Because of urinary loss of antithrombin III, decreased plasma proteins C and S, increased plasma fibrinogen, thrombocytosis, and increased platelet adherence (Table 20.2), nephrotic patients may be hypercoagulable [8, 9]. They are prone to develop deep venous thrombosis, pulmonary embolism, renal vein thrombosis, sagittal sinus thrombosis, and, occasionally, arterial thrombosis. The incidence of thromboembolic disease is highest in patients with membranous nephropathy, up to 50 %. The higher the urinary protein losses and the lower the serum albumin level, the higher is the risk of thromboembolism [8, 9].

Hyperlipidemia

Levels of proatherogenic lipoproteins, such as very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and lipoprotein (a), are increased in nephrotic syndrome [10, 11]. While high-density lipoprotein (HDL) levels are either normal or slightly decreased, it is the small, dense, and less protective HDL particles that accumulate [10, 11]. Triglyceride levels also may be increased markedly [10, 11], resulting both from delayed clearance of VLDL as well as reduced hepatic uptake of highly atherogenic IDL remnant particles. The combination of increased synthesis and impaired catabolism of lipoproteins confers a relative risk of 5.5 for myocardial infarction and of 2.8 for death from coronary artery disease [12].

Marked derangements of multiple aspects of lipid metabolism are present in the nephrotic syndrome [10, 11]. Adherence of lipoprotein lipase (LPL), an enzyme that plays an important role in the lipolysis of triglycerides, to the vascular endothelium is reduced when serum albumin is low despite a normal synthetic rate [13, 14]. Low serum albumin also induces increased albumin synthesis by the liver, accompanied by increased synthesis of many other liver-derived proteins, including fibrinogen, LDL, and Lp(a) [13, 14]. In concert, these derangements result in increased levels of triglycerides, LDL, and Lp(a). Further experimental evidence reveals that an acquired LDL receptor deficiency exists in nephrotic syndrome, leading to impaired uptake of cholesterol by the liver [10, 11]. As a result, enzymes that synthesize cholesterol are upregulated and enzymes that catabolize cholesterol by diverting it to bile synthesis are downregulated, further aggravating the hyperlipidemia. Urinary loss of LCAT in massive proteinuria interferes further with normal lipoprotein metabolism through altered apolipoprotein ratios and reduced HDL-mediated scavenging of cholesterol [10, 11].

Progressive Renal Injury

Prolonged and massive proteinuria leads to progressive renal injury with interstitial fibrosis and glomerular sclerosis [15]. The proteins and lipids in the urine are taken up by the proximal renal tubular

cells and lead to oxidative injury of the cells. Once taken up, the oxidized lipids and iron act as a chemoattractant for monocytes, stimulate proximal renal tubular production of cytokines such as NF-κB, and activate the complement cascade. The sum of these events results in tubulointerstitial inflammation, activation of profibrotic pathways, and induction of apoptosis [15].

Infection

Patients with nephrotic syndrome may develop cellulitis because of skin breakdown from tense edema, pneumonia, and spontaneous bacterial peritonitis when ascites is present (especially in children). Immunoglobulin G (IgG) and complements are lost in the urine [1–3]. Unlike liver-derived proteins, the synthesis rate of IgG does not increase [16]. Encapsulated organisms are a particular threat because such organisms require either opsonization with specific antibodies or complement fixation for killing.

Nutritional Depletion

Urinary protein losses in nephrotic syndrome lead to muscle wasting presumably due to shunting of amino acid building blocks to the liver to enhance plasma protein synthesis, in the absence of a compensatory decrease in total body protein turnover [17, 18]. Loss of erythropoietin and binding proteins that transport iron, vitamin D, and thyroxine may result in anemia, iron deficiency, hypocalcemia and rickets, and hypothyroidism, respectively [1–3, 19]. Sustained and massive proteinuria may lead also to zinc deficiency because two-thirds of circulating zinc is bound to albumin [20] and copper depletion through the urinary loss of ceruloplasmin [21]. These trace element deficiencies can induce skin rashes [22] and may result in neutropenia and anemia [21], respectively.

Patients with progressive loss of kidney function may develop metabolic acidosis, particularly when the glomerular filtration rate falls below 30 mL/min [23]. Potential adverse effects of metabolic acidosis include increased muscle catabolism, growth retardation in children, exacerbation of bone disease, impaired glucose tolerance, and reduced albumin synthesis which predisposes to hypoalbuminemia [23]. In addition, a low serum bicarbonate (<22 versus 25–26 mEq/L) may confer an increased risk for progression of CKD [23, 24], because compensatory mechanisms to augment ammonium production and urinary acidification through activation of aldosterone and kidney endothelin production may lead to increased urinary protein losses and interstitial fibrosis [25, 26]. Enhanced ammonium production is also thought to activate the alternative complement pathway, further aggravating inflammation and interstitial fibrosis [23–26].

Treatment of Nephrotic Syndrome

The main goal in treating nephrotic syndrome is to reduce or eliminate proteinuria to blunt or prevent the development of associated complications, to protect kidney function, and to reduce the risk for accelerated atherosclerosis [1–3]. Dietary management and pharmacologic management (Table 20.3) each plays a major and complementary role in this endeavor.

Table 20.3 Treatment of nephrotic patients

Dietary		Pharmacologic/other
Calorie	35 kcal/kg/day	Remove underlying cause
Protein	0.8 g/kg/day	Start immunosuppressive drugs
	Soy protein may be more beneficial	Reduce proteinuria
Fat	<30 % of total calories	Angiotensin converting enzyme inhibitor
	Cholesterol <200 mg/day	Angiotensin receptor blocker
Minerals	Sodium <2 g/day	Cyclosporine
	Iron if clearly iron deficient	Nonsteroidal anti-inflammatory drug
	Calcium if vitamin D deficient (2 g/day)	Spironolactone
	Zinc if zinc deficient (220 mg/day)	Statin therapy for hyperlipidemia
Vitamins	Calcitriol, if vitamin D deficient	Anticoagulation for hypercoagulability
Fluid	1 L/day	Antibiotics for infection
		Diuretics for edema

Specific Treatment

If possible, treatment of the nephrotic syndrome is directed at the underlying cause (Table 20.3). In the cases of drug-induced nephrotic syndrome, the offending drug is stopped. Chemotherapy, radiation therapy, and/or surgical resection of the responsible cancer may lead to resolution of malignancy-related nephrotic syndrome. Antibiotics, antiviral drugs, or immunomodulating agents are used when the suspect is an infection. For idiopathic nephrotic syndrome, depending upon the presenting histology, suppressing the immune system with drugs such as steroids, cyclophosphamide, mycophenolate, or other immunomodulating drugs may result in complete resolution of the nephrotic syndrome. A full discussion of the immunosuppressive treatment of glomerular diseases is beyond the scope of this chapter.

Nonspecific Treatment

If the nephrotic syndrome does not respond to removal of the offending agent or immunosuppressive therapy, then nonspecific measures are employed to reduce the proteinuria.

Pharmacologic Management

Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), cyclosporine, and nonsteroidal anti-inflammatory drugs (NSAID) all cause renal vasoconstriction, reduce glomerular capillary pressure, and, therefore, proteinuria [1–3, 27] (Table 20.3). In addition, ACEI and ARB also reduce the defect in the filtration barrier of the glomerular basement membrane [1–3, 27, 28]. Combining ACEI with ARB may have an additive effects on the reduction of proteinuria [1–3, 27, 28], although the incidence of hyperkalemia and acute renal failure may be unacceptably high in patients with diabetic nephropathy on dual therapy [3]. The combination of an ACEi and/or an ARB with spironolactone further reduces proteinuria in small studies, but hyperkalemia may limit its usefulness [29, 30]. No data is available regarding the cardiovascular outcomes, long-term renal outcomes, or mortality [29]. NSAID rarely are used in treating nephrotic syndrome because of the increased risk of acute renal failure and gastrointestinal bleeding.

Statins will improve the hyperlipidemia seen in nephrotic syndrome [1–3, 27, 31, 32] (Table 20.3). They also may protect nephrotic kidneys from progressive injury because of their lipid lowering and anti-inflammatory effects [27, 31, 32]. However, despite the favorable data in nephrotic animals, human data for cardiac [27, 31, 32] and renal [27, 31, 32] protection are scant.

Use of loop diuretics may be necessary when edema becomes symptomatic [3], but kidney function must be monitored carefully because of potential for precipitating acute renal failure. Adding an aldosterone antagonist may augment diuresis, given the recent discovery that plasmin in urine is responsible for activating epithelial sodium channels. If other complications of nephrotic syndrome develop (hypothyroidism, thromboembolic disease, infection), therapy targeted at the complication is started (Table 20.3).

Nutritional Management

A high-protein diet in nephrotic syndrome will increase urinary protein excretion and lead to a decline in serum albumin concentration through its adverse effects on glomerular hemodynamics [33]. In contrast, protein restriction, especially when combined with ACEI and/or ARB therapy, will reduce proteinuria [27, 34] (Table 20.3). Although some studies suggest that severe protein restriction to 0.3 g/kg/day supplemented with amino acids is of additional benefit [35], most experts recommend moderate (0.7–0.8 g/kg/day) protein restriction because of concern about precipitating malnutrition [3, 27].

The type of dietary protein is also important. Recent studies suggest that chicken and fish sources of protein may be of more benefit than pork or beef [36]. Vegetarian sources of protein such as soy [36–41] and flaxseed [42] reduce proteinuria and hyperlipidemia more than animal proteins. Studies of nephrotic rats suggest that the benefit derived from soy protein is due to a direct effect on the kidneys possibly to reduce nitrotyrosine formation rather than through changes in hepatic lipid metabolism [40, 41]. Soy protein may also reduce inflammatory cytokines, further ameliorating progressive kidney injury [38]. The types of amino acids present in plant proteins may be responsible for their beneficial effects, rather than the change in dietary lipid content, because branched chain and gluconeogenic amino acids (such as arginine and glutamate) do not increase proteinuria in animal models while other amino acids do [43, 44]. Since diets that contain animal protein also are relatively high in acid, the greater acid load accompanying greater protein loads may be contributing to progressive kidney injury.

If iron deficiency is clearly present, then cautious oral iron repletion is indicated, keeping in mind that iron may exacerbate renal injury (Table 20.3). Patients who are hypocalcemic because of vitamin D deficiency should receive oral vitamin D and calcium (Table 20.3). Other than correction of hypocalcemia, vitamin D repletion in patients with proteinuria may have beneficial effects on albuminuria [45]. Sodium and fluid restrictions will help reduce edema and hyponatremia, especially when used in conjunction with diuretics. Although lowering dietary lipids alone will not correct the observed hyperlipidemia, its effect on lipids is additive when used with statins. Finally, bicarbonate supplementation to correct metabolic acidosis may delay progression of kidney failure and improve nutritional status among patients with CKD [25].

Summary

Although the nephrotic syndrome may begin with severe proteinuria, it quickly becomes a multisystem disease. Despite the diverse causes of nephrotic syndrome, the common thread is massive urinary loss of proteins leading to an increased risk for cardiovascular disease, vascular thrombosis, anasarca, infection, nutritional depletion, and progressive kidney injury. Treatment is targeted at reducing the

proteinuria in order to prevent progressive kidney injury and to reduce the associated complications. Pharmacologic and dietary management of the nephrotic syndrome are complementary, with the mainstay of therapy being the use of ACEI or an ARB, alone or in combination with spironolactone, statin, and moderate protein restriction (preferably with plant or soy protein) to reduce proteinuria and hyperlipidemia, while waiting for immunosuppression to control the underlying cause.

References

1. Hull RP, Goldsmith DJA. Nephrotic syndrome in adults. BMJ. 2008;336(7654):1185–9.
2. Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Brenner BM, editors. Brenner and rector's the kidney. 9th ed. Amsterdam: Elsevier Saunders; 2011.
3. de Seigneux S, Martin PY. Management of patients with nephrotic syndrome. Swiss Med Wkly. 2009;139(29–30): 416–22.
4. Mundel P, Reiser J. Proteinuria: an enzymatic disease of the podocyte? Kidney Int. 2010;77(7):571–80.
5. Koomans H. Pathophysiology of oedema in idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2003;18 Suppl 6:vi30–2.
6. Rondon-Berrios H. New insights into the pathophysiology of oedema in nephrotic syndrome. Nefrologia. 2011; 31(2):148–54.
7. Doucet A, Favre G, Deschenes G. Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. Pediatr Nephrol. 2007;22:1983–90.
8. Bramham K, Hunt BJ, Goldsmith D. Thrombophilia of nephrotic syndrome in adults. Clin Adv Hematol Oncol. 2009;7(6):368–72.
9. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7:513–20.
10. Varizi ND. Molecular mechanisms of lipid disorders in nephrotic syndrome. Kidney Int. 2003;63(5):1964–76.
11. Kronenberg F. Dyslipidemia and nephrotic syndrome: recent advances. J Ren Nutr. 2005;15(2):195–203.
12. Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. Kidney Int. 1993;44:638–42.
13. Kaysen GA, de Sain-van, der Velden MG. New insights into lipid metabolism in the nephrotic syndrome. Kidney Int Suppl. 1999;71:S18–21.
14. Shearer GC, Kaysen GA. Proteinuria and plasma compositional changes contribute to defective lipoprotein catabolism in the nephrotic syndrome by separate mechanisms. Am J Kidney Dis. 2001;37(1 Suppl 2):S119–22.
15. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006;17:2974–84.
16. al-Bander HA, Martin VI, Kaysen GA. Plasma IgG pool is not defended from urinary loss in nephrotic syndrome. Am J Physiol. 1992;262(3 Pt 2):F333–7.
17. de Sain-van, der Velden M, de Meer K, Kulik W, et al. Nephrotic proteinuria has no net effect on total body protein synthesis: measurements with ^{13}C valine. Am J Kidney Dis. 2000;35:1149–54.
18. Castellino P, Cataliotti A. Changes in protein kinetics in nephrotic patients. Curr Opin Clin Nutr Metab Care. 2002;5:51–4.
19. Vaziri ND. Erythropoietin and transferrin metabolism in nephrotic syndrome. Am J Kidney Dis. 2001;38:1–8.
20. Bovio G, Piazza V, Ronchi A, Montagna G, et al. Trace element levels in adult patients with proteinuria. Minerva Gastroenterol Dietol. 2007;53:329–36.
21. Niel O, Thouret MC, Bérard E. Anemia in congenital nephrotic syndrome: role of urinary copper and ceruloplasmin loss. Blood. 2011;117(22):6054–5.
22. Shah KN, Yan AC. Acquired zinc deficiency acrodermatitis associated with nephrotic syndrome. Pediatr Dermatol. 2008;25(1):56–9.
23. Kraut JA, Madias ME. Consequences and therapy of the metabolic acidosis of chronic kidney disease. Pediatr Nephrol. 2011;26:19–28.
24. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. 2009;54:270–7.
25. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20(9):2075–84.
26. Wesson DE, Simoni J, Broglio K, Sheather S. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. Am J Physiol Renal Physiol. 2011;300(4):F830–7.
27. Wilmer WA, Rovin BH, Hebert CJ, Rao SV, et al. Management of glomerular proteinuria: a commentary. J Am Soc Nephrol. 2003;14:3217–32.

28. MacKinnon M, Shurraw S, Akbari A, Knoll GA, et al. Combination therapy with an angiotensin receptor blocker and ACE inhibitor in proteinuria renal disease: a systematic review of the efficacy and safety data. Am J Kidney Dis. 2006;48:8–20.
29. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GFM. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4:542–51.
30. Cortinovis M, Perico N, Cattaneo D, Remuzzi G. Aldosterone and progression of kidney disease. Ther Adv Cardiovasc Dis. 2009;3(2):133–43.
31. Fried LF. Effects of HMG-CoA reductase inhibitors (statins) on progression of kidney disease. Kidney Int. 2008;74:571–6.
32. Buemi M, Nostro L, Crasci E, Barilla A, et al. Statins in nephrotic syndrome: a new weapon against tissue injury. Med Res Rev. 2005;25(6):587–609.
33. Kaysen GA. Albumin metabolism in the nephrotic syndrome: the effect of dietary protein intake. Am J Kidney Dis. 1988;12:461–80.
34. Don BR, Kaysen GA, Hutchison FN, Schambelan M. The effect of angiotensin-converting enzyme inhibition and dietary protein restriction in the treatment of proteinuria. Am J Kidney Dis. 1991;17:10–7.
35. Walser M, Hill S, Tomalis EA. Treatment of nephrotic adults with a supplemented, very low-protein diet. Am J Kidney Dis. 1996;28:354–64.
36. Jenkins DJA, Kendall CWC, Marchie A, Jenkins AL, et al. Type 2 diabetes and the vegetarian diet. Am J Clin Nutr. 2003;78:S610–6.
37. Taku K, Umegaki K, Sato Y, Taki Y, et al. Soy isoflavones lower serum total and LDL cholesterol in humans: a meta-analysis of 11 randomized controlled trials. Am J Clin Nutr. 2007;85:1148–56.
38. Azadbakht L, Atabak S, Esmaillzadeh A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy. Diabetes Care. 2008;31:648–54.
39. Velasquez MT, Bhathena SJ. Dietary phytoestrogens: a possible role in renal disease protection. Am J Kidney Dis. 2001;37:1056–68.
40. Pedraza-Chaverri J, Barrera D, Hernandez-Pando R, et al. Soy protein diet ameliorates renal nitrotyrosine formation and chronic nephropathy induced by puromycin aminonucleoside. Life Sci. 2004;74:987–99.
41. Tovar AR, Murguia F, Cruz C, et al. A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome. J Nutr. 2002;132:2562–9.
42. Velasquez MT, Bhathena SJ, Ranich T, et al. Dietary flaxseed meal reduces proteinuria and ameliorates nephropathy in an animal model of type II diabetes mellitus. Kidney Int. 2003;64:2100–7.
43. Kaysen GA, al-Bander H, Martin VI, Jones Jr H, et al. Related branched-chain amino acids augment neither albuminuria nor albumin synthesis in nephrotic rats. Am J Physiol. 1991;260(2 Pt 2):R177–84.
44. Kaysen GA, Martin VI, Jones Jr H. Arginine augments neither albuminuria nor albumin synthesis caused by high-protein diets in nephrosis. Am J Physiol. 1992;263(5 Pt 2):F907–14.
45. Kim MJ, Frankel AH, Donaldson M, Darch SJ, et al. Oral cholecalciferol decreases albuminuria and urinary TGF-β1 in patients with type 2 diabetic nephropathy on established renin-angiotensin-aldosterone system inhibition. Kidney Int. 2011;80(8):851–60.

Chapter 21
Nephrolithiasis

Haewook Han and Julian L. Seifter

Key Points

- Identify the risk factors of kidney stones.
- Describe the types of diagnostic tests and their interpretation.
- Describe the medical and dietary treatments for different types of kidney stones.
- Identify methods for preventing recurrent kidney stones.

Keywords Nephrolithiasis • Kidney Stone • Hypercalciuria • Hyperoxaluria • Dietary risk factors of kidney stone • Prevention of recurrence of stone disease

Introduction

According to the most recent US statistics, the incidence of kidney stones is about 3–5 %, with the estimated cost of treatment more than $1.8 billion annually [1]. The incidence is at peak among white males age 20 and 30 years old. The National Health and Nutrition Examination Survey (NHANES) III reported that there was a 5 % prevalence of stone formation among adults in the United States and this is a 4 % increase from the NHANES II period (1976–1980) [2].

Kidney stones are more common in men than women (Table 21.1). Seventy-five percent of calcium stones are calcium oxalate (CaOx) or mixed, and 5 % are calcium phosphate (CaP) stones, as apatite or brushite. The latter are more frequently seen in females. Ten to twenty percent of stones are struvite or magnesium ammonium phosphate and these are related to chronic urinary tract infections (UTIs). Approximately 5 % of stones are uric acid and 1 % is cystine.

The prevalence of stones has increased in the past 30 years. According to epidemiologic studies the incidence is high for individuals with obesity and diabetes [3]. It has been postulated that obese people have more hypertension and type 2 diabetes, which impact stone formation especially uric acid [4, 5].

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Table 21.1 Type of stones

Type	Frequency (%)	Sex	Crystals	Radiography
Calcium oxalate/mix	75	M	Envelope	Round, radiodense, sharply outlined
Calcium phosphate (brushite)	5	F>M	Amorphous: alkaline urine	Small, radiodense, sharply outlined
Uric acid	5–15	M=F	Diamond; acid urine	Round/staghorn, radiolucent, filling defect
Struvite (Mg ammonium phosphate)	10–20	F	Coffin lid; infection/urea splitter	Staghorn, laminated radiodense
Cystine	1	M=F	Hexagon	Staghorn, radiodense

Courtesy from Dr. J. Seifter, Harvard Medical School, Renal Division Brigham and Women's Hospital, Boston

It is probably because patients with diabetes and obesity can produce more acidic urine which is more preferable for the stone formation. In addition, Lieske et al. [6] reported that obese patients who underwent bariatric surgery had a higher incidence of hyperoxaluria and an increased CaOx stone risk.

Recurrence is often seen with the absence of preventive treatments such as dietary modification and medications. The recurrence rate is 40–50 % after the first stone event and 50–60 % by 10 years. Cystinuria or primary hyperparathyroidism has higher recurrence rates secondary to prevalence of hypercalciuria. Ninety-seven percent of patients with recurrent stones have an identifiable cause such as hypercalciuria, hyperoxaluria, and hypocitraturia. Hypertension can increase stone risk for women but the mechanism is not known [7]. Few stone risks increase with decreased renal function [8].

Both inherited and environmental factors are risk factors for kidney stone formation and monogenic diseases such as cystinuria, Dent's disease, and primary hyperoxaluria are causes of hereditary kidney stone formation. The most important environmental factor for stone risk is diet.

Symptoms and Diagnosis [9]

Kidney stones may cause severe pain (renal colic) when the stone passes into the ureter. The pain is usually accompanied by nausea, vomiting, and hematuria. Patients may have urinary frequency and urgency. Symptoms quickly improve after passing the stone. These symptoms lead to emergency department visits and hospitalization. Initial evaluation includes non-contrast helical computerized tomography (CT), which can accurately visualize the size and location of the stones. A kidney, ureter, and bladder (KUB) film, though insensitive, can visualize calcium-containing, struvite, and cystine stones in the kidney or ureter, but uric acid stones are radiolucent and, therefore, they are not visualized. Complete ureteral obstruction and upper UTI are indications for stone removal by extracorporeal shock wave lithotripsy (ESWL) or surgery. Figure 21.1 shows some images of common stones.

Evaluation of New Stones

Basic evaluation of new stone includes two 24-h urine collections and patients are instructed not to change diet or fluid intake prior to urine collections to obtain accurate risks of types of stone formation. The 24-h urine analysis includes measurement of urine volume, urinary calcium, phosphorus, magnesium, oxalate, citrate, pH, uric acid, urea nitrogen, creatinine/kg, sodium, and potassium. Also measurement of blood tests such as serum sodium, potassium, bicarbonate, creatinine, calcium phosphorus, uric acid, and parathyroid hormone (PTH) levels are important to evaluate the stone risks. In addition, obtaining usual diet and fluid intake history should be conducted to evaluate different types of stone risks.

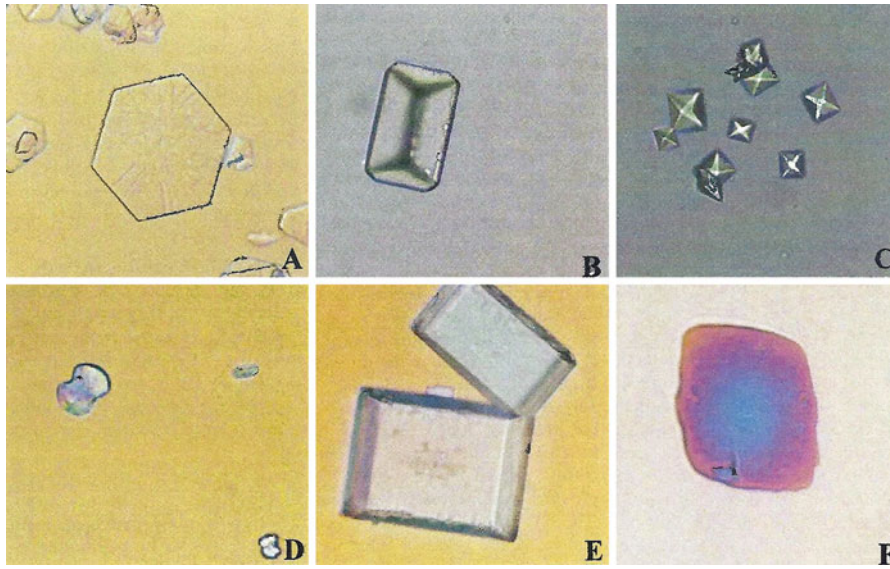

Fig. 21.1 Different type of kidney stones. Light microscopy of urine crystals. (**a**) Hexagonal cystine crystal (×200); (**b**) coffin lid-shaped struvite crystals (×200); (**c**) pyramid-shaped calcium oxalate dehydrate crystals (×200); (**d**) dumbbell-shaped calcium oxalate monohydrate crystal (×400); (**e**) rectangular uric acid crystals (×400); and (**f**) rhomboidal uric acid crystals (×400). From Asplin JR. Evaluation of the kidney stone patient. Seminars in Nephrology 28(2); 99–110, 2008. Reprinted with permission from John R. Asplin and Elsevier Limited

Evaluation of Recurrent Stones and Follow-up

After the first stone evaluation patients are advised to follow a specific diet and/or take medications for several months and are then reevaluated for stone risks. Usually one 24-h urine collection is done in 3–4 months after the first evaluation of stone formation. Then the patient is followed by 6–12 months if patient continues to have high risk of stones. Blood tests are not always recommended if patients have normal labs at the previous tests.

If patient has another episode of stone 2 years after last stone formation, patient is advised to have two 24-h urine collections as a new stone former. Table 21.2 shows the guidelines for evaluation of stones.

Stone Formation

Supersaturation (SS) and Stone Formation

Stone formation is a multistep process. Crystal formation occurs when the solute concentration in the urine exceeds its solubility product. The urine becomes supersaturated. Supersaturation means that the concentration of a stone forming salt, such as CaOx, exceeds its solubility in urine. In the supersaturated state, nuclei of substrate crystals are formed in a process called nucleation. When the nuclei begin to aggregate, crystals start to form and become stones. In the injured renal cells these crystals are retained. With low urine volume, supersaturation of calcium, oxalate, and uric acid promotes stone formation. The pH of urine is an important determinant of which type of stone precipitates. CaOx and

Table 21.2 Evaluation of stone disease

First stone	Recurrent stone and follow-up
Basic evaluation • Two 24-h urine analyses (no intervention prior to analyze stone risk): Ca, Phos, Mg, oxalate, citrate, uric acid, volume, creatinine, pH, urea nitrogen, Na, K • Blood tests: serum Na, K, CO_2, BUN, Cr, Ca, phosphorus, uric acid, and PTH • Usual dietary intake • Dietary/fluid intake history • Diet and medical treatment	• One 24-h urine analysis: Ca, Phos, Mg, oxalate, citrate, uric acid, volume, creatinine, pH, urea nitrogen, Na, K • Blood tests: serum Na, K, CO_2, BUN, Cr, Ca, phosphorus, uric acid, and PTH • Dietary and medical treatment

Adapted from Practice Guideline at Department of Nephrology, Harvard Vanguard Medical Associate
**If patient has recurrent stone after 2 years of last stone formation, two 24-h urinalyses are appropriate

uric acid stones are favorable in low pH but CaP stones are seen in high pH. Crystallization inhibitors such as citrate, nephrocalcin, uropontin, and magnesium can impede the nucleation, growth, and aggregation of crystals in vitro and have been in shown to interfere with the attachment to renal epithelial cells.

The following are steps of different stone formation. Levels of urinary supersaturation of different solutes are determinant and specific types of stones. Decreased supersaturation will decrease the risk of recurrence of kidney stone.

Steps

1. [CaOx] above which crystals start to form
2. Normal urine [CaOx] is 4× higher than solubility
3. When CaOx SS is 7–11× the solubility → ↑ nucleation
4. High urine Ca, urine Ox, low urine volumes → ↑ SSCaOx
5. Citrate forms soluble complex with Ca → low urine citrate → ↑ SSCaOx
6. Urine pH > 6.5 → ↑ proportion of divalent and trivalent phosphate ions → ↑ SSCaP
7. Nurclei, e.g., uric acid, can lower metastable limit and favor precipitation

Interpretation of Biochemical and Urine Tests

The 24-h Urine Collection

The best way to evaluate stone risk is the 24-h urine collection and analysis [10, 11]. Two 24-h urine collections are recommended for the initial evaluation [10, 11] for an accurate analysis and to determine variability. The 24-h urine collection should be several weeks after any procedures (i.e., 6–8 weeks after lithotripsy) in order to prevent or minimize risk of infection or the presence of bloods. Infection can change the pH and citrate levels. It is very important that patients continue with their usual diet and activities during the collection period. The 24-h urine creatinine excretion can give information about the adequacy of the urine collection. If 24-h urine collection is not accurate the urinary creatinine levels can be higher than normal for over-collection and lower than normal for

under-collection. In general, adult males produce 18–24 mg creatinine/kg/day and females 15–20 mg/kg/day [12].

The 24-h urine sample should include volume, calcium, phosphorus, oxalate, citrate, pH, and uric acid. These solutes provide an estimate of supersaturation and the risk of stone formation. Creatinine is tested to ensure full collection and to normalize solute excretion to the more constant amount of creatinine. Dietary factors include sulfates mostly from animal protein (the acid ash diet) and sodium since it relates to calcium potassium and magnesium excretion. Urea nitrogen is used to estimate protein catabolic rate (PCR), which in the out-patient setting is usually indicative of dietary protein intake. The relationship between urinary nitrogen appearance rate and estimated dietary protein intake is calculated (vide infra). The value of the 24-h urine is to evaluate dietary nutrients and fluid intakes and to provide guidance for management of an individual patient. For example, normal urinary calcium levels are <250 mg/day for men and <200 mg/day for women. High urinary calcium can be caused by idiopathic hypercalciuria, or diet high in sodium or protein. Low urinary calcium is probably caused by malabsorption or underline bone disease. Normal urinary oxalate level is 20–40 mg/day and high levels are due to high oxalate diet, increased endogenous production, high vitamin C consumption, and inflammatory bowel disease (IBD). Normal urinary citrate levels are >450 mg/day for men and >550 mg/day for women. High animal protein diet or renal tubular acidosis (RTA) which can increase acid production affect urinary pH with lowering citrate levels. If 24-h urine has 1000 ml(1L) volume, with urinary calcium (>250 mg), urinary oxalate (60 mg), urinary sodium (200 mEq), urinary citrate (45 mg), pH of 5.2, and PCR of 2 g/kg, this analysis can predict that the patient has low fluid intake, with high protein and high sodium diet which increase the risk of CaOx stone or uric acid stone. Table 21.3 provides a summary of the normal values of the 24-h urine collection and causes of abnormal values.

Table 21.3 Normal values of 24 h urinalysis

	Normal value	Cause of abnormal values
Ca	<250 mg/day for males <200 mg/day for females	↑ Idiopathic hypercalciuria, high Na diet (high urine Na) high protein diet ↓ With bone disease
Phosphorus	0.6–1.2 g/day	↓ With bowel disease, malnutrition, ↑ with large amount of food intake
Mg	30–120 mg/day	↓ With some laxatives, malnutrition, malabsorption
Oxalate	20–40 mg/day	↑ With high oxalate diet, high vitamin C consumption, if >80, intestinal (inflammatory bowel disease) or oxalosis
Citrate	>450 mg/day males >550 mg/day females	↓ RTA, hypokalemia, high animal protein diet, acidosis, diarrhea
Uric acid	<0.8 g/day males <0.75 g/day females	↑ With high animal protein diet (high purine), alcoholic beverages, overproduction
Volume	>2,000 mL/day	↓ With low fluid intake
pH	5.8–6.2	↓ RTA, urea splitting infection, acidosis, high animal protein intake (high purine content) ↑ Vegetarian diet, high citrus consumption, soft drink
Na	50–150 mEq/day (1,150–3,450 mg)	↑ With high Na diet ↓ With bowel disease
K	20–100 mEq/day	Less than 20 (< 20), Bowel disease, diuretics, laxatives
Cl	70–250 mEq/day	
Urea nitrogen	6–14 g/kg/day	↑ With high protein diet
PCR	0.8–1.4 g/day	↑ With high protein diet
Sulfate	20–80 mEq/day	↑ With high protein diet
Ammonium	15–60 mM/day	↑ pH >7 urea splitting infection, ↓ pH <5.5 CRI, UA stones, gout
Cr/kg	18–24 mg/kg for males 15–20 mg/kg for females	↑ With more than 24 h collection ↓ With under-collection

Range: courtesy from Litholink Corporation, Chicago, IL
RTA renal tubular acidosis, *CRI* chronic renal insufficiency, *UA* uric acid, *Cr* creatinine

Table 21.4 Risk factors of various types of kidney stones

Hereditary and other disease-related		Environment	
Genetic	Idiopathic hypercalciuria	Climate	Heat
	Hyperoxalosis		Water loss, sweating
	Cystinuria: Dent's disease		
Kidney disease-related	Medullary sponge kidney	Dietary	Na
	PKD (10 % develop stones)		Oxalate
	Horseshoe		Protein (animal)
	Metabolic causes: hypercalcemia, hyperparathyroidism, DM, and obesity		↓Acid/alkaline ash diet
			Fluid
			Fluid Excess vitamin (C, D)
Systemic disease	GI, inflammatory bowel diseases (Ox and UA stones)		Vitamins (C, D)
Hyperparathyroidism	CaP stone		Ca supplement
Renal tubular acidosis (RTA)	Hypercalcemic states, Ca phosphate		Low Ca diet
Sarcoid	Hypercalciuria, CaOx stone		High protein weight loss diet

PKD polycystic kidney disease, *DM* diabetes mellitus, *GI* gastrointestinal, *Ox* oxalate, *UA* uric acid, *CaP* calcium phosphate, *CaOx* calcium oxalate

Table 21.5 Conditions favoring development of various kidney stones

Factors	Functions
Increased urinary crystalloids	Form nucleus on existing surface
	Supersaturated urine
Decreased inhibitors	Magnesium (complexes with oxalate)
	Citrate (complexes with calcium)
	Nephrocalcin, uropontin
	Tamm Horsfall
Increased promoters	Uric acid
Dehydration	Low urine volume, supersaturated urine
Urine pH	Alkaline → Ca phosphate
	Acidic → uric acid, cystine
Diet	High protein/sodium/Ca → hypercalciuria uricosuria, oxaluria
	High oxalate → oxaluria
Medication	Furosemide: decrease volume
	Na bicarbonate: increase urinary Ca

Risk Factors for Kidney Stone

Risk factors for stone formation may be hereditary or disease-related, such as idiopathic hypercalciuria, hyperoxalosis Dent's disease, medullary kidney disease, polycystic kidney disease, hyperparathyroidism, IBD, RTA, or sarcoidosis. Patients with a family history of nephrolithiasis have a 2.5 times greater risk of stone formation [13]. Other risk factors include environment and diet (Table 21.4). Table 21.5 shows the conditions that favor stone formation.

Urinary crystalloids can form nucleus on the existing surface and supersaturate urine. Low urinary magnesium causes decreased complex formation with urinary oxalate allowing free oxalate to be

more available in the urine. Low urinary citrate also increases stone formation because citrate forms a complex with calcium so free calcium is more available for stone formation. High concentration of uric acids in the urine will promote the nuclei to start stone formation. If the patient is dehydrated, the patient will have low urine output and therefore the urine can be supersaturated. Urine pH is very important for the formation of some type of stones; low urine pH is favorable to form CaOx and uric acid stones, and high urine pH promotes CaP stone formation.

Diet causes increased risks of various stones. High sodium intake increases urinary calcium excretion. High oxalate diet and large dose of vitamin C supplement will increase urinary oxalate level. High protein diet can increase urinary calcium, decrease urine pH, and also increase urinary uric acid level. Therefore, high protein diet can increase CaOx and uric acid stone risks. Diuretics, such as furosemide, can induce dehydration which can increase risk of supersaturation of solutes.

Environmental conditions such as heat may increase non-renal evaporative skin losses, and by reducing urine volume therefore increase stone risk [14, 15]. The most challenging aspect of increasing fluid intake is that patients cannot wait for the normal thirst mechanism to drink because the hypothalamic–pituitary sensors/neurons lead to increased antidiuretic hormone levels; therefore, the urine becomes more concentrated before the thirst mechanism is triggered. One patient education method used is to remind people to drink fluid after each void.

Urine Volume

As discussed earlier, the urine needs to be supersaturated with solutes to form a crystal, the first step to form a stone. With low urine volume, the urine can be easily supersaturated with various solutes, calcium, oxalate, phosphorus, and uric acid. In addition, there are several inhibitors to prevent crystallization of these solutes. These inhibitors are present in the urine under normal conditions. If the supersaturation is very high the crystallization starts. The most direct way for the patients to decrease supersaturation is to increase the urine volume with oral fluids. However, some fluid should be avoided such as highly concentrated fructose, which may have an opposite effect on stones. It is advised to achieve an excess of 2.5 L/day of urine volume.

Hypercalciuria

Normal urine calcium excretion is less than 200–250 mg/24 h [12]. If urine calcium excretion is higher than normal, the stone risk increases. To evaluate the stone risk, measure serum calcium, urinary calcium, oxalate, urine urea nitrogen (UUN), citrate, magnesium, creatinine, and volume (Table 21.2). In patients with idiopathic hypercalciuria, the serum calcium level is normal but urinary calcium is high because of increased absorption of calcium from the gastrointestinal tract. The increased absorption of calcium will increase the ionized calcium level, decrease PTH secretion, and decrease renal tubular reabsorption of calcium. There is also evidence of reduced proximal tubular reabsorption of sodium and calcium in patients with idiopathic hypercalciuria [16]. This condition will lead to a negative calcium balance. Figure 21.2 shows the model of idiopathic hypercalciuria.

The combination of a low sodium diet and thiazide diuretics may lower urinary calcium excretion by increasing reabsorption of calcium. Thiazide diuretics are not effective with a high sodium diet. It can cause volume depletion, which will lead to hypokalemia and an increased risk of stone formation by hypocitraturia.

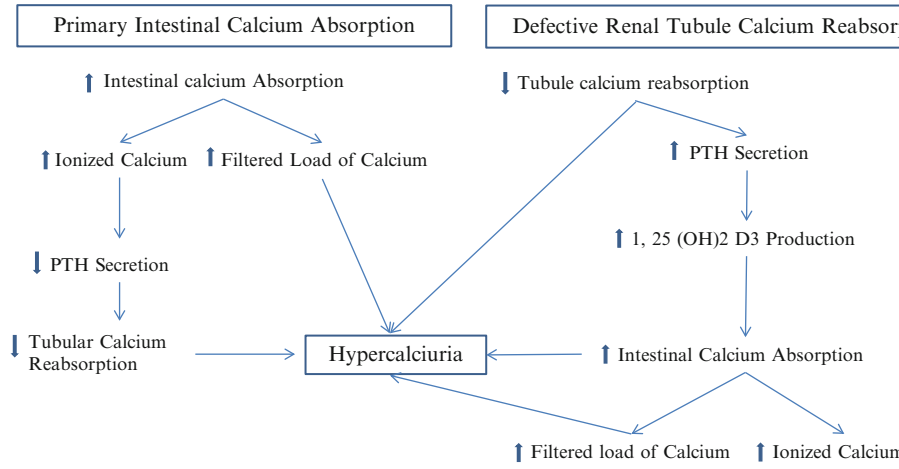

Fig. 21.2 Model of idiopathic hypercalciuria

Hyperoxaluria

The most common type of stone is CaOx (75 %) and a high urinary excretion of oxalate is a risk factor for CaOx stones. Dietary sources of oxalate include spinach, rhubarb, beets, and some berries. Oxalate is also created from endogenous sources such as metabolism of glycine, hydroxyproline, and ascorbic acid. A low oxalate diet is recommended for the prevention of CaOx stones; however, a recent study showed that dietary oxalate has little effect on urinary oxalate excretion but vitamin C has a high correlation with urinary oxalate excretion [17]. Increased urinary oxalate excretion has also been noted in patients with diabetes [18]. Patients with IBD have a high prevalence of CaOx stones with hypocalciuria due to negative calcium balance. The negative calcium balance with decrease in blood calcium level can also cause secondary hyperparathyroidism; therefore, a calcium supplement would be effective for preventing CaOx stone risk. The timing of calcium supplements is important and patients should take supplements at the meal time to bind oxalate from dietary sources. Individuals who had bariatric surgery have a high risk of hyperoxaluria due to malabsorption and increased absorption of oxalate, which may increase hyperoxaluria [19]. Recent studies by Jiang et al. and Kaufman et al. suggested that enteric colonization with *Oxalobacter formigenes*, which uses oxalate as a main energy source, reduces the risk of CaOx stone recurrence among individuals who had low calcium intake [20]. However, there is insufficient evidence to support the use of probiotics to reduce stone risk at this time.

Hypocitraturia

The urine usually has a supersaturation of solutes especially CaOx; however, the level tends to be greater than 10 times the concentration to form the CaOx crystals. This is due to the presence of citrate in the urine. Citrate in urine binds with urinary calcium to form a soluble compound and increases urine pH. CaOx stone formation is favorable in low urine pH; therefore, citrate can help prevent CaOx stone formation. RTA and chronic diarrhea can also cause decreased citrate in the urine. The normal value of urinary citrate for males is >450 mg/day and for females >550 mg/day [12] (Table 21.3). The most common form of citrate prescription is potassium citrate. However, calcium, oxalate, and urine pH should be checked before initiation of citrate treatment. If urine pH increases with citrate treatment, there is a risk of CaP stone formation. In patients who have IBD with high urinary oxalate, and

low urinary sodium level because of malabsorption and gastrointestinal loss of sodium, sodium citrate is more beneficial than potassium citrate. However, sodium citrate can increase urinary calcium excretion; therefore, it may increase the risk of CaOx stones.

pH

Urine pH is an important factor in the formation of kidney stones. A low urine pH can promote CaOx and uric acid stones, and a high urine pH can increase the risk of CaP stones. Urine pH is affected by acid- and alkaline ash from the diet. The mineral salt that predominates in foods determines whether the residue is acidic or alkaline. The minerals producing alkaline are sodium, potassium, magnesium, and calcium. Acid-forming minerals are sulfur, chlorine, and phosphorus. High animal protein diet which has high purine content and sulfa can reduce pH and will lead to an increased risk of uric acid stones. An alkaline ash diet which is high in citrate, mostly from fruits and vegetables, can increase urine pH and citrate excretion. Alkaline ash diet is preferable for the certain type of stone risk; however, a high pH without alkali therapy may increase the risk of struvite stones from a UTI (see Table 21.7 for examples of acid and alkaline ash foods).

Uric Acid

The determinant of uric acid stones is urine pH. A low urine pH has more insoluble uric acids concentration; therefore, the risk of uric acid stone is higher. The prevalence of uric acid stones is about 5 % of total kidney stone disease. Measurements of urinary calcium, uric acid, and post-prandial urine pH are used to assess the uric acid stone. The average adult consumes about 2 mg of purine/kg/day, which produces 200–300 mg of uric acid daily. Endogenous production is about 300 mg/day. In some studies, uric acid excretion is 5.6 mg/kg/day [21] and total excretion of uric acid is less than 800 mg/day. Dietary consumption of purine varies daily by individuals. Kessler et al. conducted a cross-sectional study by using bicarbonate-rich mineral water and various types of juices on uric acid stone formation. They found that black current juice decreased uric acid stone risk by increasing the urine pH [22, 23]. Ingestion of alcohol can also affect urinary uric acid excretion. If patients have gout allopurinol is usually prescribed along with low purine diet to reduce blood uric acid and uricosuria [21, 24]. Table 21.6 summarizes the management of the kidney stones.

Table 21.6 Management of all types of kidney stones

Abnormality	Evaluate	Management
Hypercalciuria	Urine Na and urea nitrogen	Na, protein restriction, thiazide, NOT LOW Ca DIET
Hypercalcemia	PTH, ionized Ca, vitamin D, malignancy, thyroid, bone disease, etc.	Parathyroidectomy, treat underlying disorder
Hyperoxaluria	Dietary oxalate, low dietary Ca, vitamin D, sweeteners, ileal disease, gastric bypass, ethylene glycol, enzyme deficiencies	Restrict oxalate, supplement magnesium, Ca, pyridoxine, cholestyramine
Hypocitraturia	Urinary citrate, serum potassium (K), creatinine, malabsorption, RTA, acetazolamide	Alkali (potassium citrate), sodium citrate if volume deplete
Hyperuricosuria	Dietary purines	Purine restriction, allopurinol, alkali
Acid urine (pH)	Exclude chronic diarrhea, gout, ileostomy	Alkali (potassium citrate)
Low urine volume	24 h urine volume	At least 2.5 L fluid intake

PTH parathyroid hormone, *RTA* renal tubular acidosis

Table 21.7 Acid ash and alkaline ash foods

Acid ash foods		Alkaline ash foods	
Meat	Meat, fish, fowl, shellfish, egg	Dairy	Milk and milk products
Dairy and other protein	All types of cheese		Butter milk
	Peanut butter		
	Peanuts		
Fat	Bacon, nuts (Brazil, filberts, walnuts)	Fat	Nuts (almonds, chestnuts, coconuts)
Starch	All types esp. whole wheat	Vegetables	All types except corn and lentils
	Crackers, cereal, macaroni, spaghetti, noodle, rice		Beets, beet greens, Swiss chard, dandelion greens, kale, mustard greens, spinach, turnip greens
Vegetables	Corn, lentils		
Fruits	Cranberries, plums, prunes	Fruits	All types except cranberries, plum, and prunes
Desserts	Plain cakes, cookies	Sweets	Molasses

Modified from Krause's Food, Nutrition & Diet Therapy, 12th Ed., Saunders, p. 952, 2008

Dietary Factors

Several dietary factors can increase risk of the stone formation. Dietary sodium, protein, potassium, calcium, magnesium, and other nutrients are discussed. These dietary factors can be modified depending on the types of different stone risks. Foods that produce acid ash after being metabolized in the body can affect the lowering of urinary pH and alkaline ash foods can increase urinary pH. These specific diets are used based on urine pH, urinary uric acid, and types of stones (Table 21.7).

Sodium

Several studies have shown that dietary sodium restriction alone decreases urinary calcium excretion [25]. Proximal tubular calcium reabsorption is increased with a low sodium diet (2,000–3,000 mg/day) and it decreases the SSCaOx. In addition of thiazide diuretics, calcium reabsorption is enhanced and further decreases hypercalciuria. However, addition of thiazide can lead to volume depletion and ion exchange and volume status will come to the steady state in a few days. If the patient continues to consume a high sodium diet, sodium will reach the distal nephron and increase the excretion of calcium and potassium along with citrate resulting in a change in the urinary pH that will eventually increase the risk of stone formation. Therefore, after analyzing the 24-h urine, a low sodium diet will help in appropriate thiazide use for patients with CaOx stones. The patients with IBD usually have low urinary sodium levels and low urinary citrates. Therefore, use of sodium citrates instead of potassium is beneficial to improve fluid status from gastrointestinal losses and increase urine volume.

Potassium

Potassium is abundant in most fruits and vegetables. However, if the patient has low urinary citrate and low urine pH, potassium citrate is commonly used to improve hypocitraturia. Monitoring 24-h urinary excretion of potassium is important to evaluate compliance to diet and medications. Taylor et al. analyzed the 24-h urine with the Diet Approaches to Stop Hypertension (DASH) diet and found that with a higher DASH score there was a decreased risk of stone formation. Because high DASH score foods are high in potassium, Mg, and phosphorus, these may increase urine pH, resulting in decreased SSCaOx and uric acid in urine as well as increased urine volume and citrate [26, 27]. If patients have chronic kidney disease and take angiotensin converting enzyme inhibitors (ACEI) as antihypertensive medication, serum potassium level should be monitored closely.

Protein

There are few markers in 24-h urinalysis to evaluate dietary protein intake, production, and excretion. Ammonium (NH_4) level should be low in patients who take alkali therapy or who present with RTA. Monitoring citrate, which is the indicator of urine acidity, can identify these problems. High ammonium and sulfate are indicators of a high protein diet, especially animal protein [4]. Also, a high protein diet (≥1.5 g/kg/day) can reduce urine pH; therefore, a moderate to low protein diet should be advised (0.8–1.4 g/kg/day). Patients who take alkali therapy especially with low citrate level have low urinary ammonium with higher pH; therefore, the risk of uric acids or CaOx can be decreased. Urea nitrogen appearance (UNA) and PCR are measurements of daily protein intake and they are calculated to kg body weight. In a normal healthy steady state, intake of protein can be equivalent to protein catabolism; therefore, PCR determines the nitrogen balance from 24-h urine urea concentration:

$$\text{PCR} = [6.25(\{24\text{h urea N}\} + \{0.031 \times \text{weight}\})] / \text{weight}$$

Patients who have acute or chronic infection are usually malnourished and catabolism occurs. Therefore, this formula should not be used to evaluate protein intake. For patients without active stress of illness, the PCR can guide protein recommendations for patients to prevent further stone risks.

Currently, most common weight loss diet promotes large amount of protein and this is not recommended for the patients who have a history of kidney stones. This diet regimen increases hypercalciuria, lowers pH of urine, and increases uric acid levels, which increase kidney stone risk. Massey et al. conducted a study to monitor the effect of stone risk in beef vs. plant protein and concluded that a moderate amount of protein intake had the same effect in reducing CaOx stone risk [28]. The amount of protein seems to be a more important factor in that study. Recently, an epidemiological study showed that animal protein intake was not independently associated with the incidence of nephrolithiasis among a large cohort of postmenopausal women [29]. However, the evaluation of stone risk is varied by individuals and complicated. Therefore, the recommendation of protein intake remains the same until there is scientific evidence.

Calcium

Approximately 20 % of dietary calcium is absorbed under normal conditions. There is substantial evidence that a higher calcium diet is associated with a lower stone formation. The higher calcium intake will bind oxalate in the gut if it is consumed with meals; therefore, oxalate absorption is reduced. Patients who consumed a diet with a normal calcium intake (i.e., 1,200 mg/day) plus a low animal protein intake had a 51 % lower incidence of recurrent stones than patients who consume 400 mg calcium diet [30]. Although data on calcium supplements is not effective in reducing stone risk, taking calcium supplement with meal is beneficial because calcium can bind with the dietary oxalate not to be absorbed.

Magnesium

Magnesium forms a complex with oxalate and decreases SSCaOx in the urine, which can reduce the risk of stone formation [26, 27]. The DASH diet, which is high in Mg, showed a decrease in stone risk by increasing pH and lowering SSCaOx [26, 27]. Magnesium can also bind with oxalate in the gastrointestinal tract to reduce oxalate absorption; however, a magnesium supplement is not recommended especially for patients with chronic kidney disease. Decreased urinary magnesium may be a sign of malabsorption, malnutrition, small bowel disease, or laxative abuse. Hypomagnesemia is not a risk factor for stone formation.

Vitamin C

Vitamin C is metabolized to dehydroascorbic acid, then converted to oxalate which is then excreted in the urine; therefore, a high vitamin C intake can be a risk for stone formation by increasing endogenous oxalate. A recent observational study showed that consumption of more than 1,000 mg/day vitamin C is associated with a 40 % higher risk of stone formation in men than in those who consumed the Dietary Reference Intake (DRI) for vitamin C [31].

Other Dietary Factors

Citrate consumption can increase urine pH, which increases citrate concentration in the urine. Citrate also decreases SSCaOx due to its capacity to form a complex with calcium ions and inhibit crystallization of CaOx [32]. However, citrate may increase the risk of CaP stones. A clinical trial conducted by Koff et al. by using potassium citrate and lemonade for 21 stone patients found that potassium citrate increased urine pH with increased urinary citrate level but lemonade did not have an effect on urinary pH or citrate levels except for increasing urine volume [33].

Phytates are found in whole grains and legumes and they can inhibit CaOx stone formation. Some studies have shown an inverse correlation with phytate intake and the risk of kidney stone formation in women [34–37].

Nutrition Assessment and Recommendation

Quantified dietary assessment is very important to treat and prevent stone formation. The dietitian should evaluate dietary intakes of calcium, oxalates, sodium, protein (both animal and plant), dietary supplements, and fluid intake that can either promote or inhibit stone formation.

There are several dietary assessment methods: the 24-h recall, food record, diet history, and food frequency questionnaire. The dietary intakes reflect on the urinalysis and it is good way to evaluate the causes of kidney stones and to prevent recurrence. The food records provide information on intake of foods, beverages, and dietary supplements over specific periods. The most appropriate diet assessment for kidney stones is the food record during a 24-h urine collection, 1–2 days before the collection. The food record should be analyzed to evaluate intakes of protein, sodium, potassium, calcium, phosphorus, magnesium, uric acid, oxalate, and fluid. Based on the food intake and urinalysis, the clinicians can provide the adequate medical and diet treatments. Table 21.8 has dietary recommendation to prevent kidney stones.

Common Mistakes

Practical Rule of Thumb

- Do not discuss risks in general BEFORE the DATA (24-h urinalysis)
  - People make stones for different reasons.
  - Too long and irrelevant lectures: there are different types of stone risks and some individuals like to follow diet to prevent all types of stones which can lead to inaccurate stone risk analysis.

Table 21.8 Dietary recommendation to prevent the kidney stones

Nutrients	Recommendation
Ca	800–1,200 mg/day
Oxalate	40–50 mg/day
Na	2,000–3,000 mg/day
Protein	0.8–1.4 g/kg/day
Fluid	>2.5 L/day
Vitamin D	Low dose if vitamin D insufficiency or deficiency (1,000 IU/day)
Vitamin C	Dietary reference intake (DRI)

Taylor, EN, Curhan, GC: Diet and fluid prescription in stone disease, Kidney Int. 70:835–839, 2006
National Kidney Foundation: Diet Guidelines for Kidney stone. Litolink Corp, Chicago IL

  - There may be bias when the patients collect the urine. This should be done without changing the diet and fluid intakes. Patients often have unnecessary restrictions of their diet, which have effects on the cause of stone risks.

- Mistake of treating without data
  - Prescribing thiazide without low Na diet, or with low urine Ca:

    24-h urine analysis performed before prescribing thiazide. If patient has high urinary Na with elevated Ca levels, a low Na diet should be instructed first. High Na diet can increase urinary Ca; therefore, diet therapy should start first.
    If thiazide is prescribed without low Na diet, patient can have polyuria until body reaches steady state with hypokalemia which can lower citrate level in the urine, which then lowers pH and eventually increases SSCaOx.

  - Prescribing citrate without knowing Ca and pH.

    Citrate will increase urine pH; therefore, urinary Ca and pH should be evaluated first. If patient has high urinary Ca with normal pH and citrate is prescribed urine pH will go up to alkaline level which will increase risk of CaP stone.

- Use of allopurinol for gout and stone risk
  - Allopurinol is commonly used for treatment of gout. However, it can lower blood uric acid level by increasing urinary uric acid. If a patient is taking allopurinol, a low purine diet should be prescribed and also urine pH should be monitored to prevent uric acid stone.

- Using sodium citrate instead of potassium citrate
  - If the patient has GI (gastrointestinal) problem such as IBD, the patient often has GI loss of Na, low volume status, and high oxalate absorption which leads to increased risk of CaOx stone. When the patient has low urine output, low urinary Na and high urinary oxalate with low urine pH sodium citrate is a better choice than potassium citrate to increase pH and Na status which will improve volume status.

- Low urinary Ca
  - If the patient has low urinary Ca level, it may decrease the risk of Ca stone but the patient should be evaluated for negative Ca balance or bone disease.

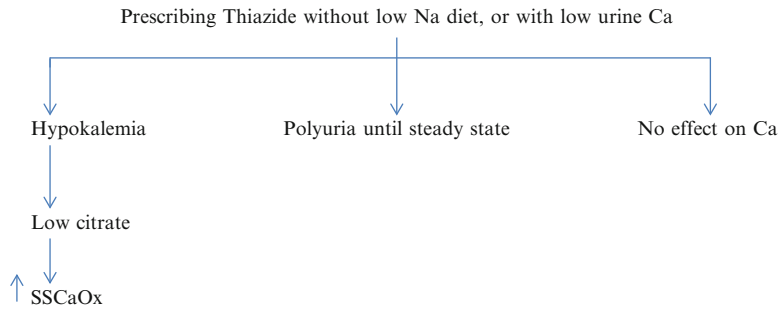

Fig. 21.3 Prescribing thiazide without low Na diet or with low urine Ca

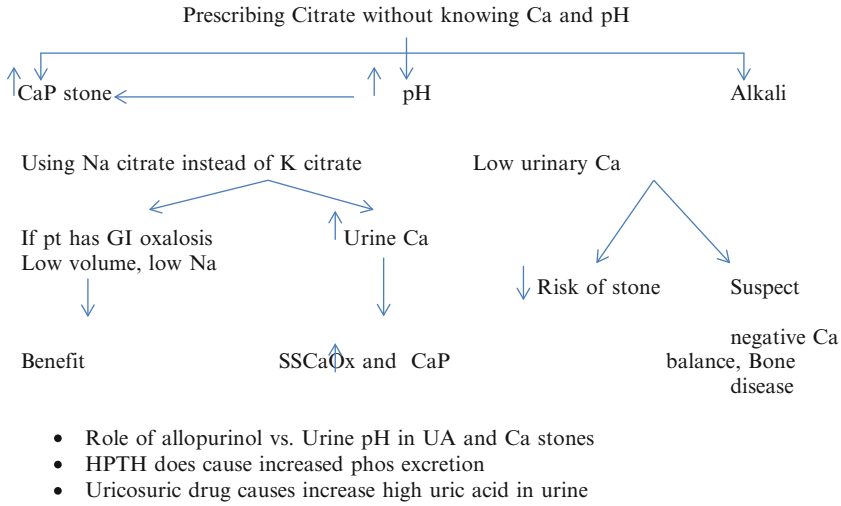

Fig. 21.4 Prescribing citrate without knowing Ca and pH

- Role of allopurinol vs. urine pH in UA and Ca stones
- HPTH does cause increased Phos excretion
- Uricosuric drug causes increase in uric acid in urine (Figs. 21.3 and 21.4)

Diet Recommendation for Kidney Stones (adapted from the Nephrology Department of Harvard Vanguard Medical Associates).

General Recommendations

- Drink plenty of fluid: 3 L/day
  - Any type of fluids except grapefruit juice
  - Water, coffee, and lemonade have shown beneficial effect
  - Produce less concentrated urine with good volume (at least 2 L/day)
- Avoid foods with high oxalate (see Table 21.9)

Table 21.9 Oxalate (mg/100g: 3.5 oz) content of foods

Foods (3.5 oz)	Oxalate (mg)
Flours & Mills	
Barley flour	56
Buckwheat flour	269
Corn meal	54
Rice flour, brown	37
Rye flour, dark	51
Semolina flour	48
Soy flour	183
Wheat flour, white unbleached	40
Wheat flour, whole	67
Wheat Germ	269
Fruits	
Bitter melon, raw	71
Papaya raw	5
Green goose berries	88
Black berries	19
Blueberries, strawberries, red raspberries	15
Black raspberries	55
Concord grapes	25
Currents	19
Lemon peel	83
Lime peel	110
Rhubarb	800
Nuts	
Almonds, roasted	469
Cashews, roasted	262
Hazelnuts, raw	222
Macadamia nuts, raw	42
Peanuts, raw	142
Pecans, raw	64
Pine nuts, raw	198
Pine nuts, roasted	140
Pistachio nuts, roasted	49
Soy nuts (1 oz)	392
Walnuts, raw	74

Foods (3.5 oz)	Oxalate (mg)
Seed containing Vegetables	
Cucumber, raw	20
Eggplant, raw	190
Eggplant, green, long, raw	55
Okra, raw	50
Pepper, raw	40
Snap beans, raw	360
Squash, raw	20
Tomato, raw	50
Yard long beans, green, raw	38
Legumes (beans & Peas)	
Anasazi beans, boiled	80
Azuki beans, boiled	25
Black beans, boiled	72
Cowpeas (blackeye peas), boiled	4
Gabanzo beans, boiled	9
Great northern beans, boiled	75
Kidney beans, red cooked	16
Lentils, boiled	8
Lima beans, large, boiled	8
Navy beans, boiled	57
Peas, green, split, boiled	6
Peas, raw	50
Peas, yellow, split, boiled	5
Pink beans, boiled	75
Pinto beans, boiled	27
Red beans, boiled	35
Soybeans, boiled	56
White beans, small boiled	78
Stem & Stalk Vegetables	
Asparagus, raw	130
Broccoli, raw	190
Cauliflower, raw	150
Celery, raw	190

Foods (3.5 oz)	Oxalate (mg)
Leafy Vegetables	
Amaranth leaves, raw	1090
Beet leaves, raw	610
Brussels sprouts, raw	360
Cabbage, green raw	100
Chicory, raw	210
Chinese cabbage, raw	6
Chinese, kale, raw	23
Chives, raw	1480
Collards, raw	450
Coriander, raw	10
Endive, raw	110
Kale, raw	20
Leek	89
Lettuce, raw	330
Parsley, raw	1700
Purslane, raw	1310
Spinach, raw	970
Turnip greens, raw	50
Watercress, raw	310
Tuber & Root Vegetables	
Beetroot, boiled	675
Carrot, raw	500
Cassava root, raw	1260
Parsnip, raw	40
Potato, raw	50
Radish, raw	480
Rutabaga, raw	30
Sweet potato, raw	240
Turnip, raw	210
Other Vegetables	
Corn, sweet, raw	10
Garlic, raw	360
Onion, raw	50
Miscellaneous Foods	
Black pepper	419
Chocolate	117
Cocoa powder	623
Indian tea (1C)	72
Soy protein	496
Soy yogurt	113
Soybean cracker	207
Tofu	275

- Spinach, berries, chocolate, wheat bran, nuts, beets, tea, and rhubarb should be eliminated from the diet

- Avoid extra calcium supplements
  - Calcium supplement should be individualized after 24 h urine calcium level and other risk factors are analyzed

- Avoid high protein diet
  - With high protein intake, kidney will excrete more calcium; therefore, it will form more stones in the kidney

- Avoid high salt diet
  - Blood pressure control is important for stone formation and high salt diet can lead to high blood pressure

- Avoid high dose of vitamin C supplement
  - Recommend to take 60 mg/day (US Dietary Reference Intake)
  - Excess amount (1,000 mg/day) may produce more oxalate in the body (Table 21.9)

Summary

The majority of nephrolithiasis patients have recurrent kidney stones throughout their lifetime. The risk of recurrence is varied by individuals; however, multiple 24-h urine collections provide information on specific risk factors of the individual which can be treated and prevent recurrence in the future. Dietary factors play a very important role in the formation of kidney stones and dietary modification can reduce the risk of recurrence. An increase in fluid intake to produce more than 2 L of urine output is the most important factor in preventing the recurrence of stones. Other dietary modifications include a moderate protein, low oxalate, low sodium diet, and an adequate amount of dietary calcium. In addition, appropriate medical treatment of thiazides and citrate will be helpful to prevent further stone formation. The dietary and medical interventions should be based on multiple 24-h urine collections.

Case Studies

Case #1 (Table 21.10)

Table 21.10 The following 24-h urine values were observed in a 45-year-old man

	Volume	Ca	Oxalate	Citrate	Uric acid	pH	Creatinine	Na	Phos	NH_4
Results	2.006	364 mg	77 mg	1,278 mg	1.806 g	5.1	3,040 mg	426 mEq	1.5 g	108 mM
Ref value	>2 L	<250	<40	200–1,000	<0.8	5.8–6.2		<150	<1.2	<60

Table 21.11 A 45-year-old woman is referred for recurrent oxalate stone formation

	Vol	SSCaOx	Ca	Ox	Cit	SSCa	UpH	SSUA	UA
Results	1.52	10.04	40	143	23	0.09	5.5	0.53	0.202
Ref value	>2	6–10	<200	20–40	>550	0.5–2	5.8–6.2	0–1	<0.75

The above is her 24-h urine result

1. What type of stone does this patient have?

   (a) Calcium oxalate
   (b) Uric acid
   (c) Struvite
   (d) Cysteine

Answer: B

- The answer is B. Uric acid stone
- Uric acid level is very high with low pH.

2. What would be the preferred treatment strategy?

   (a) Allopurinol
   (b) Na citrate
   (c) K citrate and increase urine volume to 2.5 L
   (d) Na and protein-restricted diet
   (e) Thiazide diuretics

Answer: D

- The answer is D. Sodium and protein-restricted diet.
- The patient has large excretion rate of sodium which will increase urinary calcium excretion.
- High protein intake is suggested by the elevated ammonium, uric acid, phosphate in the urine as well as suggested by the high creatinine excretion.
- One would need to confirm that this is not an over-collection.

Case #2 (Table 21.11)

1. What is the likely cause of her disorder?

   (a) Renal tubular acidosis is resulting in hypocitraturia
   (b) Dietary excess of nuts, chocolate, and berries
   (c) Hyperparathyroidism
   (d) Crohn's disease
   (e) Oxalosis

Answer: D

- The answer is D. Crohn's disease with secondary hyperparathyroidism, causing low urinary calcium excretion.
- There is low citrate, high oxalate, and low volume in this intestinal malabsorptive condition.
- RTA does not explain increased urine oxalate.
- Nuts, etc. do not explain degree of hyperoxaluria.
- Oxalosis does not explain low U citrate and low urine calcium.

2. The preferred treatment for the same patient would include all but which of the following:

   (a) Na citrate
   (b) Ca supplementations with meals
   (c) Cholestyramine
   (d) K citrate
   (e) Dietary oxalate restriction

Answer: D

- The answer is D. K citrate is not ideal.
- In this case of volume depletion associated with intestinal disorders, alkali therapy with sodium salts is preferable as it may increase the extracellular volume and urine output.
- Restrict dietary oxalate.
- Use cholestyramine to bind intestinal oxalate.
- Calcium with meals binds intestinal oxalate.

References

1. Lipkin ME, Preminger GM. Demystifying the medical management of nephrolithiasis. Rev Urol. 2011;13:34–8.
2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int. 2003;63:1817–23.
3. Curhan GC, Willett WC, Rimm EB, Speizer FE, Stampfer MJ. Body size and risk of kidney stones. J Am Soc Nephrol. 1998;9:1645–52.
4. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. J Am Soc Nephrol. 2006;17:1422–8.
5. Borghi L, Meschi T, Guerra A, Briganti A, Schianchi T, Allegri F, Novarini A. Essential arterial hypertension and stone disease. Kidney Int. 1999;55:2397–406.
6. Lieske JC, Kumar R, Collazo-Clavell ML. Nephrolithiasis after bariatric surgery for obesity. Semin Nephrol. 2008;28(2):163–73.
7. Gillen DL, Coe FL, Worcester EM. Nephrolithiasis and increased blood pressure among females with high body mass index. Am J Kidney Dis. 2005;46:263–9.
8. Rule AD, Krambeck AE, Lieske JC. Chronic kidney disease in kidney stone formers. Clin J Am Soc Nephrol. 2011;6:2069–75.
9. Worcester EM, Coe FL. Nephrolithiasis. Prim Care. 2008;35(2):369–91.
10. Parks JH, Goldfisher E, Asplin JR, Coe FL. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol. 2002;167:1607–12.
11. Asplin J, Parks J, Lingeman J, Kahnoski R, Mardis H, Lacey S, Goldfarb D, Grasso M, Coe F. Supersaturation and stone composition in a network of dispersed treatment sites. J Urol. 1998;159:1821–5.
12. Litholink Stone Prevention Program. Chicago, IL: Litholink Corp.
13. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. Family history and risk of kidney stones. J Am Soc Nephrol. 1997;8:1568–73.
14. Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. Kidney Int. 2008;73:207–12.
15. Fakheri RJ, Goldfarb DS. Ambient temperature as a contributor to kidney stone formation: implications of global warming. Kidney Int. 2011;79:1178–85.
16. Worcester EM, Coe FL, Evan AP, Bergsland KJ, Parks JH, Willis LR, Clark DL, Gillen DL. Evidence for increased postprandial distal nephron calcium delivery in hypercalciuric stone-forming patients. Am J Physiol Renal Physiol. 2008;295:F1286–94.
17. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol. 2008; 3:1453–60.
18. Eisner BH, Porten SP, Bechis SK, Stoller ML. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. J Urol. 2010;183:2244–8.
19. Tasca A. Metabolic syndrome and bariatric surgery in stone disease etiology. Curr Opin Urol. 2011;21:129–33.
20. Jiang J, Knight J, Easter LH, Neiberg R, Holmes RP, Assimos DG. Impact of dietary calcium and oxalate, and Oxalobacter formigenes colonization on urinary oxalate excretion. J Urol. 2011;186:135–9.

21. Moran M. Uric acid stone disease. Front Biosci. 2003;8:S1339–55.
22. Kessler T, Hesse A. Cross-over study of the influence of bicarbonate-rich mineral water on urinary composition in comparison with sodium potassium citrate in healthy male subjects. Br J Nutr. 2000;84:865–71.
23. Kessler T, Jansen B, Hesse A. Effect of blackcurrant-, cranberry- and plum juice consumption on risk factors associated with kidney stone formation. Eur J Clin Nutr. 2002;56:1020–3.
24. Kenny JE, Goldfarb DS. Update on the pathophysiology and management of uric acid renal stones. Curr Rheumatol Rep. 2010;12:125–9.
25. Nouvenne A, Meschi T, Prati B, et al. Effect of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr. 2010;91:565–70.
26. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol. 2009;20:2253–9.
27. Taylor EN, Stampfer MJ, Mount DB, Curhan GC. DASH-style diet and 24-hour urine composition. Clin J Am Soc Nephrol. 2010;5:2315–22.
28. Massey LK, Kynast-Gales SA. Diets with either beef or plant proteins reduce risk of calcium oxalate precipitation in patients with a history of calcium kidney stones. J Am Diet Assoc. 2001;101:326–31.
29. Soresen MD, Kahn AJ, Reiner AP, et al. Impact of nutritional factors in incident kidney stone formation: a report from the WHI OS. J Urol. 2012;187:1645–50.
30. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;246:77–84.
31. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15:3225–32.
32. Ashyby RA, Sleet R. The role of citrate complexes in preventing urolithiasis. Clin Clim Acta. 1992;210:157–65.
33. Koff SG, Paquette EL, Cullen J, Gancarczyk KK, Tucciarone PR, Schenkman NS. Comparison between lemonade and potassium citrate and impact on urine pH and 24-hour urine parameters in patients with kidney stone formation. Urology. 2007;69:1013–6.
34. Grases F, Costa-Bauza A. Phytate (IP6) is a powerful agent for preventing calcifications in biological fluids: usefulness in renal lithiasis treatment. Anticancer Res. 1999;19:3717–22.
35. Grases F, March JG, Prieto RM, Simonet BM, Costa-Bauza A, Garcia-Raja A, Conte A. Urinary phytate in calcium oxalate stone formers and healthy people—dietary effects on phytate excretion. Scand J Urol Nephrol. 2000;34:162–4.
36. Grases F, Costa-Bauza A, Prieto RM. Renal lithiasis and nutrition. Nutr J. 2006;5:23.
37. Grases F, Isern B, Sanchis P, Perello J, Torres JJ, Costa-Bauza A. Phytate acts as an inhibitor in formation of renal calculi. Front Biosci. 2007;12:2580–7.

Part V
Additional Nutritional Considerations in Kidney Disease

Chapter 22
Public Policy and Renal Nutrition Practice: Past, Present, and Future

Mary H. Hager

Key Points

- The heart of professional advancement is recognition and inclusion in public policies that support patient access to appropriate care.
- Understanding the makeup and functions of many government bodies, both elected and administrative, is a fundamental requirement for professionals in a variety of disciplines to affect public policy.
- The workforce needs more registered dietitian/nutritionists who specialize in renal nutrition to ensure the future of mandatory inclusion in healthcare law.

Keywords Medicare • Reimbursement • Public policy

Public Policy and Renal Nutrition Practice: Past, Present and Future

The heart of professional advancement is recognition and inclusion in public policies that support patient access to appropriate care. Nearly all areas of nutrition and dietetics practice are touched in some way by public policy, but none as significantly as the area of renal nutrition.

In a period of less than a century, care of patients with chronic kidney disease has tremendously improved and the cadre of professionals who tend to their medical needs has grown greatly. Before the development of dialysis and transplantation in the mid-twentieth century, individuals with chronic kidney failure faced certain death. With the entry of lifesaving medical interventions—including nutritional treatments—chances for survival were greatly improved. The costs, however, remained prohibitive for most patients.

Recognizing the growing costs of care and the inability of many to pay for it, the federal and state governments initiated public health insurance programs. Part of the expense of coverage was related to personnel and clinical overhead in addition to materials and equipment. Securing coverage for both sets of expenses became the goal of many advocacy groups, including the National Kidney Foundation and similar patient advocacy groups as well as professional associations such as the Academy of Nutrition and Dietetics (formerly American Dietetic Association), which advocates for direct payment for registered dietitian/nutritionist (RD/N) services.

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It takes many years of advocacy efforts to achieve such public policy victories. Understanding the makeup and functions of many government bodies, both elected and administrative, is a fundamental requirement for professionals in a variety of disciplines to affect public policy.

The Role of Federal and State Governments

The US Constitution established a government based on "federalism," or the sharing of power between the national and state (and/or) local governments. States also have their own constitutions; but all provisions must agree with the US Constitution or at the very least not be in disagreement. Under the US Constitution, state governments are allowed exclusive powers to issue licenses and provide for public health and safety and a variety of other actions. As a consequence, it is important for nutrition professionals to be informed of both national and state government activities and provisions, and sometimes even those of local governments.

Over time, particularly after such events as the Civil War and the Great Depression, federalism in the United States tended to shift towards a stronger federal government. One striking example is the federal government's establishment of Social Security in 1935 with the intent to provide economic security based on resources beyond those of family and local community. The year before (1934), President Franklin Roosevelt created a Committee on Economic Security to study the problem of economic security and make recommendations to Congress that could serve as the foundation for legislation.

Known as the Social Security Act, the bill was signed into law by President Roosevelt on August 14, 1935. The new law established Social Security to pay a continuing income to retired workers age 65 or older. In addition, the law provided employment insurance, old age assistance, and aid to dependent children and grants to the states to provide various forms of medical care.

From the 1930s to the 1960s, several amendments were made to broaden the scope of the Social Security Act. But it was not until the 1960s that the cost of illness was addressed for the aged and disabled. On July 30, 1965, President Lyndon Johnson signed the Medicare bill into law. Social Security Administration was now responsible for administering a new social insurance program called Medicare (under Title XVIII of the Social Security Act) that extended health coverage to almost all Americans aged 65 or older. In addition to Medicare, the new law enacted Medicaid (under Title XIX) a state-run healthcare assistance program supported in part by federal funds for qualified low-income individuals living at or below poverty levels. The law extended health assistance to low-income children deprived of parental support, their caretaker relatives, the elderly, the blind, and individuals with disabilities.

In 1972, Medicare eligibility was extended to individuals under 65 with long-term disabilities and to individuals with end-stage renal disease (ESRD). Enabling access to Medicare was a significant step forward for individuals with chronic kidney disease [1].

Direct Payment to Nutrition and Dietetics Practitioners

In 1965, when the Medicare bill was signed into law, there was no national registry of dietitians nor were dietitians licensed to practice in any state within the union. Consequently, there was no coverage for nutrition counseling provided by registered dietitians included in the 1965 Medicare law. In addition, it was not until 1975 that the first state, Alabama, enacted a regulation law for dietetics [2].

By the mid-1970s, registered dietitians began to work in private practice. Insurance coverage for their nutrition counseling services was virtually nonexistent. The Commission on Dietetic Registration

was set up in 1969, and once established, CDR grandfathered 19,457 registered dietitians that year [3]. In 1970, 56 individuals took the first registration exam. As of 2011, CDR reports there were 81,619 registered dietitians (RDs) and 4,237 dietetic technicians, registered, (DTRs) on the registry. The exact number of these individuals actively working full time in dietetics is currently unknown. Even if all registered dietitians were employed full time in the profession, there is only one RD per 3,800 US citizens based on projected 2011 census data [4]. Government officials have expressed concern that other practitioners need to provide nutrition counseling to meet the needs of the population.

The demand for dietitians specializing in renal nutrition increased as scientific evidence showed nutrition to be key to slowing the progression of chronic renal failure and critical for optimal dialysis care and renal transplantation success. Articles began to appear in the Journal of the American Dietetic Association attesting to the need for third-party insurance coverage for dietitians [5].

In summary, Social Security Act provisions were the foundation upon which coverage for nutrition counseling services was established. Inclusion in Medicare—the nation's public health insurance plan for individuals age 65 and over and for persons with disabilities—set in motion the expansion of private health insurance to cover nutrition counseling services.

ADA formalized its public policy program in 1971; the first dietitians were grandfathered as registered dietitians in 1969. The then-extant Advisory Committee on Legislation and Public Policy served as the precursor of current advocacy programs. The committee began its work by developing guidelines and procedures for ADA to engage in legislative and public policy work [6].

By 1985, ADA's Board of Directors approved the establishment of an office in Washington, DC to increase advocacy effectiveness and to build relationships with members of Congress and the Executive Branch staff [7]. Federal efforts to improve Medicare and Medicaid led to continual development of bills and offered an opportunity to include legislative language that would allow for Medicare coverage of nutrition counseling services, now referred to as medical nutrition therapy.

The MNT Benefit

After several years of advocating for Medicare reimbursement for dietitians, Congress finally passed a Medicare Part B MNT provision in December 2000 as part of the Benefits Improvement and Protection Act ("BIPA"; P.L. 106-554) [7]. There were several important provisions; most notably that renal patients who were not receiving dialysis now had access to registered dietitians or licensed nutrition professionals, including posttransplantation MNT upon physician referral. This benefit became effective January 1, 2002. Patients diagnosed with diabetes mellitus were also provided this benefit.

Passage of BIPA was considered a major success for the dietetics profession. Since that time, efforts have continued to expand this benefit to other disease diagnoses. But obtaining coverage for professional services is universally a lengthy and complicated process that requires actions by practitioners at both the local and national levels.

The US Constitution provides states the right to license professionals and regulate practice, thus determining who can be a qualified practitioner. While the federal government can specify the qualifications of facility staff (hospital, dialysis clinic, nursing facility, and so forth) in order to pay for care in that facility, it recognizes that states have full authority to define and license qualified individuals. Therefore, registered dietitians and other qualified nutrition professionals need to ensure they are recognized by the states in which they work. In addition, the federal government allows states to define who provides specific interventions for state Medicaid programs. Therefore, qualified nutrition professionals should also be in continual dialog with the office of the Medicaid Director in their state.

What You Can Do to Promote Patient Access to Nutrition Care Provided by RD/Ns

Below is a list of several activities that qualified licensed nutritionists and RD/Ns in renal nutrition can engage in to promote their services and efforts to secure direct reimbursement. Recognition involves ongoing professional visibility. Professional visibility requires a willingness to engage key decision makers at the state and federal level, both elected and permanent staff.

Total healthcare dollars are not going to increase; but patient needs may. Availability of healthcare resources should be focused on area of high patient need. Dietitians in independent practice, in facilities, and in other settings are important components of the healthcare system. Their commitment to their patients requires ongoing surveillance of public policy issues and developments, and along with this, an active role in ensuring public policy decisions that benefit the patient.

There are several ways to become engaged in promoting dietetics practice as a key component of an overall patient care program [8].

- Because local regulations can be more inclusive than national decisions, work with state/local Medicare and Medicaid officials to seek local coverage and ensure that RD/N services are included in new benefits related to renal care.
- Support efforts to obtain licensure for RD/Ns (and for those with equivalent education and training) to facilitate local coverage for RD/Ns services. The Centers for Medicare & Medicaid Services leaves it to the states to determine who is the qualified health practitioner to perform certain medical interventions, including MNT.
- Support efforts to lobby Congress to mandate expanded coverage.
- Network and participate as team members with qualified primary care practitioners who coordinate patient care.
- Support education of new practitioners and growth of the profession by volunteering as a preceptor of supervised practice.

Renal dietitians are uniquely trained and deserve to be represented as an essential part of the medical team. It is critical to increase the numbers of renal dietitians who are legally recognized by the state in which they practice. It is equally important to increase the numbers of practitioners to ensure inclusion in legislation and rule making, particularly at the federal level. The workforce needs more registered dietitian/nutritionists who specialize in renal nutrition to ensure the future of mandatory inclusion in healthcare law.

References

1. US Social Security Administration (Official Social Security Website). Historical Background and Development of Social Security. http://www.ssa.gov/history/briefhistory3.html. Accessed 7 Sept 2013.
2. Smith J, Patrick S. Growing on the roots of ADA's public policy. J Am Diet Assoc. 2008;108:1988–90.
3. Commission on Dietetic Registration. Setting the Standard Since 1969. http://cdrnet.org/vault/2459/web/files/SettingtheStandardssince1969.pdf. Accessed 4 Sept 2013.
4. US Census Bureau. Population Estimates. Vintage 2011:National Tables, Table 1. Monthly Population Estimates for the United States: April 1, 2010 to November 1, 2013. http://www.census.gov/popest/data/historical/2010s/vintage_2011/index.html. Accessed 7 Sept 2013.
5. Trithart E, Noel MB. New dimensions: the dietitian in private practice. J Am Diet Assoc. 1978;73:60–2.
6. Borra ST, Earl R, Gilbride JA. At a crossroads: ADA and public policy. J Am Diet Assoc. 2002;102:464–465.
7. Smith RE, Patrick S, Michael P, Hager M. Medical nutrition therapy: the core of ADA's advocacy efforts (part 1). J Am Diet Assoc. 2005;105:825–34.
8. Hager MH. The Centers for Medicare & Medicaid Services expands obesity coverage to include "Intensive Behavioral Treatment". Nutr Today. 2012;47(2):72.

Chapter 23
Dietary Supplements

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Key Points

- Define dietary supplement and delineate safety and efficacy issues.
- Identify dietary supplements that may be used by people with kidney disease.
- Describe dietary supplements that may be associated with kidney dysfunction.
- Discuss considerations for health professionals regarding dietary supplements.

Keywords Kidney disease • Complementary medicine • Dietary supplements • Herbs • Botanicals

Introduction

Complementary and alternative medicine (CAM) may be thought of as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" [1]. Practices considered as CAM may evolve over time and be adopted into conventional healthcare when therapies are proven safe and effective [1]. "CAM" may literally be divided into therapies that are "complementary," referring to practices that are adjunctive to conventional practice; they may be "alternative," referring to practices that are used instead of conventional practices; or, increasingly used in the vernacular, the term "integrative" refers to a merging of allopathic approaches and CAM therapies for which evidence on safety and efficacy exists. The integrative approach seeks to deliver healthcare that is superior to any one modality alone [1]. After the formation of the National Center for Complementary and Alternative Medicine (NCCAM) within the National Institutes of Health, NCCAM categorized CAM practices into three broad categories of natural products, mind and body medicines, and manipulative and body-based practices [1]. Dietary supplements are considered part of the natural products category. While people with kidney disease may wish to explore one or more of the CAM domains, the focus of this chapter is with regard to non-vitamin, non-mineral dietary supplements and kidney disease.

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Dietary Supplements

The availability and usage of dietary supplements have increased notably in the past decade, with sales reported to be more than $25 billion in 2010. The American Botanical Council noted that sales of herbal products specifically have increased approximately 2 % annually since 2000 to $5.2 billion in 2010 [2].

The surge in availability and use of dietary supplements may be attributed to the Dietary Supplement Health and Education Act (DSHEA) of 1994 [3]. At that time, the Congress acknowledged that there may be a positive relationship between dietary practices, such as dietary supplements, and health promotion and disease prevention, which may translate into reduced healthcare burden. DSHEA amended the Food, Drug, and Cosmetic Act of 1958 to exclude dietary supplements from the pre-market safety evaluations that food and drugs undergo. DSHEA mandated a definition of dietary supplements (see Box 23.1) and guidelines for product claims and labels, including a disclaimer that the FDA has not evaluated the product for safety or efficacy. DSHEA authorized FDA to establish good manufacturing practices (GMP) for the supplement industry and provided for the creation of the Office of Dietary Supplements to promote research on dietary supplements [3].

Efficacy and Safety of CAM Therapies

Among the key issues concerning healthcare professionals regarding CAM use is the uncertainty over efficacy and safety of many CAM practices (see Box 23.2). Many CAM modalities are inherent in other cultures; however, in the United States, a CAM practice may be used in a manner not intended (such as "more is better") and, in the case of botanicals, may differ from those of other regions due to species, soil, water, and growing conditions and use. Additionally, in certain populations, such as persons diagnosed with kidney disease, dietary supplements may be contraindicated due to impaired renal function or possible drug interactions.

Through NCCAM, researchers have started the foundation for investigating efficacy and safety of various CAM modalities. NCCAM's mission is to subject CAM practices to rigorous scientific scrutiny, train CAM researchers, and provide credible information to both consumers and healthcare professionals [4]. For those CAM modalities that are found to be health promoting, efficacious, and safe, the expectation is that they will be integrated into mainstream medicine. Until then, the rise in demand and availability, ease of obtaining products, and limited proof of efficacy and safety are cause for concern.

The FDA guidelines on GMP provide consumers and clinicians some confidence in the quality of dietary supplements from reputable manufacturers that must follow the standard practices. There are also several independent monitoring agencies (see Box 23.3) and independent certification programs

Box 23.1 Definition of Dietary Supplement [3]

"A product intended to supplement the diet to enhance health that contains one or more of the following:

- Vitamin, mineral, amino acid, herb or botanical
- Dietary substance to supplement the diet by increasing total dietary intake
- Concentrate, metabolite, constituent, extract or combination of any ingredient above
- Intended for ingestion as capsule, powder, gelcap and is not represented as a conventional food or as a sole item of a meal or the diet"

Box 23.2 Deciding For or Against the Use of Dietary Supplements

FOR

- "Natural" medicines are natural.
- Many therapies used for centuries.
- May reduce need for drugs and associated side effects when used properly.
- Other countries have been prescribing herbs safely for years.

AGAINST

- "Natural" medicines have biologic activity.
- Limited scientific testing.
- Sold without knowledge of action; active ingredient concentrations vary.
- May displace/enhance/interfere with current therapy.
- St. John's Wort interferes with indinavir in HIV treatment.
- Ginkgo may enhance anticoagulation therapies.
- Quality control.
- No federal regulation prior to sale.
- May be subject to misidentification, adulteration, contamination.

Box 23.3

MedWatch at http://www.fda.gov/medwatch
National Council Against Health Fraud (http://www.ncahf.org/)
ConsumerLab: independent evaluation with periodic reports; part of the report is available free, some by nominal subscription (http://www.consumerlab.com)

that a manufacturer can seek to endorse the product. These independent organizations will evaluate, on a voluntary basis from the manufacturer, for purity, accuracy of ingredient labeling, and manufacturing practices. One is from the United States Pharmacopeia (USP) who will evaluate products upon specified criteria and allow the manufacturers to use the designation, DSVP for Dietary Supplement Verification Program, if the product passes the rigorous testing (see http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements). Another similar program is set up by the NSF International to obtain the right to use the NSF mark (see http://www.nsf.org/consumer/dietary_supplements/dietary_certification.asp?program=DietarySup).

Dietary Supplements and Kidney Disease

The increasing use of CAM practices within the United States has been documented [5–8], and use remains a significant issue in current healthcare practice with continued interest and popularity among Americans using dietary supplements as CAM [9, 10]. Although there is a dearth of published literature on the actual patterns of use of dietary supplements by people with kidney disease [11], people may choose to use dietary supplements in an attempt to prevent further renal deterioration or may use CAM as an adjunct to mitigate side effects of the disease or treatments [12, 13]. Supplement use may

be classified as those with potential protective effects and those that should be avoided in kidney disease. Additional considerations include dietary supplements that may be toxic and lead to kidney dysfunction and those that may have interactions with prescribed drugs.

Dietary Supplements with Potential Protective Effects

Preventing renal deterioration by using herbs and supplements would be a fortunate asset. Chinese cultures may not have dialysis abundantly available, and traditional medicine using herbs may be one of the first choices in treatment. Thus, Chinese formulations or single herbs may be promising treatments. However, most of the published research is with animal studies; human applicability, safety, efficacy, and potential interaction with other medications must be explored. Astragalus (*Astragalus membranaceus*), an adaptogenic herb and antioxidant, may reduce proteinuria in glomerulonephritis [13–15]. Traditional Chinese Medicine uses astragalus often in combination with other herbs for its immune-enhancing potential; hence, individuals on immunosuppressants or those with autoimmune diseases should avoid its use [16]. The antioxidant properties of ginger (*Zingiber officinale*) may be linked to reduced inflammation in rats [17]. Other herbs such as milk thistle (*Silybum marianum*) and cordyceps (*Cordyceps sinensis*) may offer protection against nephrotoxic drugs [16, 18].

Given that people with kidney disease often also have hypertension, diabetes, or hyperlipidemia, herbs and supplements with anti-inflammatory activity may be of interest in an attempt to mitigate cardiovascular risk factors [13]. Omega-3 fatty acids found in foods, mainly fish, are also available in the form of dietary supplements as anti-inflammatory agents. A review article on the benefits of fish oil supplementation in renal patients suggests that omega-3 fatty acids may also be beneficial to reduce the severity of pruritus and reduce the risk of thrombosis after placement of vascular graft [19]. Evening primrose (*Oenothera biennis*) and borage (*Borago officinalis*) oil are sources of gamma-linolenic acid (GLA), an omega-6 fatty acid [16]. GLA may be converted to compounds that have anti-inflammatory properties. Judicious use of anti-inflammatory agents by people with kidney disease may be beneficial. Certainly side effects and drug interactions should be monitored and noted; fish oils can decrease platelet aggregation so large doses predispose a bleeding risk and may have additive effects with anticoagulant or antiplatelet medications [16].

Dietary Supplements to Avoid in Kidney Disease

While there is still much research to be done with dietary supplements and specifically in populations with kidney disease, most supplements should be approached with caution. Published literature on case reports, with either positive or negative outcomes, should not be generalized to a larger population. Theoretical mechanisms of action need testing in vivo before affirmation of use; both demonstrated and theoretical drug–herb interactions must be heeded.

Dandelion root (*Taraxacum officinale*) and Scotch broom (*Cytisus scoparius*) may have diuretic effects [16]. Parsley (*Carum petroselinum*), juniper (*Juniperus communis*), lovage (*Levisticum officinale*), and goldenrod (*Solidago virgaurea*) have constituents that irritate the kidney and increase renal blood flow and glomerular filtration, thus acting as aquaretics that increase water loss but not electrolyte excretion [16, 20]. These herbs should be considered contraindicated in kidney disease.

Kidney disease may alter the pharmacokinetics of drugs. Given the dietary supplements are natural forms of active biochemical agents, and that often the active ingredient or the mechanism of action is not fully understood in healthy individuals, people with kidney disease must use caution when considering the metabolism, distribution, and excretion of natural products. For example, it is known that

St. John's Wort (*Hypericum perforatum*), used for mild depression, interferes with a metabolic pathway shared by many drugs [16, 21]. When prescribed drugs and St. John's Wort are used concomitantly, the blood concentration of the drug may be lower than expected and often not therapeutic.

Dietary Supplements and Kidney Dysfunction

Perhaps the most infamous case of herbs causing kidney dysfunction is the case of "Chinese herb nephropathy" or "aristolochic acid nephropathy." In an attempt at weight loss, a Belgian population took an herbal supplement with a misidentified herb containing aristolochic acid, a nephrotoxic and carcinogenic herb. It was later reported that numerous people who took the supplement needed dialysis or renal transplant and several developed urothelial carcinoma [22]. Other less common herbs implicated in kidney dysfunction, mainly used in Africa and China, have been reported and summarized in a literature review by Colson and De Broe [14]. It would be prudent for practitioners whose patient populations have strong cultural ties to Africa and Asia to familiarize themselves with particular regimens inherent in certain populations. Refer to Table 23.1 for a list of herbs with adverse effects on the kidney.

Considerations for Healthcare Providers

Conscientious healthcare providers understand the current science in health promotion and disease management and strive for the best possible outcomes in patient care [23]. Recognizing that patients may seek to include dietary supplements as a part of their healthcare regimen is vital for open

Table 23.1 Herbs with adverse renal effects

Herb (scientific name)	Effect	Remark
Aristolochia (*Aristolochia auricularia*)	Renal fibrosis, carcinoma	Contains aristolochic acid which is nephrotoxic and carcinogenic FDA prohibits products containing aristolochic acid Other herbs such as asarabacca and costus root may be adulterated with aristolochic acid
Neem (*Azadirachta indica*)	Nephrotoxic	Leaf or seed oil may be nephrotoxic; flower, fruit, and twigs may be safe
Licorice (*Glycyrrhiza glabra*)	Hypernatremia, hypokalemia, edema	Numerous drug interactions
Senna (*Senna alexandrina*), Cascara (*Rhamnus purshiana*)	Hypokalemia	Used as laxatives. Senna leaf is not for long-term use
Noni fruit (*Morinda officinalis*)	Hyperkalemia	Fruit contains high concentration of potassium
Juniper berry (*Juniperus communis*), dandelion (*Taraxacum officinale*), asparagus tea (*Asparagus officinalis*), rupturewort (*Herniaria glabra*), Scotch broom (*Cytisus scoparius*), stinging nettle (*Urtica dioica*), uva ursi (*Arctostaphylos uva-ursi*)	Diuresis, electrolyte imbalance	May increase water loss without sodium excretion

Adapted from refs. [16, 18]

communication and treatment. Healthcare providers must be willing to ask questions relative to dietary supplement use and be prepared to answer questions or dialogue the pros and cons of a given regimen. Often, however, the area of dietary supplements may be intimidating when faced with numerous supplements with uncommon names or formulations with several ingredients. Suggested approaches would be to identify those dietary supplements common to one's practice area, for example, in kidney disease, then research the evidence for safety and efficacy through either scientific publications or databases that synthesize the information into a quick, sound reference such as http://www.consumerlabs.com or http://www.naturaldatabase.com. Once the provider has background knowledge on the supplement, he or she is usually more comfortable dialoguing with the patient regarding dietary supplements. Likewise, a patient who perceives that his healthcare provider is willing to discuss the subject is more likely to disclose the truth about contemplative or actual use. Pertinent information to discuss is what the patient wants to use and why. The "what" is relatively straightforward but the "why" aspect may be more nebulous. Find out the source of the patient's information and identify the patient's expectations. Is the patient taking the dietary supplement to treat a side effect of the disease of hoping that the supplement may cure his disease? Understanding the patient's issues and the safety and efficacy of the supplements leads to an open discussion to support or discourage their use. The issues of safety and efficacy can be measured or assessed independently by first evaluating for evidence of efficacy, then evaluating for evidence of harm [23]. Where do the results of the assessment point to on an evidence-versus-harm scale? If there is some evidence of efficacy and no or minimal risk of harm, then the dietary supplement may be worthwhile, such in the case of fish oil. On the contrary if the evidence for harm outweighs any benefit, such as with senna, then the patient should be counseled on other therapies. If the patient understands the issues around dietary supplements and still intends to take one or some, healthcare providers may allow a trial period if the supplement is not harmful and the patient can afford the out-of-pocket expense. In that case, providers may advise the patient to start with one supplement at a time, monitor and report any side effects, allow 4–6 weeks to notice the desired effect, and report back to the provider all positive, negative, or neutral experiences. As expected with all patient contact, providers must document the dialogue and communicate the patient's actions with the healthcare team.

Summary

With the increase in use of dietary supplements, and the relative ease with which they may be marketed by manufacturers and purchased by consumers, healthcare providers need to be aware of common supplements and cognizant of the safety concerns or interactions they may have with disease status and medication regimens. Healthcare providers can identify the notable dietary supplements that may be encountered in practice and research the safety and efficacy issues with regard to their use or misuse. Honest, open communication with patients who may wish to explore the use of dietary supplements is essential for patient–provider relations and optimal health outcomes.

Resources

Websites worth noting are the following:

- American Botanical Council, http://www.herbalgram.org
- National Center on Complementary and Alternative Medicine, http://nccam.nih.gov
- Natural Medicines Comprehensive Database, http://www.naturaldatabase.com
- Office on Dietary Supplements, http://ods.od.nih.gov/

- American Herbal Foundation (many good links), http://www.herbs.org
- NCCAM tips for consumers, http://nccam.nih.gov/health/decisions/index.htm
- Natural Standards, http://www.naturalstandards.com

References

1. What Is Complementary and Alternative Medicine (CAM)? http://nccam.nih.gov/health/whatiscam/. Accessed 19 June 2012.
2. Blumenthal M, Lindstrom A, Lynch ME, Rea P. Herb sales continue growth: up 3.3% in 2010. 2011. http://cms.herbalgram.org/herbalgram/issue90/MarketReport.html. Accessed 19 June 2012.
3. Dietary Supplement Health and Education Act of 1994. http://www.fda.gov/food/dietarysupplements/default.htm. Accessed 19 June 2012.
4. About the National Center for Complementary and Alternative Medicine. http://nccam.nih.gov/about/ataglance. Accessed 19 June 2012.
5. Eisenberg DM, Davis RB, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA. 1998;280(18):1569–75.
6. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med. 1993;328(4):246–52.
7. Kessler RC, Davis RB, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. Ann Intern Med. 2001;135(4):262–8.
8. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary alternative medicine use among adults: United States. Adv Data. 2002;2004(343):1–19.
9. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. National health statistics reports; no 12. Hyattsville, MD: National Center for Health Statistics. 2008.
10. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. Arch Intern Med. 2005;165(3):281–6.
11. Burrowes JD, Van Houten G. Use of alternative medicine by patients with stage 5 chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(3):312–25.
12. Gabardi S, Munz K, Ulbricht C. A review of dietary supplement-induced renal dysfunction. Clin J Am Soc Nephrol. 2007;2:757–65.
13. Markell MS. Potential benefits of complementary medicine modalities in patients with chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(3):292–9.
14. Colson CR, De Broe ME. Kidney injury from alternative medicines. Adv Chronic Kidney Dis. 2005;12(3):261–75.
15. Li X, Wang H. Chinese herbal medicine in the treatment of chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(3):276–81.
16. Natural Medicines Comprehensive Database. http://www.naturaldatabase.com. Accessed 19 June 2012.
17. Ojewole JA. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of Zingiber officinale (roscoe) rhizomes (zingiberaceae) in mice and rats. Phytother Res. 2006;20(9):764–72.
18. Combest W, Newton M, Combest A, Kosier JH. Effects of herbal supplements on the kidney. Urol Nurs. 2005;25(5):381–6.
19. Vergili-Nelsen JM. Benefits of fish oil supplementation for hemodialysis patients. J Am Diet Assoc. 2003;103(9):1174–7.
20. Awang D. Tyler's herbs of choice: the therapeutic use of phytomedicinals. 3rd ed. Boca Raton, FL: CRC Press; 2009.
21. Henney JE. Risk of drug interactions with St John's Wort. JAMA. 2000;283(13):1679.
22. Vanherweghem LJ. Misuse of herbal remedies: the case of an outbreak of terminal renal failure in Belgium (Chinese herbs nephropathy). J Altern Complement Med. 1998;4(1):9–13.
23. Rakel D. Integrative medicine. 3rd ed. St. Louis, MO: Elsevier Saunders; 2012.

Chapter 24
Vitamin and Trace Element Needs in Chronic Kidney Disease

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Key Points

- Vitamin and trace element status may be altered in patients with chronic kidney disease.
- Altered vitamin or trace element status may impact morbidity and mortality if untreated; thus, careful assessment and appropriate interventions must be conducted in this population.

Keywords Vitamins • Minerals • Malnutrition • Dietary reference intake

Introduction

Malnutrition and the broader term of "protein–energy wasting" have the potential to impact not only macronutrient metabolism but also vitamin and trace element status in patients with chronic kidney disease (CKD). Evidence for this is clearly shown in a recent study on vitamin K status. In this study the researchers determined which parameters predicted vitamin K status [1]. Patients with worsening vitamin K status had significantly lower body mass index (BMI), more years on dialysis, higher C-reactive protein (CRP) concentrations, and poorer survival [1]. Thus, those patients with lower body stores and higher inflammation had lower vitamin K serum concentrations and ultimately significantly increased risk of death. This is an excellent example of why vitamin and mineral status should be assessed, problems identified and treated, and clinical symptoms monitored in the CKD population.

Data from the National Health and Nutrition Examination Survey (NHANES) [2] and the Modification of Diet in Renal Disease (MDRD) Study [3] show that the daily ingestion of nutrients begins to decline as early as stage 3 CKD [2, 4, 5]. This reduction in intake may affect

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energy-producing nutrients (carbohydrates, protein, and fat), macro-minerals, vitamins, and trace elements. However, more than intake alone affects vitamin and trace element. Metabolic alterations in CKD patients may affect absorption, utilization, and excretion of micronutrients. Uremic toxicity, comorbidities, and finally the treatment of ESRD may all contribute to a heightened inflammatory status which affects the status of many micronutrients especially those with antioxidant properties, such as vitamins C and E, retinol, and minerals such as selenium.

Whereas vitamin D nutrition has received substantial attention, less is written or known concerning the optimal intake or body burden of vitamins and trace elements in CKD. This lack of information may have important clinical consequences because clinicians either may not recognize an inadequate or excessive body burden of these nutrients or may provide insufficient nutritional therapy or excessive supplementation of one or more vitamin or trace elements. Few of these nutrients have been extensively studied in the CKD population in this regard. Thus, the lower and upper ranges of body burden of these nutrients for their optimal metabolic functions are not known. For example, there are few studies that have demonstrated that CKD patients need either additional or possibly reduced amounts of a vitamin. For example, advanced CKD patients display an increased need for dietary for vitamin B6 (pyridoxine hydrochloride) [6], and a reduced tolerance for vitamin A, due to excessive serum vitamin A levels, and dietary intolerance to rather small increases in the intake of this vitamin [7]. Determining the optimal nutritional status and recommended intake to maintain or reestablish this optimal status can be difficult and can require careful monitoring by knowledgeable healthcare providers. The purpose of this chapter is to assist healthcare providers to make more rational and informed clinical decisions, evidence based where possible, regarding the vitamin and trace element status and nutritional needs of their CKD patients.

Vitamin B1: Thiamin

Thiamin is a hydrophilic B vitamin involved with many metabolic functions such as serving as a cofactor for oxidative decarboxylation reactions. The dietary reference intake (DRI) for thiamin (age 50–70 years) is 1.2 and 1.1 mg/day for normal men and women, respectively [8]. Dietary sources of thiamin include pork, oat bran, whole grains, and enriched grains [9].

Thiamin and CKD: Dietary intake and nutritional status for thiamin in patients with CKD ($n = 14$) were assessed by Frank et al. [10]. Stage 4 and 5 CKD patients consumed an average of 1.26 mg of thiamin/day from the foods in their diet. Their mean plasma thiamin concentration was 64.2 nmol/L, and their ETK-AC (erythrocyte transketolase activity coefficient, an indicator of thiamin adequacy) was 1.18 ± 0.19 (SD) (an ETK-AC indicating no deficiency is <1.20). ETK-AC has been regarded as a good functional indicator of thiamin status [11]. Thus, according to the data generated by Frank et al. [10], a substantial proportion of both CKD 4 and 5 patients had ETK-AC values greater than 1.20, indicating a thiamin-deficient status. While evidence does not indicate that all patients are deficient in thiamin, but suggests an increased risk and prevalence of insufficient or deficient concentrations in CKD patients. Whether the DRI for normal adults is sufficient for patients with CKD is unknown. However, a daily supplement at the DRI to augment dietary intake seems prudent to prevent possible deficiencies.

Vitamin B2: Riboflavin

Riboflavin is a water-soluble B vitamin with phosphorescent properties and promotes oxidation–reduction reactions. The DRI for riboflavin is 1.1 mg/day for women and 1.3 mg/day for men [8].

Some rich dietary sources of riboflavin are liver, duck, milk, eggs, mushrooms, spinach, chicken, and enriched grains [9].

Riboflavin and CKD: Porrini et al. [12] studied patients with advanced CKD who were not undergoing dialysis using the α-erythrocyte glutathione reductase stimulation index (α-EGR) to assess riboflavin status. In this study, 8 % of patients were found to have elevated α-EGR, thus indicating riboflavin deficiency. When the prescribed protein intake of these patients was intentionally reduced to 1.0 or 0.6 g protein/kg/day, from the patients' usual intake, according to the research protocol, the prevalence of elevated α-EGR increased from 8 to 25 % and 41 %, respectively. The increased prevalence of elevated α-EGR was attributed to the fact that riboflavin is particularly abundant in foods containing animal proteins. Indeed, several works have recommended riboflavin supplements for CKD patients, especially when they ingest very low-protein diets (i.e., <0.6 g protein/kg/day) [5, 13, 14].

Niacin: Vitamin B3

Niacin is another water-soluble B vitamin that is ingested as either nicotinamide from animal sources or nicotinic acid from plant sources. These molecules are necessary cofactors for many oxidation–reduction reactions. Niacin also prevents and is the therapeutic agent for pellagra, which is a condition caused by niacin deficiency and often referred to by "the D's": dermatitis, diarrhea, dementia, and death. Pellagra is associated with the chronic intake of low-riboflavin diets, alcoholism, and food faddism, and when untreated, maize is a primary staple of the diet [15]. The DRI for normal individuals is 14 mg/day for females and 16 mg/day for males [8]. Niacin is unusual in that it has an amino acid precursor, tryptophan; some of the tryptophan in the body is routinely converted to niacin. Thus, when niacin stores are low, the conversion of tryptophan can become a source of niacin. Primary food sources that are rich in niacin are meat, fish, legumes, coffee, and tea [9], all of which tend to be reduced in low-protein, low-phosphorus diets.

Niacin and CKD: It is possible that CKD patients who are prescribed low-protein diets (such as 0.6 g protein/kg/day) with phosphorus restriction (such as 800 mg/day) may be at increased risk for niacin deficiency due to the low niacin content of plant food; thus, their dietary niacin intake may be quite low. However, the authors are unaware of any clinical trials that have examined the niacin intake of CKD patients and whether that amount is sufficient to maintain adequate niacin status. Additionally, the niacin metabolite, nicotinamide, has been successfully used to reduce serum phosphorus concentrations in maintenance hemodialysis patients using megadoses of niacin, 500–1,500 mg/day given twice daily [16, 17]. The mechanisms of action involve the inhibition of the sodium/phosphorus type IIb cotransporter (NaPi-2b) and the type IIa cotransporter (NaPi-2a), which are the major transporters of inorganic phosphorus in the intestinal brush border and in the proximal renal tubular epithelial cells of the kidneys, respectively [18, 19]. Therefore, it is likely that in nondialyzed CKD 3–5 patients, the action of nicotinamide on the NaPi-2b and NaPi-2a cotransporters not only will inhibit phosphorus absorption in the intestinal brush border but will also inhibit renal tubular phosphorus reabsorption and thereby increase phosphorus excretion in both feces and urine. Nicotinamide use is associated with many side effects: most relevant are flushing; thrombocytopenia; hepatotoxicity (especially with sustained release doses); gastrointestinal symptoms such as diarrhea, vomiting, and constipation; and increased serum uric acid concentrations [19]. The increased serum uric acid may be of concern, because hyperuricemia has been associated with both hypertension and more rapid progression of renal failure [20]. In summary, while there is not sufficient evidence of niacin deficiency in CKD patients, those with chronically suboptimal dietary intake may benefit from a supplement at the DRI level to prevent deficiency.

Vitamin B6: Pyridoxine

Action: Vitamin B6 exists in vivo as six compounds. These are pyridoxal, pyridoxine, pyridoxamine, and the 5′-phosphate derivatives of these three compounds. Pyridoxal-5'-phosphate (PLP) is a cofactor for many enzymes, particularly the ones involving amino acid metabolism. Possibly relevant to the anemia of CKD, PLP is a cofactor for (δ)-aminolevulinate synthase to initiate heme synthesis. The DRI for pyridoxine in men is 1.7 mg/day and for women is 1.5 mg/day [8]. Substantial dietary sources of vitamin B6 are liver, fish, meat, poultry, plums, bananas, plantains, barley, sweet potatoes, potatoes, and enriched grains [9].

B6 and CKD: Kopple et al. [6] conducted both dietary and biochemical assessments of pyridoxine status on patients with different stages of CKD. In a cross-sectional analysis, the amount of vitamin B6 consumed in foods declined as GFR decreased, from 2.2 ± 0.8 (SD) mg/day in six patients with stage 3 and 4 CKD (serum creatinine from 2.1 to 3.5 mg/dL) to 1.2 ± 0.5 mg/day in seven nondialyzed patients with stage 4 and 5 CKD [6]. The mean intake of vitamin B6 for patients with severe CKD was significantly lower than the DRI for their age cohort. These declining intakes were reflected in the stimulation index of erythrocyte glutamic pyruvic transaminase (EGPT) activity. EGPT activity and the EGPT index are measurements of adequacy of body pyridoxine levels. An EGPT index greater than 1.25 is an indicator of vitamin B6 deficiency. The mean EGPT stimulation index rose (indicating vitamin B6 deficiency) inversely with the stage of CKD, where patients with higher GFR levels (CKD stages 3 and 4) had a mean EGPT index of 1.23 ± 0.09 (SD); CKD patients with lower GFR levels (stages 4 and 5) had a mean index of 1.30 ± 0.11. These were all significantly higher than the normal control values of 1.16 ± 0.06.

Podda et al. [21] found significantly lower serum PLP concentrations, 37.3 ± 51.7 versus 79.3 ± 65.6 pmol/mL, in patients with the nephrotic syndrome as compared with healthy controls. The serum B6 values inversely correlated with the magnitude of their proteinuria ($r = 0.41$, $p < 0.001$). These studies provide evidence that there are suboptimal levels of serum vitamin B6 in many patients with CKD.

Many medicines and other compounds can interfere with the actions or metabolism of vitamin B6 and may increase the likelihood that patients will develop B6 deficiency. This is especially likely to occur in CKD patients, because their vitamin B6 intake is often low, they may have increased dietary needs for B6 [13], and it is likely that they may be prescribed some of these latter medicines. These interfering compounds include isoniazid, thyroxine, iproniazid, theophylline, hydralazine, caffeine, penicillamine, ethanol, and oral contraceptives. The data presented here suggests that patients at stage 3 CKD or higher are at an increased risk for deficient concentrations of vitamin B6 and therefore should be supplemented adequately. It has been recommended by both the ESPEN and CARI guidelines that vitamin B6 be supplemented daily at a dose of 5 mg [22–24].

Folic Acid

Folic acid is a pteroylmonoglutamic acid which provides methyl groups for pyrimidine and purine synthesis and is necessary for histidine catabolism and the conversion between of glycine to serine and of homocysteine to methionine, in addition to other processes. Deficiency of folic acid results in megaloblastic anemia. The DRI for both healthy males and females is 400 μg/day [8]. Dietary sources of folic acid are legumes, orange juice, spinach and other leafy greens, broccoli, beets, artichokes, papaya, and enriched grains [9].

Folic acid and CKD: Low folate intake can be an important contributor to folate deficiency in CKD patients. The primary source of dietary folic acid is fresh green vegetables which, due to their high potassium content, are frequently restricted in the CKD diet. Medicines that interfere with folic acid and

may lead to deficiency, particularly in people with low folate intakes, include barbiturates, primidone, cycloserine, pyrimethamine, diphenylhydantoin, triamterene, methyltrexate, trimethoprim, Mysoline, pentamidine, salicylazosulfapyridine, and ethanol.

In advanced CKD (such as stages 4 and 5 prior to dialysis), the metabolism of folic acid or handling of its metabolites appears to be altered, although the cause and timing at which the alterations begin to occur are not well defined. Hannisdal et al. [25] compared the serum concentrations of folate and folic acid metabolites between healthy volunteers and nondialyzed patients with stages 3–5 CKD. Folate metabolites were analyzed by liquid chromatography–tandem mass spectrometry. The samples from patients with CKD had 22–30 times higher concentrations of folate metabolites than in sera from healthy volunteers. These elevated serum metabolite levels may reflect impaired excretion rather than altered metabolism of folic acid.

The optimal or safe daily intake for folate for CKD patients prior to dialysis is unknown. Considering that there is currently no evidence for impaired folate activity or metabolism for nondialyzed people with stages 3–5 CKD, the daily intake for these individuals may be similar to that of people who do not have CKD.

Cyanocobalamin: B12

B12 is critical for two major reactions, (1) as a coenzyme in the reaction that converts homocysteine to methionine and (2) for the reaction that converts L-methylmalonyl-CoA to succinyl-CoA [11]. B12 is unique because it requires an intrinsic factor for absorption by the brush border of the ileum [13]; therefore, patients with a history of stomach or bowel resection may over time become vitamin B12 deficient. The DRI for B12 is 2.4 μg/day for both men and women [8], and the primary dietary sources are liver, beef, chicken, eggs, trout, and salmon. Additionally, fortified foods, such as breakfast cereal, are also good sources of B12 [9].

B12 and CKD: In healthy adults, there is a 3–6-year body supply of B12 [11]. Therefore, if a healthy person consumed insufficient quantities of B12 for a short period of time (less than 3 years), they should not develop vitamin B12 deficiency. However, there are no data concerning the amount of body B12 storage in patients with CKD. A paucity of data has suggested that maintenance hemodialysis patients respond favorably and quickly when they are supplemented with B12, even when the plasma values indicate normal ranges [26]. This may be related to the fact that plasma B12 concentrations are not a sensitive indicator of B12 status. Plasma methylmalonic acid and homocysteine are more sensitive indicators of B12 status. Vitamin B12 is more abundant in high-protein foods. Thus, patients who consume low-protein or very low-protein diets for extended periods of time, for example, greater than 3 years, with no B12 supplementation, may become vitamin B12 deficient. Information on plasma and body levels of vitamin B12 is limited, and what data are available does not indicate that most or even many CKD patients are deficient. However, it may still be prudent to prescribe supplemental vitamin B12 equivalent to the DRI, i.e., about 3 μg/day, to CKD patients prescribed diets low (0.6 g protein/day) or very low (0.3 g protein/day supplemented with keto acids and essential amino acids) in protein.

Homocysteine

Serum total homocysteine concentrations appear to be increased to roughly 1.5–2 times the upper limit of normal in the majority of stage 5 CKD patients [27]. While elevated homocysteine concentrations in the general, non-CKD population are associated with an increased incidence of adverse cardiovascular

events and mortality [28], the relationship between this magnitude of elevated concentrations and adverse outcomes is less clear in CKD patients. Hyperhomocysteinemia of this level has been associated with both increased and reduced mortality in the CKD population [29, 30], probably because of the interaction of serum homocysteine levels with protein–energy wasting.

Several clinical trials have tested treatment of stage 4 and 5 CKD patients with large doses of folic acid, pyridoxine HCl, and often vitamin B6 to reduce elevated plasma homocysteine levels. Perhaps the largest randomized prospective clinical trial with the longest follow-up concerning vitamins to lower homocysteine concentrations and improve clinical outcome was the HOST study. This was a randomized, double-blind, placebo-controlled trial conducted in 2,056 Veterans Administration patients with stage 4 and 5 CKD who were not dialyzed ($n=1{,}305$) or who were undergoing maintenance hemodialysis ($n=751$) [27]. All patients were hyperhomocysteinemic (Hcy > 15 μmol/L), and they were randomized to receive daily treatment with 40 mg folic acid, 100 mg pyridoxine HCl, and 2 mg vitamin B12 or with placebo. Patients were treated for a mean of 4.5 years. Serum homocysteine levels decreased by 25.8 % in the vitamin group ($p<0.001$) as compared to the placebo group [27]; however, there were no significant differences between the treatment group and the control group with regard to mortality, myocardial infarction, or amputations.

In a recently published study, patients with 238 diabetic nephropathy and nephrotic syndrome, stage 3 or earlier, were randomized to treatment with either placebo or a combination of folic acid 2.5 mg/day, pyridoxine HCl 25 mg/day, and vitamin B12 1 mg/day, for a mean of 31.9 months [31]. Patients randomized to vitamin treatment had a significantly faster decline in GFR (-16.5 ± 1.7 mL/min, mean change at 36 months) compared to patients receiving placebo (-10.7 ± 1.7 mL/min, $p=0.045$). The patients taking the vitamins were significantly more likely to have a myocardial infarction, stroke, revascularization, or all-cause mortality [31].

Thus, there currently does not appear to be any clinical advantage to the routine use of megavitamin therapy to lower the modestly elevated serum homocysteine levels found in typical patients with advanced CKD.

Pantothenic Acid

Pantothenic acid is derived from pantothenate and is used in the synthesis of coenzyme A which is critical for many metabolic processes such as fatty acid oxidation, transport of proteins, and the formation of acetyl CoA, a key molecule in energy metabolism [11]. There is inadequate information to determine a DRI for pantothenic acid for normal adults; however, the adequate intake level is set at 5 mg/day for men and women over 51 years of age [8]. Pantothenic acid appears to be ubiquitous in the food supply; the following foods are rich sources: beef, poultry, whole grains, potatoes, tomatoes, and broccoli [9].

Pantothenic Acid and CKD: There are currently no published reports demonstrating pantothenic acid deficiency in patients with CKD. Given the ubiquitous nature of pantothenic acid in the general food supply and the lack of evidence for insufficiency or deficiency in CKD patients, an intake beyond the adequate intake level does not appear warranted.

Vitamin C

Vitamin C, or ascorbic acid, is a hydrophilic, six-carbon lactone that is capable of inhibiting the oxidation of other compounds by donating up to two electrons and, in the process, undergoing oxidation. Vitamin C scavenges reactive oxygen species in the body, thereby reducing the threat of cellular damage.

The DRI for vitamin C is 75 mg/day for women and 90 mg/day for men [32]. Examples of dietary sources high in vitamin C are citrus fruits, berries, papaya, peppers, mangos, pineapple, broccoli, cauliflower, melons, greens, tomatoes, and tubers [9].

Vitamin C and CKD: Vitamin C intake is likely to be low in CKD patients because of dietary potassium restriction and because healthcare providers are often cautious in recommending vitamin C supplementation above the DRI due to the risk of increased oxalate production. Oxalate is a metabolite of ascorbic acid, and urine oxalate and, in renal failure patients, serum oxalate may increase when individuals ingest supplemental ascorbic acid [13]. A direct correlation between serum ascorbic acid and serum oxalate concentrations has been reported in MHD patients. However, in a recent study of people without CKD who were at increased risk for oxalate formation, 500 mg/day of vitamin C did not increase 24-h urinary oxalate excretion [33]. To better assess the risk of supplemental ascorbic acid intakes, Chan et al. [34] conducted a study on the safety and efficacy of oral versus intravenous vitamin C administration in MHD patients and, not surprisingly, found no increase in the incidence of nephrolithiasis at 250 or 500 mg/day doses. Serum oxalate levels were not measured, and the possibility could not be ruled out that there might have been oxalate deposition in soft or other tissues.

Given the potential increase in oxidative stress due to uremic toxins and dialysis treatment, maintaining optimal concentrations of antioxidant status in CKD patients may improve clinical outcomes. In a study with peritoneal dialysis patients, ascorbic acid insufficiency and deficiency were demonstrated, respectively, in 74 % and 44 % of those individuals who were not receiving ascorbate supplements and in 22 % and 17 % of patients who were taking supplemental ascorbic acid [35]. A larger study by Zhang et al. [36] similarly demonstrated high prevalence of vitamin C deficiency for both MHD and chronic peritoneal dialysis patients, who were not receiving ascorbic acid supplements, with 33 % patients deficient and 31 % insufficient using plasma vitamin C values as the indicator. This study also showed an increased prevalence of clinical measures that are associated with suboptimal vitamin C status, such as elevated serum CRP and decreased serum prealbumin (transthyretin). Furthermore, in a recent meta-analysis where vitamin C was given at a dose of 500 mg to hemodialysis patients, this supplement was associated with an increase in hemoglobin levels and decreased doses of erythropoietin-stimulating agent [37].

Fat-Soluble Vitamins

Vitamin A

Vitamin A is a set of fat-soluble compounds classified as retinoids. Humans ingest preformed vitamin A (retinyl esters) or the vitamin A precursors, carotenoids. Retinal and retinoic acid (the acid form) are required for various reactions in the eye that support vision. Retinoic acid also promotes embryonic development, and retinoids are necessary for normal immune function. Carotenoids are composed of β-carotene, α-carotene, and β-cryptoxanthin [38] with β-carotene being the most common form of the carotenoids. β-Carotene can be converted to retinol; however, it has only approximately 50 % of the activity of retinyl esters. The current recommended dietary allowance for healthy men and women is 900 and 700 μg retinol activity equivalents (RAE)/day, respectively, and the upper safe limit is 3,000 μg RAE/day [39]. Abundant dietary sources of vitamin A include liver, fish-liver oils, dairy products, butter, and eggs. β-Carotene is found in red- and yellow-colored fruits and vegetables such as cantaloupe, carrots, sweet potatoes, and winter squash and in dark-green leafy vegetables, such as spinach [9].

Vitamin A and CKD: A 2010 study in MHD patients and healthy controls compared lipid profiles, total antioxidant capacity, and vitamin A levels [40]. This study showed that both before and after a

hemodialysis, MHD patients had elevated serum values of vitamin A in comparison to the healthy controls (MHD patients, 133.2 ± 47.8 SD μg/dL before and 89.3 ± 39 μg/dL after hemodialysis; controls, 58.3 ± 11 μg/dL, $p < 0.05$). Potential mechanisms for the increased vitamin A levels include decreased catabolism of retinol-binding proteins. Frey et al. [41] showed that isoforms of retinol-binding protein 4 (the main transporter or retinol in blood) are increased in CKD, and this may partly explain elevated plasma concentrations in CKD patients. The NHANES III data demonstrated an association between elevated serum creatinine and elevated serum vitamin A concentrations [42]; this correlation was consistent across ethnicities and persisted after adjustment for confounding factors. This finding reinforces earlier studies that described elevated vitamin A levels in nondialyzed patients with CKD, ESRD patients, and kidney transplant recipients [43–45].

However, the story on vitamin A may be a bit more complicated. A recent cross-sectional analysis in peritoneal dialysis patients showed not only that these patients consume less vitamin A but that their vitamin A intake was associated with their serum levels of CRP, an inflammatory marker. Patients with high serum CRP had a significantly lower intake of vitamin A (207 vs. 522 μg/day) [46]. Furthermore, Espe et al. [7] demonstrated that patients with lower retinol status had significantly higher mortality. A similar relationship of serum vitamin A levels to mortality, both all cause and cardiovascular, was also found by Kalousova et al. [47].

Since serum vitamin A concentrations begin to increase when the serum creatinine starts to rise [41], there would seem to be no need to provide supplemental vitamin A for CKD patients, unless dietary intake is low or there is the unusual circumstance that serum retinol concentrations are below normal. This is consistent with the current recommendations against the need for supplemental vitamin A in CKD unless the patient is commonly ingesting less than the RDA for vitamin A [23]. In this latter circumstance, a supplement to increase vitamin A intake to the recommended daily allowance can be given [13].

Vitamin E

Vitamin E is fat soluble and typically resides in cell membranes. It acts as an antioxidant, and it remains highly stable even after it scavenges free radicals. Vitamin E exists in four forms, α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol; however, only α-tocopherol has an established recommended dietary allowance. The DRI for vitamin E (α-tocopherol) is 15 mg/day for both normal men and women [32]. Dietary sources of vitamin E are vegetable oils, unprocessed grains, nuts, fruits, vegetables, and meat [9].

Vitamin E and CKD: It has become increasingly evident that oxidative stress may act as a pathological agent in a number of disease states, and vitamin E has been considered as a potential treatment for this condition. Plasma vitamin E levels in CKD patients do not appear to be different from healthy controls [48, 49], even when dietary intake of vitamin E is reduced [49]. The results of clinical trials evaluating the effectiveness of vitamin E for the prevention of cardiovascular disease in people with CKD have been mixed.

Mann et al. [50] examined the outcomes in patients with mild–moderate kidney failure (serum creatinine, 1.4–2.3 mg/dL; approximately stage 3 CKD) and increased risk for cardiovascular events who were given 400 IU/day of vitamin E as part of the HOPE trial. Patients with and without CKD in the HOPE trial were selected to be individuals at higher risk for adverse cardiovascular events. Consistent with the findings in the HOPE trial patients who did not have CKD, there was no cardiovascular benefit to taking this dose of vitamin E. Moreover, the long-term use of this dose (400 IU/day or 363 mg/day) of supplemental vitamin E in individuals with or without CKD in the HOPE trial resulted in an increased incidence of heart failure, heart failure-related hospitalizations, and all-cause

mortality (hazard ratio 1.13; 95 % CI 1.01–1.26, $p=0.4$) [38, 39]. This increased risk was associated with vitamin E intakes as low as 150 IU/day (136 mg/day) [51, 52].

Two studies examined vitamin E use as an antioxidant in MHD patients [53, 54]. In the Boaz et al. [53] study, MHD patients ($n=196$) were randomized to receive either an oral dose of vitamin E, 800 IU/day, or a placebo and followed for a median of 519 days. Treatment with vitamin E resulted in a reduction of the primary end point, a cardiovascular composite score (16 % vs. 33 %, $p=0.014$). A more recent, but much smaller, study ($n=80$) examined treatment with both silymarin and vitamin E for 21 days on plasma malondialdehyde (MDA), red blood cell glutathione peroxidase, and hemoglobin levels. Supplementation led to a significant decrease in MDA and an increase in red blood cell glutathione peroxidase and hemoglobin levels [54].

These studies, taken together, suggest that among people at high risk for cardiovascular events, supplemental vitamin E may not be indicated in the general population or in non-dialysis CKD patients. However, in the MHD population, vitamin E may be beneficial.

Vitamin K

Vitamin K participates in posttranslational carboxylation enabling the protein to bind to calcium and interact with other compounds. This is a necessary step for processes involving calcium interactions such as blood clotting and bone mineralization. The dietary form of vitamin K is phylloquinone. Phylloquinone is absorbed in the jejunum and ileum and is primarily stored in the liver. Bacteria in the gut also produce vitamin K in the form of menaquinones which are absorbed from the distal bowel and stored in the liver. If vitamin K deficiency occurs, body proteins may be undercarboxylated. Carboxylation status of proteins, such as osteocalcin, can be measured and used to diagnose vitamin K deficiency. The normal adequate intake for vitamin K is 90 μg/day for females and 120 μg/day for males. Formally, enough vitamin K was thought to be produced in the intestinal tract to prevent frank vitamin K deficiency even in the absence of dietary vitamin K intake. Newer evidence (see below) has led to a revision in this thinking. Dietary sources of vitamin K are green vegetables, cabbage, and plant oils [9].

Vitamin K and CKD: A decrease in dietary intake of vitamin K (phylloquinones) and/or a reduction in vitamin K production by gut bacteria can lower vitamin K levels. Antibiotics that suppress gut flora, and hence bacterial production of vitamin K, may increase the risk of vitamin K deficiency and impaired blood clotting. This is especially likely to happen if the patient is also not eating or taking vitamin supplements and therefore has a low vitamin K intake. Two new studies have provided clinicians with evidence suggesting that a large proportion of patients with CKD may be deficient in vitamin K.

The first study by Holden et al. [55] in 172 patients with CKD stages 3–5 found that, depending on the vitamin K indicator used, 6–97 % of patients were vitamin K deficient. When serum phylloquinone was used as a measure of adequate vitamin K status, a 6 % deficiency was found in this population. However, when the measurement was the more *sensitive* marker, the % of the osteocalcin protein that is under carboxylated (%ucOC), 60 % of the patients were found to be deficient in vitamin K. Finally, when PIVKA-II, a less used but a potentially very accurate marker of vitamin K status, was measured, 97 % of the patients were found to be deficient [55].

In the second study, by Schlieper et al. [1], 64 % of MHD patients ($n=188$) were identified as deficient in vitamin K using PIVKA-II as an indicator. As mentioned at the beginning of this article, when MHD patients were categorized according to their serum desphospho-carboxylated MGP, those patients with serum values below 6,139 pmol/L had significantly worse survival. Furthermore, when 17 patients were supplemented with oral doses of 135 μg/day of menaquinone-7 for 2 weeks, serum PIVKA-II decreased significantly, from 5.6 ± 3.2 to 3.4 ± 2.2 ng/mL, $p<0.001$.

These new studies suggest that a large number of nondialyzed stage CKD patients as well as maintenance dialysis patients are deficient in vitamin K and may benefit from vitamin K supplements. Further studies need to be conducted to confirm the optimal doses and duration for such vitamin K supplements.

Minerals and Trace Elements

Many minerals, including iron, calcium, manganese, magnesium, chromium, copper, selenium, phosphorus, and zinc, are essential nutrients and necessary components to metabolism in healthy individuals and CKD patients. However, some trace minerals when ingested can be nephrotoxic. These include arsenic [56], cadmium [57], chromium [58], germanium [59], lead [60], mercury [61], and silicon [61]. Obviously, supplements with these mineral should not be taken by CKD patients. Serum levels of some trace minerals appear to decline as kidney failure progresses; examples of these include calcium, copper, selenium, and zinc [62, 63]. It is noteworthy that copper, selenium, and zinc are all associated with lipid peroxidation, and patients with kidney failure can have augmented lipid peroxidation [64–66]. In a recent study by Guo et al. [67], chronic dialysis patients had significantly higher levels of MDA and superoxide dismutase (SOD) when compared with healthy controls, suggesting increased lipid peroxidation. The increased peroxidation may be attributed to uremic toxins, inflammatory and oxidant processes, nutrient imbalances, iron supplementation, or possibly other unrecognized factors [68].

Copper

Copper is a necessary cofactor for many enzymes including ferroxidases which facilitate iron binding to transferrin by changing its oxidation state. The DRI for copper is 900 μg/day for healthy individuals, and the upper safe limit for dietary intake is 10,000 μg/day. Abundant dietary sources of copper are organ meats, seafoods, nuts, seeds, whole grains, and cocoa.

Copper and CKD: Copper deficiency has been associated with cardiovascular dysfunction [69], and conversely copper toxicity has been associated with lipid peroxidation and accelerated atherogenesis [70]. Very high serum copper levels may cause hemolysis. Yilmaz et al. [62] measured erythrocyte copper concentrations in patients at stages 1 through 5 CKD and found concentrations to be decreased as kidney failure progressed. In stage 1 CKD patients, their mean erythrocyte copper concentration was 0.9 ± 0.2 (SD) μg/mL. In stage 5 (not dialyzed) CKD, the mean concentration was 0.24 ± 0.7. These values were significantly lower than in the control group which had a mean erythrocyte copper concentration of 1.06 ± 0.14 μg/mL. In these same patients, serum MDA levels rose with increasing stages of CKD. At stage 1 CKD, MDA was 2.48 ± 0.49 nmol/mL as compared to stage 5 CKD where the concentration was 8.06 ± 0.52 nmol/mL. Guo et al. [67] reported that continuous ambulatory peritoneal dialysis patients had higher serum copper concentrations than did healthy controls (0.90 ± 0.25 vs. 0.53 ± 0.14 μg/mL, $p < 0.05$) and higher copper to zinc ratios (1.97 ± 1.31 vs. 0.67 ± 0.21, $p < 0.05$). As expected the peritoneal dialysis patients also had higher MDA concentrations (4.90 ± 2.12 vs. 2.24 ± 0.76 nmol/L, $p < 0.05$). We are unaware of any clinical trials that measure the effect of copper supplementation on MDA in CKD patients.

Molybdenum

Molybdenum is involved in the metabolism of purines, pyrimidines, pteridines, aldehydes, and oxidation [71]. Excessive intakes of molybdenum may be associated with hypercalcemia and

hyperparathyroidism [72]. Interestingly, Smythe et al. [73] found significantly elevated molybdenum concentrations in the liver of uremic patients versus healthy control subjects (4.75 ± 2.05 μg/g vs. 3.52 ± 1.72, $p < 0.05$). However, at present there is insufficient evidence to indicate molybdenum supplementation or restriction is warranted in CKD patients. The DRI for molybdenum is 45 μg/day for men and women over the age of 30 years.

Magnesium

Magnesium is also a cofactor for many enzymes. The DRI for magnesium is 420 mg/day for men and 320 mg/day for women. Abundant dietary sources of magnesium are wheat bran, almonds, spinach, cashews, and soybeans.

Magnesium and CKD: There are some case study reports of patients with hypercalciuria and nephrocalcinosis who may have hypomagnesemia. These patients are characterized by low serum magnesium, normal to high urinary magnesium, high urinary calcium, and normal circulating calcium, potassium, and acid–base balance [74]. There is insufficient evidence to suggest a need for magnesium supplements for CKD patients except for rare cases of magnesium-losing disorders associated with kidney disease [74]. Endogenous magnesium is largely excreted by the kidneys, and in renal insufficiency, magnesium supplements could engender hypermagnesemia.

Manganese

Manganese is also a cofactor for enzymes and is important in brain function, collagen synthesis, bone growth, urea synthesis, and glucose and lipid metabolism. The DRI for manganese is 2.3 mg/day for men and 1.8 mg/day for women with an upper safe limit of 11 mg/day. Major dietary sources of manganese are whole grains, nuts, leafy vegetables, and teas.

Manganese and CKD: One small study examined the relationship between serum manganese and neurological basal ganglia changes in MHD patients and observed that all five patients with these neurological disorders had had elevated serum manganese as compared to controls [75]. The patients with elevated serum manganese were more likely to have pathological changes in the basal ganglia and, for example, Parkinson's symptoms. There are no published studies indicating abnormally low serum manganese concentrations in CKD patients.

Selenium

Selenium is a cofactor for such enzymes as glutathione peroxidase, 5′-deiodinase, and thioredoxin reductase and, as such, helps to protect cells against destruction by hydrogen peroxide and free radicals [76]. The DRI is 55 μg/day for both women and men. Major dietary sources are grains, meat, Brazil nuts, poultry, fish, and dairy products.

Selenium and CKD: Deficiency has been associated with many adverse side effects such as anemia, cancer, cardiovascular disease, immune dysfunction, and skeletal myopathy [13]. Smythe et al. [73] found differences between healthy normal subjects in Australia and the United States, with Australian's having significantly lower selenium concentrations in all tissues measured. Additionally, these investigators found in patients with advanced renal failure some organs with significantly lower

concentrations of selenium (e.g., in heart and lungs) but with significantly higher concentrations in brain. Both whole blood and plasma selenium concentrations were significantly reduced in CKD patients as compared to healthy controls at the baseline of a clinical trial conducted by Zachara et al. [77]. In this study, supplementation of CKD patients with 200 μg of selenium per day for 3 months resulted in marked increases in their red cell and whole blood concentrations. Furthermore, baseline plasma glutathione peroxidase activity was 37 % lower ($p<0.0001$) than healthy controls at baseline and, following supplementation, activity of this enzyme increased by 15 % ($p<0.05$). Similar results were found by Yilmaz et al. [62]; they found selenium concentrations and glutathione peroxidase activity to significantly decline as the CKD stage rose. In a 2010 study, serum selenium concentrations were found to be below the normal range (60–120 μg/L) in 98.7 % of MHD patients studied ($n=81$, mean serum selenium $=18.8\pm17.4$ μg/L) [78]. After supplementation with one Brazil nut per day (average selenium content 290.5 μg per nut) for 3 months, the mean serum selenium concentration increased to $104+65$ μg/L, a change that was highly statistically significant ($p<0.0001$) and which brought serum values to within the normal range. These studies indicate that selenium deficiency may not be uncommon in both nondialyzed CKD patients and MHD dialysis patients and that supplementation can replete stores to normal values and increase glutathione peroxidase activity.

Zinc

Action: Zinc is a cofactor for dozens of enzymes that facilitate the synthesis of large numbers of proteins as well as other compounds. Zinc is a necessary building block for hundreds of proteins. Its function includes catalysis, regulation, and structural activities. The DRI for zinc is 8 mg/day for women and 11 mg/day for men. Zinc is found in foods with higher protein contents such as beef, liver, and poultry and also whole grains.

Zinc and CKD: Piper [79] suggested that zinc supplementation may be necessary for patients fed very low-protein diets. However, Smythe et al. [73] found no significant difference in tissue concentrations of zinc between healthy controls and CKD patients. In contrast, McGregor [80] found decreased plasma zinc concentrations in CKD. Yilmaz [62] found a stepwise reduction in erythrocyte zinc levels with advancing stages of CKD.

Summary

Knowledge of vitamin and mineral requirements for patients with CKD remains incomplete. Given the data reviewed in this article, it would seem reasonable to state that many patients with CKD may be at risk for altered vitamin and mineral status. This may be particularly true for stage 4 and 5 CKD patients and MHD and CPD patients. Observational trials describing micronutrient status, dose–response pharmacological trials, and finally double-blind, randomized prospective clinical trials testing the effect of supplements with vitamins and trace elements need to be conducted before nutrient-specific recommendations for CKD patients can be generated with confidence. As suggested above, much work needs to be done to ascertain the sufficiently accurate and sensitive methods for determining nutritional adequacy for these nutrients. Until such time, micronutrient status, especially in those patients receiving low- or very low-protein diets, should be given careful consideration. Dietary, physical, and biochemical assessments should be routinely conducted in CKD patients as they approach stages 3 and below to ensure optimal nutritional care.

References

1. Schlieper G, Westenfeld R, Kruger T, Cranenburg EC, Magdeleyns EJ, Brandenburg VM, et al. Circulating nonphosphorylated carboxylated matrix gla protein predicts survival in ESRD. J Am Soc Nephrol. 2011; 22(2):387–95.
2. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The relationship between nontraditional risk factors and outcomes in individuals with stage 3 to 4 CKD. Am J Kidney Dis. 2008;51(2):212–23.
3. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57(4):1688–703.
4. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004;65(3):1031–40.
5. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant. 2009;24(4):1232–7.
6. Kopple JD, Mercurio K, Blumenkrantz MJ, Jones MR, Tallos J, Roberts C, et al. Daily requirement for pyridoxine supplements in chronic renal failure. Kidney Int. 1981;19(5):694–704.
7. Espe KM, Raila J, Henze A, Krane V, Schweigert FJ, Hocher B, et al. Impact of vitamin A on clinical outcomes in haemodialysis patients. Nephrol Dial Transplant. 2011;26(12):4054–61.
8. Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Institute of Medicine (U.S.). Panel on Folate Other B Vitamins and Choline, Institute of Medicine (U.S.). Subcommittee on Upper Reference Levels of Nutrients. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998.
9. Combs G. The vitamins, fundamental aspects in nutrition and health. New York: Academic; 1998.
10. Frank T, Czeche K, Bitsch R, Stein G. Assessment of thiamin status in chronic renal failure patients, transplant recipients and hemodialysis patients receiving a multivitamin supplementation. Int J Vitam Nutr Res. 2000;70(4): 159–66.
11. Institute of Medicine. For thiamin, riboflavin, niacin, vitamin B6, folate, B12, pantothenic acid, biotin/choline. Washington, DC: National Academies Press; 2000.
12. Porrini M, Simonetti P, Ciappellano S, Testolin G, Gentile MG, Manna G, et al. Thiamin, riboflavin and pyridoxine status in chronic renal insufficiency. Int J Vitam Nutr Res. 1989;59(3):304–8.
13. Joel D, Kopple SGM. Kopple and Massry's nutritional management of renal disease. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
14. Andreucci VE, Fissell RB, Bragg-Gresham JL, Ethier J, Greenwood R, Pauly M, et al. Dialysis Outcomes and Practice Patterns Study (DOPPS) data on medications in hemodialysis patients. Am J Kidney Dis. 2004;44(5 Suppl 2):61–7.
15. Seal AJ, Creeke PI, Dibari F, Cheung E, Kyroussis E, Semedo P, et al. Low and deficient niacin status and pellagra are endemic in postwar Angola. Am J Clin Nutr. 2007;85(1):218–24.
16. Takahashi Y, Tanaka A, Nakamura T, Fukuwatari T, Shibata K, Shimada N, et al. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. Kidney Int. 2004;65(3):1099–104.
17. Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3(4):1131–8.
18. Laroche M, Boyer JF. Phosphate diabetes, tubular phosphate reabsorption and phosphatonins. Joint Bone Spine. 2005;72(5):376–81.
19. Berns JS. Niacin and related compounds for treating hyperphosphatemia in dialysis patients. Semin Dial. 2008;21(3):203–5.
20. Feig DI. Uric acid and hypertension in adolescents. Semin Nephrol. 2005;25(1):32–8.
21. Podda GM, Lussana F, Moroni G, Faioni EM, Lombardi R, Fontana G, et al. Abnormalities of homocysteine and B vitamins in the nephrotic syndrome. Thromb Res. 2007;120(5):647–52.
22. Pollock C, McMahon L. The CARI guidelines. Biochemical and haematological targets guidelines. Haemoglobin. Nephrology. 2005;10 Suppl 4:S108–15.
23. Cano N, Fiaccadori E, Tesinsky P, Toigo G, Druml W, Kuhlmann M, et al. ESPEN guidelines on enteral nutrition: adult renal failure. Clin Nutr. 2006;25(2):295–310.
24. Pollock C, Voss D, Hodson E, Crompton C. The CARI guidelines. Nutrition and growth in kidney disease. Nephrology. 2005;10 Suppl 5:S177–230.
25. Hannisdal R, Ueland PM, Svardal A. Liquid chromatography-tandem mass spectrometry analysis of folate and folate catabolites in human serum. Clin Chem. 2009;55(6):1147–54.
26. Bastow MD, Woods HF, Walls J. Persistent anemia associated with reduced serum vitamin B12 levels in patients undergoing regular hemodialysis therapy. Clin Nephrol. 1979;11(3):133–5.
27. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA. 2007;298(10):1163–70.

28. Menon V, Wang X, Greene T, Beck GJ, Kusek JW, Selhub J, et al. Homocysteine in chronic kidney disease: effect of low protein diet and repletion with B vitamins. Kidney Int. 2005;67(4):1539–46.
29. Suliman M, Stenvinkel P, Qureshi AR, Kalantar-Zadeh K, Barany P, Heimburger O, et al. The reverse epidemiology of plasma total homocysteine as a mortality risk factor is related to the impact of wasting and inflammation. Nephrol Dial Transplant. 2007;22(1):209–17.
30. Mallamaci F, Zoccali C, Tripepi G, Fermo I, Benedetto FA, Cataliotti A, et al. Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. Kidney Int. 2002;61(2):609–14.
31. House AA, Eliasziw M, Cattran DC, Churchill DN, Oliver MJ, Fine A, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. JAMA. 2010;303(16):1603–9.
32. Institute of Medicine (U.S.). Panel on Dietary Antioxidants and Related Compounds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids: a report of the Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press; 2000.
33. Moyad MA, Combs MA, Crowley DC, Baisley JE, Sharma P, Vrablic AS, et al. Vitamin C with metabolites reduce oxalate levels compared to ascorbic acid: a preliminary and novel clinical urologic finding. Urol Nurs. 2009;29(2): 95–102.
34. Chan D, Irish A, Dogra G. Efficacy and safety of oral versus intravenous ascorbic acid for anaemia in haemodialysis patients. Nephrology (Carlton). 2005;10(4):336–40.
35. Singer R, Rhodes HC, Chin G, Kulkarni H, Ferrari P. High prevalence of ascorbate deficiency in an Australian peritoneal dialysis population. Nephrology (Carlton). 2008;13(1):17–22.
36. Zhang K, Liu L, Cheng X, Dong J, Geng Q, Zuo L. Low levels of vitamin C in dialysis patients is associated with decreased prealbumin and increased C-reactive protein. BMC Nephrol. 2011;12:18.
37. Deved V, Poyah P, James MT, Tonelli M, Manns BJ, Walsh M, et al. Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1089–97.
38. Intakes CoDR. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.
39. Institute of Medicine (U.S.). Panel on Micronutrients. DRI: dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc : a report of the Panel on Micronutrients … and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press; 2001.
40. Montazerifar F, Hashemi M, Karajibani M, Dikshit M. Hemodialysis alters lipid profiles, total antioxidant capacity, and vitamins A, E, and C concentrations in humans. J Med Food. 2010;13(6):1490–3.
41. Frey SK, Nagl B, Henze A, Raila J, Schlosser B, Berg T, et al. Isoforms of retinol binding protein 4 (RBP4) are increased in chronic diseases of the kidney but not of the liver. Lipids Health Dis. 2008;7:29.
42. Chen J, He J, Ogden LG, Batuman V, Whelton PK. Relationship of serum antioxidant vitamins to serum creatinine in the US population. Am J Kidney Dis. 2002;39(3):460–8.
43. Smith FR, Goodman DS. The effects of diseases of the liver, thyroid, and kidneys on the transport of vitamin A in human plasma. J Clin Invest. 1971;50(11):2426–36.
44. Yatzidis H, Digenis P, Fountas P. Hypervitaminosis A accompanying advanced chronic renal failure. Br Med J. 1975;3(5979):352–3.
45. Kelleher J, Humphrey CS, Homer D, Davison AM, Giles GR, Losowsky MS. Vitamin A and its transport proteins in patients with chronic renal failure receiving maintenance haemodialysis and after renal transplantation. Clin Sci (Lond). 1983;65(6):619–26.
46. Martin-Del-Campo F, Batis-Ruvalcaba C, Gonzalez-Espinoza L, Rojas-Campos E, Angel JR, Ruiz N, et al. Dietary micronutrient intake in peritoneal dialysis patients: relationship with nutrition and inflammation status. Perit Dial Int. 2012;32(2):183–91.
47. Kalousova M, Kubena AA, Kostirova M, Vinglerova M, Ing OM, Dusilova-Sulkova S, et al. Lower retinol levels as an independent predictor of mortality in long-term hemodialysis patients: a prospective observational cohort study. Am J Kidney Dis. 2010;56(3):513–21.
48. Karamouzis I, Sarafidis PA, Karamouzis M, Iliadis S, Haidich AB, Sioulis A, et al. Increase in oxidative stress but not in antioxidant capacity with advancing stages of chronic kidney disease. Am J Nephrol. 2008;28(3):397–404.
49. Galli F, Buoncristiani U, Conte C, Aisa C, Floridi A. Vitamin E in uremia and dialysis patients. Ann N Y Acad Sci. 2004;1031:348–51.
50. Mann JF, Lonn EM, Yi Q, Gerstein HC, Hoogwerf BJ, Pogue J, et al. Effects of vitamin E on cardiovascular outcomes in people with mild-to-moderate renal insufficiency: results of the HOPE study. Kidney Int. 2004; 65(4):1375–80.
51. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA. 2005;293(11):1338–47.

52. Miller III ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142(1):37–46.
53. Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, et al. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. Lancet. 2000;356(9237):1213–8.
54. Roozbeh J, Shahriyari B, Akmali M, Vessal G, Pakfetrat M, Raees Jalali GA, et al. Comparative effects of silymarin and vitamin E supplementation on oxidative stress markers, and hemoglobin levels among patients on hemodialysis. Ren Fail. 2011;33(2):118–23.
55. Holden RM, Morton AR, Garland JS, Pavlov A, Day AG, Booth SL. Vitamins K and D status in stages 3–5 chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(4):590–7.
56. Prasad GV, Rossi NF. Arsenic intoxication associated with tubulointerstitial nephritis. Am J Kidney Dis. 1995;26(2):373–6.
57. Griffin JL, Walker LA, Troke J, Osborn D, Shore RF, Nicholson JK. The initial pathogenesis of cadmium induced renal toxicity. FEBS Lett. 2000;478(1–2):147–50.
58. Dartsch PC, Hildenbrand S, Kimmel R, Schmahl FW. Investigations on the nephrotoxicity and hepatotoxicity of trivalent and hexavalent chromium compounds. Int Arch Occup Environ Health. 1998;71(Suppl):S40–5.
59. Takeuchi A, Yoshizawa N, Oshima S, Kubota T, Oshikawa Y, Akashi Y, et al. Nephrotoxicity of germanium compounds: report of a case and review of the literature. Nephron. 1992;60(4):436–42.
60. Staessen JA, Nawrot T, Hond ED, Thijs L, Fagard R, Hoppenbrouwers K, et al. Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. Lancet. 2001;357(9269):1660–9.
61. Nuyts GD, Van Vlem E, Thys J, De Leersnijder D, D'Haese PC, Elseviers MM, et al. New occupational risk factors for chronic renal failure. Lancet. 1995;346(8966):7–11.
62. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. Am J Kidney Dis. 2006;47(1):42–50.
63. Cuppari L, Carvalho AB, Draibe SA. Vitamin D status of chronic kidney disease patients living in a sunny country. J Ren Nutr. 2008;18(5):408–14.
64. Durak I, Akyol O, Basesme E, Canbolat O, Kavutcu M. Reduced erythrocyte defense mechanisms against free radical toxicity in patients with chronic renal failure. Nephron. 1994;66(1):76–80.
65. Mimic-Oka J, Simic T, Djukanovic L, Reljic Z, Davicevic Z. Alteration in plasma antioxidant capacity in various degrees of chronic renal failure. Clin Nephrol. 1999;51(4):233–41.
66. Richard MJ, Arnaud J, Jurkovitz C, Hachache T, Meftahi H, Laporte F, et al. Trace elements and lipid peroxidation abnormalities in patients with chronic renal failure. Nephron. 1991;57(1):10–5.
67. Guo CH, Chen PC, Yeh MS, Hsiung DY, Wang CL. Cu/Zn ratios are associated with nutritional status, oxidative stress, inflammation, and immune abnormalities in patients on peritoneal dialysis. Clin Biochem. 2011;44(4):275–80.
68. Mimic-Oka J, Savic-Radojevic A, Pljesa-Ercegovac M, Opacic M, Simic T, Dimkovic N, et al. Evaluation of oxidative stress after repeated intravenous iron supplementation. Ren Fail. 2005;27(3):345–51.
69. Klevay LM. Ischemic heart disease: nutrition or pharmacotherapy? J Trace Elem Electrolytes Health Dis. 1993; 7(2):63–9.
70. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation. 1993;87(3 Suppl):II56–65.
71. Food and Nutrition Board Institute of Medicine. Molybdenum. In: Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2001. p. 420–41.
72. Hosokawa S, Yoshida O. Role of molybdenum in chronic hemodialysis patients. Int J Artif organs. 1994;17(11): 567–9.
73. Smythe WR, Alfrey AC, Craswell PW, Crouch CA, Ibels LS, Kubo H, et al. Trace element abnormalities in chronic uremia. Ann Intern Med. 1982;96(3):302–10.
74. Benigno V, Canonica CS, Bettinelli A, von Vigier RO, Truttmann AC, Bianchetti MG. Hypomagnesaemia-hypercalciuria-nephrocalcinosis: a report of nine cases and a review. Nephrol Dial Transplant. 2000;15(5):605–10.
75. da Silva CJ, da Rocha AJ, Jeronymo S, Mendes MF, Milani FT, Maia Jr AC, et al. A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: manganism symptoms and T1 hyperintense changes in the basal ganglia. AJNR Am J Neuroradiol. 2007;28(8):1474–9.
76. Gropper S, Smith J, Groff J. Advanced nutrition and human metabolism. Belmont, CA: Wadsworth Cengage Learning; 2009.
77. Zachara BA, Koterska D, Manitius J, Sadowski L, Dziedziczko A, Salak A, et al. Selenium supplementation on plasma glutathione peroxidase activity in patients with end-stage chronic renal failure. Biol Trace Elem Res. 2004;97(1):15–30.

78. Stockler-Pinto MB, Mafra D, Farage NE, Boaventura GT, Cozzolino SM. Effect of Brazil nut supplementation on the blood levels of selenium and glutathione peroxidase in hemodialysis patients. Nutrition. 2010;26(11–12): 1065–9.
79. Piper CM. Very-low-protein diets in chronic renal failure: nutrient content and guidelines for supplementation. J Am Diet Assoc. 1985;85(10):1344–6.
80. McGregor DO, Dellow WJ, Lever M, George PM, Robson RA, Chambers ST. Dimethylglycine accumulates in uremia and predicts elevated plasma homocysteine concentrations. Kidney Int. 2001;59(6):2267–72.

Chapter 25
Issues Affecting Dietary Adherence

Jerrilynn D. Burrowes

Key Points

- Dietary adherence is a key component for successful treatment of chronic kidney disease (CKD).
- A patient's lifestyle, attitudes towards disease, socioeconomic status, culture, and social support may impact dietary adherence.
- Strategies for achieving dietary adherence in patients with CKD will be reviewed in this chapter.

Keywords Dietary adherence • Dietary compliance • Chronic kidney disease • Behavior change models • Nutrition counseling

Introduction

Medical nutrition therapy (MNT) is an integral component for successful treatment outcomes in patients with chronic kidney disease (CKD). Treatment requires adherence to a complex dietary prescription that changes throughout the stages of kidney disease. A number of factors (positive and negative) may influence a patient's ability to follow the recommended diet prescription. Factors that may improve adherence include social support from family and/or caregivers and the health practitioner's knowledge of the patient's culture, food habits, beliefs, and practices. On the other hand, inhibitors of dietary adherence include the patient's lifestyle, attitude towards the disease, socioeconomic status, and cultural barriers. The health-care practitioner needs to understand these factors that may influence dietary adherence. This chapter will present strategies for achieving dietary adherence in patients with CKD.

Definitions

The terms adherence and compliance are often used interchangeably. Adherence is the extent to which a person's behavior (e.g., taking medications, following a diet, and/or executing lifestyle changes) corresponds with agreed or prescribed recommendations from a health-care provider. Compliance

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suggests that the patient is passively following the practitioner's instructions and that the treatment plan is not based on a contract established between the patient and the practitioner [1]. The primary difference between the two terms is that adherence requires the patient's agreement with the recommendations, since the patient and/or family member is an active collaborator with the practitioner in the treatment process. To the contrary, compliance entails obedience to a directive (e.g., "take this medication three times a day") [2]. The term adherence will be used throughout this chapter since patients should be active participants in their health care.

Adherence is the single most important modifiable factor that compromises treatment outcome. It is also a primary determinant of the effectiveness of treatment because poor adherence attenuates optimum clinical benefit [3, 4]. The best treatment can be rendered ineffective by poor adherence [2].

Dietary Adherence

Adherence to the diet prescription is critical for successful management of CKD. Poor dietary adherence places patients at risk for complications such as fluid overload, hyperkalemia, hyperphosphatemia, and malnutrition. It can also complicate the patient-practitioner relationship and prevent an accurate assessment of the quality of care provided. In addition, patients with CKD usually have multiple comorbidities such as diabetes and cardiovascular disease, which can make their treatment regimen more complex and increase the likelihood of poor treatment outcomes [2]. For example, a dietary regimen such as the renal diabetes diet is more likely to be poorly adhered to because of the complexity of the diet.

Poor adherence wastes health-care resources, it increases health-care expenditures, it jeopardizes patient care, and it increases morbidity and mortality risk [5]. Poor adherence to a dietary regimen usually goes undetected by health-care providers unless self-reported by the patient or until laboratory tests are obtained and reviewed. However, the latter monitor usually reflects recent behavior [6]. Nonadherence can confuse the clinical picture and diagnostic process and may contribute to unnecessary testing and procedures, resulting in inappropriate regimen changes such as an increase in phosphate binders or changes in the dialysis prescription.

Factors Affecting Dietary Adherence

Adherence is a multidimensional phenomenon determined by the interaction of several factors (see Table 25.1). Health-care practitioners must understand how these factors influence adherence in order to develop strategies that incorporate them in the education process.

Social and Economic Factors

Some of the social and economic factors that affect adherence include poverty, illiteracy, a low level of education, unemployment, a lack of effective social support networks, unstable living conditions, traveling a long distance to and from the treatment center, the high cost of transportation to the dialysis unit, the high cost of medication(s), cultural and lay beliefs about illness and treatment, and family dysfunction.

Table 25.1 Barriers affecting dietary adherence to medical nutrition therapy for the control of chronic kidney disease and strategies to improve adherence

Barriers affecting dietary adherence	Strategies to improve adherence
Social and economic	Assessment of social needs including shopping and meal preparation
	Family preparedness
Health-care team and system-related	Multidisciplinary care
	Improve patient/caregiver-practitioner relationship
	Training of health professionals on adherence
	Identification of the treatment goals and development of strategies to meet them
	Continuing education for health professionals about the disease
	Continuous monitoring and reassessment of treatment
	Nonjudgmental attitude and assistance
	Training in communication skills for health-care providers
	Reinforce desirable behavior
	Emphasize the value of the diet and the effect of adherence
Condition-related	Education on proper use of medications (e.g., phosphate binders)
	More in-depth nutrition education
Therapy-related	Simplification of treatment regimens
	Education on proper use of medications (e.g., phosphate binders)
	Improve patient/caregiver-health-care provider relationship
Patient-related	Provide behavior modification techniques
	Improve patient/caregiver-health-care provider relationship, considering the patient's beliefs and social and cultural norms
	Self-management of disease and treatment
	Assessment of psychological needs
	Motivate patients to comply
	Increase patient's knowledge about treatment regimen
	Reduce the complexity of the diet regimen
	Provide easy-to-read, simple education materials tailored for the patient
	Provide patient-centered education

Patient and family characteristics constitute additional sets of social factors that influence adherence. In fact, the attitude and support of the family are possibly the most important motivators for positive adherence [2]. Therefore, family members and/or significant others should be encouraged to attend nutrition counseling sessions with the patient to learn more about their condition and its treatment.

Health-Care Team and System-Related Factors

Little research has been conducted on the effects of the health-care team and the effect of system-related factors on adherence. A good patient-practitioner relationship may improve adherence; however, there are many factors that have a negative effect on adherence. These include a lack of knowledge and training for health-care practitioners on managing chronic diseases, overworked practitioners, lack of feedback on performance, short consultations, and lack of knowledge about adherence and effective interventions for improvement [2]. Failure on the part of the health-care practitioner to follow up with the patient about nonadherence when detected may enhance the negative behavior [7].

Condition-Related Factors

Illness-related demands faced by the patient such as the severity of symptoms, level of disability (e.g., physical, psychological, social, and vocational), rate of progression and severity of the disease, and the availability of effective treatment are examples of condition-related factors. The impact of these factors on adherence depends on how they influence the patients' risk perception, the importance of following the treatment, and the priority placed on adherence [2].

Therapy-Related Factors

Therapy-related factors that affect adherence include the complexity of the medical regimen, the duration of treatment, previous treatment failures, frequent changes in the treatment prescription, immediate beneficial effects, negative side effects, and the availability of the health-care practitioner to manage the side effects [2]. A patient's ability to carry out the regimen as prescribed depends on the complexity of the regimen and the support systems available to assist the patient [6].

Dietary adherence is best achieved when the initial regimen is simple, with complexities introduced gradually. For example, nutrition education about the renal diet can begin with limiting high-potassium foods, whereas a more complex regimen may be educating the patient about the renal diet exchange system. Furthermore, practical social difficulties such as not being able to coordinate the timing of phosphate binders with meals may also jeopardize adherence. Continuous reassurance by the practitioner may promote increased adherence when (and if) challenges arise.

Patient-Related Factors

The patient's knowledge, attitudes, beliefs, perceptions, and expectations represent patient-related factors that affect adherence. Knowledge and beliefs about the illness, motivation to manage it, confidence (self-efficacy) in the ability to engage in illness-management behaviors, and expectations regarding the outcome of treatment and the consequences of poor adherence influence behavior [2]. A patient's motivation to adhere to a prescribed treatment regimen is influenced by the value that he or she places on following the regimen (cost-benefit ratio) and the degree of confidence in being able to follow it [8]. Long-term and particularly lifetime regimens that require repeated daily behavior such as adhering to the renal diet requires commitment.

Behavior Change Models

Learning new, complex patterns of behavior normally requires modifying many of the small behaviors that compose an overall complex behavior. Some behavior change models have many similarities (i.e., they address how individual factors such as knowledge, attitudes, beliefs, prior experience, and personality influence behavioral choices). These include the health belief model, the theory of reasoned action/theory of planned behavior, and the transtheoretical model of behavioral change/the stages of change model (see Table 25.2). Each model implies that patients make rational decisions regarding future events and, given the appropriate skills, they can establish goals and modify or regulate behavior to achieve these goals [9]. However, counseling patients based on the stages of change model appears to be effective because the focus of the counseling session depends on where the patient is in the stage of change.

Table 25.2 Behavior change models and theories that address how individual factors such as knowledge, attitudes, beliefs, prior experience, and personality influence behavior choices

Theory/model	Focus	Key concepts
Health belief model	Peoples' perceptions of the threat of a health problem and appraisal of behavior recommended to prevent or manage a problem	Perceived susceptibility Perceived severity Perceived benefits of action Perceived barriers to action Cues to action Self-efficacy
Theory of planned behavior	People are rational beings whose intention to perform a behavior strongly relates to its actual performance through beliefs, attitudes, subjective norms, and perceived behavioral control	Behavioral intention Subjective norms Attitude towards behavior Perceived behavioral control Social norm
Stages of change/transtheoretical model	Readiness to change or attempt to change a health behavior varies among and within individuals over time	Precontemplation Contemplation Preparation Action Maintenance Relapse

Stages of Change

Identifying the patient's readiness to make dietary changes is useful when planning interventions. The transtheoretical model of behavioral change is the dominant theoretical foundation for behavioral interventions. It suggests that behavioral change is a process that occurs gradually, although it is not a linear process. This model requires many trials of the new behavior, moving back and forth through a series of fairly predictable stages (i.e., from precontemplation [not considering change], to motivation to change [contemplation], before making a commitment to change [preparation], actually making the change [action], and working to prevent relapse [maintenance]). Relapse is a common occurrence, and it is part of the normal process of working towards lifelong change (see Table 25.3) [10]. Each patient's readiness to change must be assessed continuously and nutrition counseling should be tailored according to the patient's stage of change.

Strategies for Achieving Dietary Adherence

Strategies to improve dietary adherence fit into one of three categories: educational, behavioral, and organizational [11–13]. Effective nutrition education is the first step in achieving dietary change. Education regarding the nutrition management of CKD should raise the patient's level of adherence to an acceptable level, but probably not to a desired level. Nutrition education is better than no intervention, but it is not sufficient to raise dietary adherence to the desired level [14].

Educational strategies rely on the transmission and dissemination of information and instructions with or without motivational appeal, with the intermediate objective of affecting a patient's knowledge and attitudes [15]. Innovative educational activities such as the use of interactive games and videotapes should be used. Nutrition information should be sensitive to the personal characteristics of the patient, including attitudes, cultural norms, beliefs, and reading skills [16]. However, education alone is usually not sufficient to achieve long-term dietary adherence and sustain behavioral change.

Table 25.3 Stages of change model and implications for nutritional counseling

Stage of change	Patient characteristics	Implications for nutritional counseling
Precontemplation	Not intending to take action in the foreseeable future (up to 6 months) Often characterized as lacking control Denial or resignation is common Not yet convinced of seriousness of condition	Relationship building is key Educate about the underlying disease process Put minimal emphasis on specific dietary changes Focus on overcoming individual barriers
Contemplation	Considering advantages and disadvantages of changing behavior Apprehensive about behavior change because it may have failed in the past Not ready to commit to making a change	Educate about the long-term complications of disease, the role of diet in medical management, and expected benefits Begin to establish a timeline for change
Preparation	Ready to change behavior (within the next 2 weeks) Need assistance with problem-solving and social support Taking tentative steps to change behavior	Provide initial simplified diet instruction Begin to set goals and encourage self-management/self-monitoring behaviors Reinforce initial successful behavioral changes Build self-efficacy
Action	Taking significant steps to change behavior	Use progressive nutrition education to develop self-management skills Offer continued reinforcement for successful incorporation of new behaviors into the individual's lifestyle Develop goal-setting and self-monitoring skills
Maintenance	Incorporating new behaviors into lifestyle and sustaining them Maintenance change in behavior	Develop self-management and coping skills Develop skills for managing diet in new/difficult social situations Build self-management, goal-setting, and monitoring skills
Relapse	Experiencing a normal part of the process of change Usually feels demoralized	Reinforce self-management skills and develop social supports Address factors associated with relapse Build self-efficacy and self-monitoring skills Emphasize what can be learned from relapse versus focusing on failure

Behavioral strategies are procedures that attempt to influence specific nonadherent behaviors directly through the use of techniques such as reminders, tailoring, contracting, self-monitoring, reinforcement, and family/peer support, but with information and instruction playing a secondary role [11]. However, behavioral strategies fail to maintain consistent change in the long term [12].

Lastly, organizational strategies focus primarily on the convenience of the dialysis unit and on the utilization of personnel for fostering dietary adherence [13]. Organizational change can prevent or reduce adherence problems, often without the need for altering the practitioner's workloads or increasing budgets. Examples include making special appointments at odd hours or telephoning patients at home with abnormal lab results.

Summary

Dietary adherence is a critical component for successful management of CKD. Several factors can inhibit or improve dietary adherence. Educational, behavioral, and organizational strategies may also improve adherence. Dietitians who educate patients with CKD and/or their family members need to be aware of these factors and the strategies that may improve or inhibit adherence.

References

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–97.
2. World Health Organization. Adherence to long term therapies: evidence for action. World Health Organization. 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed 15 Mar 2012.
3. World Health Organization. The world health report, 2002. Reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.
4. Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. Annu Rev Nurs Res. 2000;18:48–90.
5. DiMatteo MR. Variations in patients' adherence to medical recommendations. Med Care. 2004;42(3):200–9.
6. DiMatteo MR, Reiter RC, Gambone JC. Enhancing medication adherence through communication and informed collaborative choice. Health Commun. 1994;6(4):253–65.
7. LaRosa JC. Poor compliance: the hidden risk factor. Curr Atheroscler Rep. 2000;2:1–4.
8. Miller W, Rollnick S. Motivational interviewing. New York: Guilford Press; 1999.
9. Brawley LR, Culow-Reed SN. Studying adherence to therapeutic regimens: overview, theories, recommendations. Control Clin Trials. 2000;21:156S–63.
10. Prochaska JO, Johnson S, Lee P. The transtheoretical model of behavior change. In: Schumaker SA, Schron E, Ockene JK, McBee WL, editors. The handbook of health behavior change. 2nd ed. New York: Springer; 1998. p. 59–84.
11. Dunbar JM, Marshall GD, Hovell MF. Behavioral strategies for improving compliance. In: Haynes RB, Taylor DW, Sacket DL, editors. Compliance in health care. Baltimore: Johns Hopkins University Press; 1979. p. 174–90.
12. Leventhal H, Cameron L. Behavioral theories and the problem of compliance. Patient Educ Couns. 1987;10:117–38.
13. Gibson ES. Compliance and the organization of health services. In: Haynes RB, Taylor DW, Sacket DL, editors. Compliance in health care. Baltimore: Johns Hopkins University Press; 1979. p. 278–85.
14. Elliott WJ. Compliance strategies. Curr Opin Nephrol Hypertens. 1994;3:271–8.
15. Green LW. Educational strategies to improve compliance with therapeutic and preventive regimens: the recent evidence. In: Haynes RB, Taylor DW, Sacket DL, editors. Compliance in health care. Baltimore: Johns Hopkins University Press; 1979. p. 157–73.
16. Sherman AM, Bowen DJ, Vitolins M, Perri MG, Rosal MC, Sevick MA, et al. Dietary adherence: characteristics and interventions. Control Clin Trials. 2000;21:206S–11.

Chapter 26
Counseling Approaches

Kathy Keenan Isoldi and Jerrilynn D. Burrowes

Key Points

- Patients with chronic kidney disease (CKD) experience several psychosocial detriments that may interfere with their readiness to make dietary and lifestyle changes.
- To achieve the best outcome, patients with CKD should receive nutritional counseling in a supportive and engaging environment that focuses on empowerment and in increasing self-efficacy in managing food choices.
- It is essential that dietitians who counsel patients consider the stage of change each patient is in according to the Transtheoretical Model and provide nutrition counseling accordingly.
- Cognitive behavioral therapy and motivational interviewing have shown promise in promoting dietary adherence in patients who are prescribed dietary restrictions in the treatment of CKD.

Keywords Transtheoretical Model • Cognitive behavior therapy • Motivational interviewing • Counseling strategies

Introduction

The prevalence of chronic kidney disease (CKD) has been rising over the past 2 decades and currently afflicts more than 20 million Americans over the age of 20 years [1]. In 2007, there were approximately 110,000 adults in the United States who began treatment for end-stage renal disease (ESRD), with more than 570,000 receiving treatment for ESRD in 2008 [2, 3]. Unfortunately, patients with CKD are 16–40 times more likely to die before they reach ESRD [1]. In addition to the obvious physical detriments associated with CKD, patients also experience psychosocial detriments that influence how they view the dietary restrictions of the renal diet and their personal motivation aimed at self-care efforts [4–6]. Complicating life further for people with CKD are the psychological and social burdens that ripple towards the patient's expanded circle of family and friends, thereby creating a negative impact on an even greater number of individuals. These burdens undoubtedly influence the high prevalence of depression seen in patients with CKD, which is reported to be up to 30 % of CKD patients [7–9].

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Research supports that the transition from CKD to ESRD may be slowed through dietary and lifestyle choices. In addition, individuals with ESRD may improve their longevity and quality of life by following an appropriate dietary protocol [10–13]. However, adherence to dietary restrictions in this population is low [9]. Researchers performed qualitative interviews with 16 patients receiving maintenance hemodialysis that led to the development and distribution of a survey to 156 similar patients. The results of this qualitative and quantitative study revealed that very few patients perceived any immediate positive effects from following their dietary restrictions. The researchers believe this may be one reason for poor dietary adherence [5]. Clearly, there is a need for dietitians to guide patients with CKD to a better understanding about the influence of appropriate diet and lifestyle choices, as well as a need to confer a sense of empowerment to the patient with CKD.

It is essential that dietitians use effective strategies during nutrition counseling sessions to improve outcomes. Nutrition counseling approaches in the past have often involved education-based, expert-centered guidance. More recently, patient-centered counseling approaches that focus on empowerment and shared decision-making have emerged and have shown improved patient outcomes [5, 14, 15]. The recommendation to use collaborative management in counseling patients with chronic illnesses has been suggested for over a decade [16]. However, implementing the theories of patient-centered, jointly owned planning in nutrition counseling has taken time to develop. Currently, there is an extensive toolbox to draw upon to enhance counseling that promotes behavior change and improvement in health outcomes.

The use of the Transtheoretical Model (TTM) in guiding dietitians in identifying the stage of change each patient is in has become a practical tool to use during the counseling process. Cognitive behavioral therapy (CBT) and motivational interviewing (MI) have also emerged as efficacious models to employ in promoting change in patient's food and lifestyle behaviors [5, 17, 18]. This chapter will review techniques and strategies inherent in several models that can be used by dietitians while counseling patients with CKD to achieve increased dietary adherence, ultimately resulting in improved health outcomes, quality of life, and longevity.

The Transtheoretical Model

The onset of kidney disease does not wait for a patient to be ready to accept the diagnosis. Patients are often in need of guidance about changes in health and food behaviors that need to be taken even though they are not ready physically, psychologically, or emotionally to take action. Dietary nonadherence has been associated with incorrect matching of the proper counseling techniques with the stage of change the patient is in based on the principles of the TTM. If a patient arrives for guidance and is not ready to take action, and the counseling session amounts to a laundry list of what to do and what to eat, the likelihood of progress will be poor [19]. Patients often seeking help arrive at the dietitian's office or at the hemodialysis unit at different stages of readiness to change.

The TTM was first created by Prochaska et al., and although it has received some criticism, the theory has revolutionized the way dietitians approach patient counseling. A review of the TTM and examples of application of the model has been outlined in Chap. 25. The essential elements of the TTM are basic to any discussion about behavior change. Briefly, the TTM is comprised of six stages: pre-contemplation, contemplation, preparation, action, maintenance, and relapse. This model was first devised to address smoking cessation, and it has since been shown to be very effective in promoting behavior change. The aim of the TTM is to match counseling strategies with the patient's stage of readiness, with the ultimate goal of forward progression [19].

Patients in pre-contemplation do not see a link between their behaviors and health outcomes or negative consequences, and they are often reported as being in denial of the link between actions and health consequences. Patients in the contemplation stage report an association between their

behaviors and a negative consequence, but they cannot see how they can make the necessary changes to reap the benefits of change. Patients in the stages of pre-contemplation and contemplation are not ready to take action and make necessary changes. In the preparation stage, patients are cognizant of the need to make changes and they are ready to plan to make changes in food and health-related behaviors, usually within the next month. Patients in the action phase of the TTM are ready to take action immediately, or they are currently taking action to incorporate the changes needed to make lifestyle and/or dietary changes. During maintenance, patients focus on cementing the changes incorporated, and they maintain focus on all the behaviors implemented during the action phase. Finally, relapse occurs when a patient reverts back to his or her old, detrimental habits instead of moving forward or stabilizing in the maintenance phase. Research reports that the majority of patients who need to make dietary changes arrive for professional guidance while in either the pre-contemplation or contemplation stage [19, 20].

People who misunderstand the model assume that progress can only be made during the action phase. However, at each stage in the TTM, substantial progress can be made. Changes in thoughts and readiness to act are dynamic processes that include progress and regression. The role of the dietitian is to identify the stage the client is in, to work with strategies that are stage appropriate, and to guide the patient forward towards the next stage. In addition, the dietitian needs to work with the patient towards avoiding regression (or relapse). However, if relapse occurs, the dietitian should plan counseling techniques geared towards recovery and movement forward towards the next stage of readiness. The following sections review several strategies useful in guiding patients in a forward motion and in cementing new behaviors. In addition, there are several questions that can be posed to patients that allow for their inner thoughts and concerns to be heard.

Inquiries and Responding to Patients

During counseling sessions, dietitians can formulate several types of questions and responses to patients' comments that can influence the outcome of the session. Constructing questions and responses that allows for in-depth discussions can help to guide patients to a better understanding of potential obstacles that may interfere with meeting food-related behavior goals. In a rushed environment, dietitians may resort to formulating their questions based solely on obtaining facts about the patient in order to complete the nutrition assessment, and he or she may avoid questions that focus on exploring the patient's thoughts and concerns [20]. See Table 26.1 for examples of the different types of questions often used in nutrition counseling.

Closed-Ended Questions

Closed-ended questions are often formed to elicit a one-word response from the patient, and there may be times when it is appropriate to use closed-ended questions when speaking with a patient. For example, when time is limited and a patient needs information quickly, it may be appropriate to ask, "Do you need a list of potassium-rich foods to avoid before you leave the unit today?" However, closed-ended questions that are general in nature should be avoided during counseling such as "Are you following your renal diet?" or "Are you taking all of your medications?"

There are several problems inherent in using too many closed-ended questions during a counseling session. For example, patients will not have the opportunity to express concerns and ambivalence or explore misunderstandings when closed-ended questions are posed. In addition, these types of questions may lead the patient to believe that the dietitian is disinterested in exploring issues that might be of concern [20].

Table 26.1 Types of questions typically used during counseling

Type	Question	Comment
Closed-ended	"Do you avoid phosphorus-rich foods?"	Response from patient will offer very little insight into his/her actions and thoughts
	"Do you have a problem following your prescribed diet?"	The patient may feel disinterested or demoralized and not want to explore this topic. The question offers the patient the opportunity to just respond "No." Will not offer any insight
Leading	"Which phosphorus-rich foods do you avoid?"	Assumes patient is avoiding phosphorus-rich foods. Likely to result in an answer the patient thinks the dietitian wants to hear. Will not offer insights into patient's cognitions
	"What do you like about your new diet?"	The question makes the assumption that the patient has things about the diet that he or she likes. It does not allow the patient to express any dislike for the diet as the question *leads* the patient to address what is liked
Open-ended	"Can you tell me about the types of foods and beverages you usually eat on most days?"	No assumptions are embedded in the question. Creates the foundation for an honest conversation about current dietary intake
	"Can you share with me any difficulties you might be experiencing while following your renal diet?"	Offers a platform for an open dialogue for the patient. Offers the patient an opportunity to share his/her inner thoughts and concerns regarding the diet

Leading Questions

Leading questions implicitly express the dietitian's bias, and using this form of questioning will interfere with understanding what the patient is thinking and wants to share with the dietitian. When a patient is posed a leading question that infers professional bias, the patient may feel too embarrassed to respond honestly. Instead, the patient may answer the question to please the dietitian rather than express true feelings and opinions. Consider the following two versions of a question inquiring about daily food intake: (1) "Can you tell me what you ate for breakfast today?" or (2) "Can you tell me about the foods and beverages you ate after waking up this morning?" The first version of the question assumes that the patient eats breakfast, and this may not be true. The patient may be ashamed to admit that he or she skips breakfast and does not eat until lunchtime. In the second version the patient is asked to report on the first foods eaten upon waking. Asking the question in this way is more likely to result in an honest response. Knowing that the patient skips breakfast is an important piece of dietary information and allows the dietitian to address this food behavior once it is revealed. Leading questions can interfere with an honest dialogue between the patient and the dietitian and should be avoided during nutrition counseling [20].

Open-Ended Questions

Open-ended questions have the greatest potential to promote collaboration and dynamic interviewing. These types of questions will open the door for the patient to express his or her thoughts, cognitions, fears, and concerns. It is under these circumstances that the dietitian can explore concerns with the patient and make substantial progress towards behavior change. Of course, the dietitian needs to be ready for a variety of responses—expected and unexpected. Therefore, using open-ended questioning when time does not permit an appropriate response or discussion from the dietitian can serve to be

Table 26.2 Responding to the patient's concerns using reflective listening*

Type of reflective listening	The nutrition professional may respond
Simple reflection • Restating what is said, but changing the wording	"What I hear you saying is that you do not believe that you can lower your potassium"
Amplified reflection • Reflecting emotional overtones	"What I think I hear you saying is that you would like to be able to reduce your potassium, but you are feeling concerned and frustrated that you have not been able to achieve that as yet"
Two-sided reflection • Revealing both sides of the patient's ambivalence	"So, on the one hand you know it's important to maintain a lower serum potassium, but you are struggling to find a way to make that happen"
Reframing reflection • Reframing to help the patient think differently about the situation	"I can hear your sense of frustration in trying to follow a diet to lower your serum potassium, and I wonder if you've considered looking into getting some support to help you with this task"

*The patient will say, "I know how important it is to lower the amount of potassium in my blood, but I can't seem to do it. I try, but it just isn't working. I can't do it!"

detrimental to the counseling process. The dietitian should ask primarily open-ended questions and a sufficient amount of time should be given to the patient to express his or her concerns, as well as to promote an open dialogue.

Using open-ended questions also serves to promote in-depth discussions about diet and behavior change with those patients who are less likely, for a variety of reasons, to share their concerns [20]. Asking a patient "Can you please tell me how you are managing or coping with your new renal diet?" will open the door for an important discussion regarding all the factors surrounding eating a limited diet. One way to gauge if a dietitian is using enough open-ended questions is to estimate the percentage of time during the counseling session that the patient is talking and compare this to how much time the dietitian is talking. Sessions that provide in-depth discussions with favorable outcomes result from the patient doing most of the talking.

Respond Using Reflective Listening

Reflective listening is a powerful communication technique that allows for clarification of messages sent and communicates to the patient that the dietitian is fully engaged and listening. The goal of this type of questioning is to reflect back to the patient what the dietitian believes he or she has heard the patient say. This serves to confirm messages received from the patient and to clarify their meaning, either stated or implied. Reflective listening can be simple reflections that constitute restating what has been said with little interpretation, or it can include interpretation of the feeling the dietitian believes is embedded in the patient's statement. More in-depth forms of reflective listening include amplified reflections that include the emotional feeling sensed by the dietitian, double-sided reflections that reveal the perceived ambivalence sensed, and reframing reflections that involves reframing the patient's statement to help him or her think differently about the situation. Reflective listening signals to patients that the dietitian is listening and understands and accepts their thoughts and concerns. In addition, it helps to generate discussions that will develop self-awareness about any ambivalence the patient may feel regarding the food and lifestyle changes recommended [21]. See Table 26.2 for examples of different types of reflective listening.

Social Learning Theory and Self-Efficacy

The social learning theory proposed by Bandura [22] informs us that patients can learn within a social context by observing and modeling others [23]. Bandura has outlined four components that will increase the likelihood that one will learn the modeled behavior; these include attention, retention (remembering), reproduction (ability to imitate the behavior), and motivation (having a good reason to want to adopt the behavior) [23]. Application of the social learning theory during nutrition counseling might include the use of successful patient testimonials or demonstrations to help promote behavior change through modeling [17].

Bandura stresses the need to increase self-efficacy to promote behavior change [20, 22]. Self-efficacy is described as one's belief or confidence in being able to carry out a task [20]. Support for the use of social learning strategies to promote nutrition behavior change has not yet been strongly supported in research [17]. However, self-efficacy has been positively and strongly associated with several health indicators including improved blood glucose control, fewer depressive symptoms, and better quality of life in patients with chronic illness [24, 25]. Strategies aimed at improving self-efficacy in CKD patients are recommended. Self-efficacy can be influenced through a patient's physiological state, verbal persuasion received, vicarious experiences, and personal performance accomplishments [22]. Physiological states including discomfort, anxiety, and fear can detrimentally impact a patient's sense of self-efficacy. Positive verbal persuasion received from the dietitian will serve to promote a patient's self-efficacy. Similarly, patient group support meetings that include patients who adhere to the renal diet and who are doing well will serve as role models to others. However, the most effective way to improve self-efficacy is through performance accomplishments because it is based on personal mastery experiences [20, 22]. Therefore, helping patients with CKD set small, achievable goals will go a long way in improving self-efficacy through promoting a sense of personal performance accomplishment.

Behavior Modification and Cognitive Behavioral Therapy

The basic tenets of behavior modification include the belief that behavior is influenced by the environment, and within that environment behavior is driven by a series of positive and negative consequences [20]. Food-related habits are formed by associated habits that are cemented over time. For example, the worker who comes home every night and eats dinner in front of the television is very likely to get hungry whenever he or she sits down to watch television. In this scenario, watching television becomes the unconditioned stimulus that will prompt eating, even in the absence of hunger. Behavior modification theory states that healthy behaviors can also be learned or conditioned/reinforced (rewarded).

Behavioral theory and CBT interventions have the longest history in nutrition counseling and have been tested with the most frequency. These interventions are also referred to as behavior or lifestyle modification [17]. However, it is noteworthy that CBT focuses on promoting behavior change through modifying the patient's external factors (the environment) and internal factors (thoughts or cognitions). There is strong evidence supporting the use of behavior modification techniques to improve patient outcomes in changing food and lifestyle behaviors [17, 26]. Several strategies have been used to help guide patients towards positive change during behavior modification sessions. These include self-monitoring, social support, stress management, stimulus control, problem-solving, and reward strategies [17, 20]. See Table 26.3 for strategies to use to promote behavior change during nutrition counseling using the principles of CBT.

Table 26.3 Behavioral strategies useful in counseling that use the principles of cognitive behavioral therapy

Strategy	Purpose	Example
Self-monitoring	To track food, behaviors, thoughts, or physical activity for patient self-revelation	Maintain a food log and/or a log of adherence to medication schedule
		Maintain a log of daily fluid intake
		Maintain a log of feelings associated with eating
Social support	To offer emotional support to the patient	Have a family member or friend join the patient during a counseling session to enhance understanding
		Offer/direct patient to group support meetings
Stress management	To target and reduce environmental stress	Use of relaxation techniques such as deep breathing or yoga to help to reduce stress
		Encourage hobbies that the patient finds enjoyable
Stimulus control	To reduce social or environmental cues that trigger undesirable behavior	Have the patient limit sodium intake to help reduce the desire to drink fluids
		Remove high-potassium fruits and vegetables from the home
Problem-solving	To forecast trouble or handle current obstacles	Have the patient make a list of obstacles that he or she is experiencing
		Have brainstorming sessions to plan ahead for challenging events, such as holiday and family parties
		Weigh the pros and cons of options available to address potential problems
Rewards	To support and encourage helpful and newly created health behaviors	Patient rewards self with a new book when the goal of not eating high-potassium fruits is maintained for 1 month
		Patient rewards self with an additional hour of reading time after going for a 30-min walk

Cognitions

Cognitions are created through the processes of knowing through memory, remembering and processing information [26]. They can be positive or negative in nature. Cognitions prompt self-talk that can move a patient forward or hold him or her back from trying something new. An example of positive self-talk emerges from a positive cognition and is displayed by saying to oneself "I am strong enough to do this." On the contrary saying "I knew I couldn't follow this new diet plan because I have no willpower" is an example of negative self-talk generated from negative cognitions. Cognitions are influenced by one's childhood and prior experiences [20]. In fact, cognitions about circumstances and life choices are very powerful in driving behavior. Encouraging positive cognitions and positive self-talk is fundamental to CBT [20, 26].

Cognitive Distortions

Cognitive distortions are negative and detrimental to personal growth and progress towards behavior change. They promote negative self-talk and hold patients back from making progress. A patient who is struggling to manage his or her renal diet may eat the wrong foods one day and feel discouraged and report, "I'm an idiot; I know what to eat and yet I made all the wrong choices." Self-talk that

involves *negative labeling* can create a lack of confidence and reduce self-efficacy resulting in a lack of progress and possible regression.

Another common cognitive distortion is *all or nothing thinking* and occurs when patients believe that one error in their plan means that their whole plan has been ruined and that they should not bother attempting to do anything right. When this happens, a patient may report, "I forgot to take my phosphate binders today so why bother trying to follow my diet. I might as well give up and eat what I want." If a patient voices a cognitive distortion, the dietitian needs to help the patient understand how this thinking interferes with progress, is unproductive, and is an irrational way to handle mistakes. An effective way to address cognitive distortions is through cognitive restructuring [17, 20].

Cognitive Restructuring

Cognitive restructuring is a process whereby the dietitian enhances the patient's awareness of his or her perceptions and reveals irrational (negative) cognitions held by the patient and helps to redirect (restructure) the thinking towards a rational (positive) cognition. In the process, patients are taught to turn negative self-talk into positive self-talk [17, 20]. For example, a patient who typically adheres to his or her diet states, "I am so dumb. I ate pizza for lunch and got so thirsty that I drank way too much fluid. I drank so much that I had swelling in my legs all day yesterday. I am so stupid and I just feel so discouraged right now." This represents an irrational thought. Just because the patient ate pizza and drank too much fluid in 1 day does not make the patient dumb. This situation presents an opportunity for the dietitian to discuss with the patient that occasional missteps with dietary restrictions occur and they can be overcome. Using amplified reflective listening can help. The dietitian can respond, "I think I hear what you're saying, and you are really angry and frustrated with yourself for the choices you made for lunch yesterday. And even though you usually make the right choices this one event is enough to worry you and make you feel discouraged about yourself. Did I get that right?" Hopefully framing the reflective listening in this way can help the patient see that one poor choice will not undo all the hard work put into dietary adherence for the rest of the week. Now the discussion can continue with a focus on what the patient can do to use the information learned to avoid eating pizza in the future. The negative self-talk can change to positive self-talk by helping the patient verbalize how well he or she has done in the past with diet adherence and how he or she can be resilient following this event. After a few minutes of reflective listening and use of open-ended questions, the patient may even end the session by saying "I guess I'm just human and not perfect. I know I can get back on track because I am strong and determined." Hence, the irrational thought has been reconstructed into a rational thought and negative self-talk has been transformed into positive self-talk.

Goal Setting

Goal setting is an essential component of behavior modification. Patients should be involved in setting their goals with the dietitian. This can be accomplished through setting SMART goals (*s*pecific, *m*easurable, *a*chievable, *r*ealistic/*r*elevant, and *t*imed). They need to be clearly understood and manageable for the patient [27]. Patients who can achieve their goals are more likely to increase their self-efficacy, so it is wise to help patients choose goals that are manageable [20]. For example, after a consultation with the patient, both parties agree that the patient will keep a food log for 3 days during the following week (1 weekend and 2 weekdays) and will record all foods and beverages consumed starting with the following Monday. This goal is specific, measurable, achievable, realistic/relevant, and timed, and both parties agree. Conversely, having the patient record all foods and beverages consumed every day

of the week starting when the patient feels up to it is a goal that is both unrealistic (every day is too often) and does not give the patient a specific start date to begin logging food intake.

Motivational Interviewing

The presence of an illness such as CKD is not enough to motivate all patients to incorporate behavior changes. Research supports that patients with CKD who adhere to dietary restrictions experience less medical complications and improved quality of life, and it can increase their life expectancy by 2 decades or more [28]. However, studies report nonadherence with diet and/or fluid restrictions in 30–75 % of patients [28, 29]. Durose et al. [29] found no association between dietary knowledge and improved adherence. It is clear that providing nutrition information and guidance is not enough to motivate patients with CKD to adhere to their prescribed diet. Patients need to be motivated to make the lasting changes needed.

Motivation is a complex concept that is influenced by conscious and unconscious processes [30]. The philosophy and strategies inherent in the theory of motivational interviewing (MI) have become appealing to dietitians who are working to guide patients towards behavior change [31]. The concepts of MI were developed by Miller and Rollnick, working off the foundation of patient-centered counseling concepts that were first introduced by Rodgers in 1951 [21]. MI techniques were first applied to treat individuals with drug and alcohol addictions. More recently, MI has been used in many counseling settings where behavior change is the desired outcome. It is aimed at helping patients explore and resolve their personal struggles with ambivalence about behavior change [32].

Rollnick et al. describe MI as a gentle approach to counseling. In stark contrast to lecturing, the patient becomes an active participant in the process. Over time the goal is to create "change talk." During change talk the patient experiences a change in focus and reveals to himself or herself the reasons to make changes and will begin a self-dialogue that leads to motivation to take action. Four guiding principles are used while counseling patients to promote change talk; these principles are outlined using the acronym RULE [32].

1. *R*esist the righting reflex
   Dietitians are trained to help patients make the changes needed to stay healthy and improve their lives. However, while using MI, it is important to resist the urge to lead and to tell patients what the dietitian thinks is best for them to do. The dietitian should avoid arguing the case or trying to convince the patient how important it is to make the necessary changes. When a patient is ambivalent about change, pushing harder can result in greater resistance towards efforts aimed at persuasion. This creates a tug of war between the dietitian and the patient, rather than a respectful, collaborative effort. The goal is for the patient to experience change in beliefs and to convince himself or herself how important it is to make the necessary changes.
2. *U*nderstand and explore the patient's own motivations
   The patient will respond strongly to his or her own thoughts and feelings. Helping a patient explore his or her reasons for wanting (or not wanting) to make dietary and lifestyle changes will result in progress. Amplified reflective listening and the use of open-ended questions during counseling will promote the exploration of the patient's source of motivation.
3. *L*isten with empathy
   Patients will respond to thoughtful understanding. In addition to helping to establish rapport, shared understanding of the patient's struggles and obstacles can be a prelude to change talk. Patients with CKD have many fears and struggles to manage on a daily basis. Using reflective listening can amplify the message that the dietitian understands these burdens and is there to help the patient make changes, knowing the multitude of difficulties the patient is facing.

4. *E*mpower the patient, encouraging hope and optimism
   Exploring how patients can make a difference in their own lives and thereby offering empowerment can be very effective in making lasting changes. Outcomes are better when patients are actively involved in their own case. Patients ultimately become a consultant for the dietitian on how goals can best be met. The dietitian serves as a facilitator and encourages the patient to bring his or her expertise to the consultation.

To successfully execute the basic four tenets of the RULE philosophy of MI, it is suggested that dietitians use open questions, affirmations, reflections, and summaries (referred to as OARS). In addition to the use of open-ended questions and reflective listening during counseling, the dietitian should highlight an individual's strength using affirmations to promote self-efficacy. Telling a patient that "You've done a wonderful job in lowering your serum phosphorus since last month," *or* "I can see how hard you are working on making the changes in your diet, and all your efforts are working," will help the patient feel confident and empowered. Summaries provide opportunities for the dietitian to collect multiple change talk statements and link them together to create a fuller picture for the patient and also link discrepant statements that capture ambivalence. For example, the dietitian may say, "Mrs. Jones, I remember when you first started on hemodialysis you said that you wanted to do everything possible to be as healthy as possible, and you have been very successful in reaching your goal. However, it seems as if you have had difficulty adhering to your diet these past few months. Can you share your thoughts about this with me?" [18].

In a systematic review of 72 studies, MI was found to outperform traditional advice given in 80 % of the studies reviewed [33]. In addition, according to Spahn et al. [17], MI was found to be a highly effective counseling strategy for diet and lifestyle modifications. Most studies investigating the benefits of MI were conducted on patients who were obese, had diabetes, or had cardiovascular disease. However, a recent study investigating the efficacy of using MI techniques was done in 29 hemodialysis patients [34]. The results revealed that MI delivered by the hemodialysis staff (i.e., registered dietitians, nurses, dialysis technicians, and social workers) resulted in improvements in dialysis attendance and serum phosphorus and albumin levels. However, there was no effect noted on interdialytic weight gain. The study included few participants and was conducted for only 3 months. Regardless, the researchers were optimistic that this small study shows promise and that future research efforts conducted with a larger group of participants for longer periods of time may support the concept that MI is efficacious in counseling patients with ESRD [34].

Special Considerations for Patients Receiving Hemodialysis

Providing nutrition counseling to patients receiving maintenance hemodialysis has both benefits to reap and difficulties to combat. Patients are often dialyzed in a hemodialysis unit at specified times, three times per week for extended periods. Therefore, there is ample opportunity for the dietitian to build a rapport with patients and to use this time to counsel them. However, most units do not offer privacy at the chair side and it can become quite noisy during counseling sessions. There may not be much that the dietitian can do to modify the setting, but closing a curtain and sitting in a chair or on a stool can help to make the session more private and personal. Moreover, sitting at the same eye level as the patient is desirable. It is useful to remember that the patient is immobilized by being connected to a dialysis machine for several hours. Under these circumstances, it is very important to consider the lack of power the patient has as he or she cannot get up and leave. The dietitian may stop by the patient's treatment area to discuss dietary and medication adherence issues when it appears to be most convenient. However, this may not be the best time for the patient to discuss these issues. Checking in with the patient at treatment initiation and asking for permission to schedule an appointment later that day or at a subsequent session will express respect for the patient, and it will give the patient

decision-making power about when a counseling session can take place. Finally, if absolute privacy is needed, a time can be arranged to meet with the patient in a private area before or after treatment.

In addition, hemodialysis patients often have several components to their dietary restrictions. Addressing all components of the restriction at once can be overwhelming. Providing a focus on one component at a time and asking the patient to choose the component that he or she wants to discuss during that session (e.g., how to increase dietary intake of high-quality protein) may improve patient involvement and offer the patient the power of choice during the session [18]. These simple measures may go a long way in promoting positive, effective counseling sessions.

Future Directions

There are many psychological and social issues that are burdens for the patient with CKD. However, researchers have reported a lack of substantial research related to ESRD and psychology. There are far fewer studies investigating the psychological issues associated with ESRD than for cardiovascular disease or cancer. Researchers cite the relative lower prevalence of ESRD as one potential reason for the lack of data. Kaptein et al. [14] suggest six topics for researchers to explore based on the gaps they identified in the current literature. These topics include:

1. Common sense model of illness, illness perceptions, and treatment perceptions
2. Sexuality
3. Suicide
4. Qualitative methods
5. Family support
6. Self-management interventions

Hopefully this research agenda will drive forward our improved understanding of the challenges and concerns a patient with CKD experiences. A more informed dietitian will be better able to make strides in connecting with the patient with CKD and be more productive during counseling sessions.

Summary

The prevalence of CKD is rising and dietitians are best poised to offer important, perhaps lifesaving, guidance to patients. However, nonadherence with dietary recommendations is common. Patient-centered counseling techniques fundamental to CBT and motivational interviewing have been found to enhance patient outcomes for several chronic diseases, including CKD. Patients with CKD experience many psychosocial detriments and these burdens must be further explored to better understand how to meet the patient's needs, as this improved understanding may enhance change talk and dietary adherence.

Case Study

Robert is a 52-year-old man who has had CKD for 3 years prior to starting hemodialysis. He has been receiving hemodialysis three times per week for the past 3 months. The social worker reports that Robert is single, lives alone, works full time in sales, and does not have a lot of friends or family members that live close by. Robert has been instructed on the diet for hemodialysis and he was friendly

during the first few encounters with the dietitian, but he has not posed any questions. He politely answers the dietitian's questions asked with a smile, but he seems a bit quiet. Last month Robert's phosphorus level was elevated, and when the dietitian went by to speak with him, he said that he had forgotten his phosphate binders for a few days, but that he had them now and would take them as prescribed. While reviewing Robert's most recent blood results, the dietitian found that his potassium and phosphorus were elevated and the nurse reported that he has been gaining too much fluid weight in between treatments. The dietitian approached Robert to review his labs and pointed out that his levels of phosphorus and potassium were both elevated, as was his interdialytic weight gain. He responded, "I know, I know, I have not been able to get my act together yet, but I will get it done."

Questions for Case Study

1. What stage in the Transtheoretical Model do you believe Robert is in? State your reasons.
2. What *types* of questions should you use to ask Robert about his usual dietary intake to get him talking? What *types* of questions do you believe would not work in helping the dietitian understand Robert's issues?
3. What strategies or techniques would you use to help Robert? (See Table 26.3.)
4. How would you respond to Robert's comment (final quote)? How could you phrase a response to express reflective listening? What type of reflective listening would be effective? (See Table 26.2.)
5. What special considerations should you keep in mind while counseling Robert on the hemodialysis unit?

Answers to Case Study

1. Robert is in the contemplation stage of the TTM. He appears aware of the need to restrict his dietary intake of potassium, phosphorus, and fluid. However, he is unable or unwilling to discuss how to proceed to make the changes necessary for dietary adherence.
2. Robert needs to be asked *open-ended* questions to give him an opportunity to reveal his thoughts and concerns. Asking open-ended questions will allow Robert to explore obstacles in managing his dietary restrictions with the dietitian. Examples of open questions that would help Robert open up include "Robert, can you tell me how you are managing your diet since you started hemodialysis?" and "I'd like to hear about any struggles you might be having in restricting your fluid intake. Can you share your thoughts with me?" Robert appears to have difficulty with several components of the diet and he seems to be avoiding these issues. Asking him closed-ended or leading questions will just continue his reluctance to open up and share.
3. Based on what is known about Robert, he would benefit from *social support*. Robert does not have friends and family that live nearby. Perhaps he could join a patient support group to help to fill this void. In addition, if Robert is willing, he should *self-monitor* food and fluid intake a few days a week to help him reveal to himself the types and amounts of foods and beverages that he typically consumes. Finally, *stress management* may be useful in helping Robert manage all that is required of him now that he is on hemodialysis. Working full time while managing hemodialysis is taxing. Low-level exercise during the day and deep breathing may help him reduce pent-up stress.
4. Robert's comment has stress and frustration embedded in the statement. It would be beneficial to use *amplified reflective listening* to help him open up about his concerns so that he can make progress towards improved dietary adherence. Responding to his *comment by saying* "I think what I hear you saying is that you are determined to address your new dietary restrictions, but you have

not been able to do so as yet and that is frustrating to you." The dietitian can continue to express interest and empathy by saying "I would like to hear more about your thoughts regarding your diet and see where I can offer assistance."

5. The next time Robert arrives for hemodialysis the dietitian should ask him in advance to schedule a time to come by his treatment area. Sitting in a chair or on a stool at eye level with Robert will help promote a connection. If Robert seems uncomfortable talking at his treatment area, offer an alternative private location when he completes his dialysis treatment. Robert may be overwhelmed discussing phosphorus, potassium, and fluid restrictions on the same day. The dietitian should ask Robert to make the choice as to which one of the three areas of his diet he would like to discuss, while reminding him that the potassium restriction is the most important because of its effect on the heart. This will offer Robert respect and empowerment and encourage him to take an active part in the counseling process.

References

1. Centers for Disease Control and Prevention (CDC). National chronic kidney disease fact sheet: general information and national estimates on chronic kidney disease in the United States, 2010. http://www.cdc.gov/diabetes/pubs/pdf/kidney_Factsheet.pdf. Accessed 3 March 2012.
2. United States Renal Data System (USRDS). Incidence, prevalence, patient characteristics and treatment modalities. http://www.usrds.org/2011/pdf/v2_ch01_11.pdf. Accessed 18 March 2012.
3. National Institutes of Diabetes and Digestive and Kidney Diseases. Kidney and urologic disease statistics for the United States. http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/. Accessed 3 March 2012.
4. Tsay SL, Lee YC, Lee YC. Effects of an adaptation training programme for patients with end-stage renal disease. J Adv Nurs. 2005;50(1):39–46.
5. Krespi R, Bone M, Ahmad R, Worthington B, Salmon P. Haemodialysis patients' beliefs about renal failure and its treatment. Patient Educ Couns. 2004;53(2):189–96.
6. King N, Carroll C, Newton P, Dornan T. "You can't cure it so you have to endure it": the experience of adaptation to diabetic renal disease. Qual Health Res. 2002;12(3):329–46.
7. Fallon M. Depression in end-stage renal disease. J Psychosoc Nurs Ment Health Serv. 2011;49(8):30–4.
8. Blevins C, Toutman MF. Successful aging theory and the patient with chronic renal disease: application in the clinical setting. Nephrol Nurs J. 2011;38(3):255–60, 270.
9. Khalil AA, Frazier SK, Lennie TA, Sawaya BP. Depressive symptoms and dietary adherence in patients with end-stage renal disease. J Ren Care. 2011;37(1):30–9.
10. Cliffe M, Bloodworth LL, Jibani MM. Can malnutrition in predialysis patients be prevented by dietetic intervention? J Ren Nutr. 2001;11(3):161–5.
11. Mitch WE, Remuzzi G. Diets for patients with chronic kidney disease, still worth prescribing. J Am Soc Nephrol. 2004;15(1):234–7.
12. Akpele L, Bailey JL. Nutrition counseling impacts serum albumin levels. J Ren Nutr. 2004;14(3):143–8.
13. Garneata L, Mircescu G. Nutritional intervention in uremia—myth or reality? J Ren Nutr. 2010;20(5 Suppl):S31–4.
14. Kaptein AA, van Dijk S, Broadbent E, Falzon L, Thong M, Dekker FW. Behavioural research in patients with end-stage renal disease: a review and research agenda. Patient Educ Couns. 2010;81(1):23–9.
15. Nygardh A, Malm D, Wikby K, Ahlstrom G. The experience of empowerment in the patient-staff encounter: the patient's perspective. J Clin Nurs. 2012;21:897–904.
16. Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH. Collaborative management of chronic illness. Ann Intern Med. 1997;127(12):1097–102.
17. Spahn JM, Reeves RS, Keim KS, Laquatra I, Kellogg M, Jortberg B, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. J Am Diet Assoc. 2010;110(6):879–91.
18. Martino S. Motivational interviewing to engage patients in chronic kidney disease management. Blood Purif. 2011;31:77–81.
19. Prochaska JO, Norcorss JC, DeClemente CC. Changing for good. New York: HarperCollins; 1994.
20. Holli BB, O'Sullivan-Maillet J, Beto JA, Calabrese RJ. Communication and education skills for dietetics professionals. 5th ed. New York: Williams & Wilkins; 2009.
21. Miller NH. Motivational interviewing as a prelude to coaching in healthcare settings. J Cardiovasc Nurs. 2010; 25(3):247–51.

22. Bandura A. Self-efficacy: toward a unifying theory of behavior change. Psychol Rev. 1977;84(2):191–215.
23. Blackman MC, Kvaska CA. Nutrition psychology: improving dietary adherence. Boston: Jones & Bartlett; 2010.
24. Weng LC, Dai YT, Huang HL, Chiang YJ. Self-efficacy, self-care behaviors and quality of life of kidney transplant patients. J Adv Nurs. 2010;66(4):828–38.
25. Wells JR, Anderson ST. Self-efficacy and social support in African Americans diagnosed with end-stage renal disease. ABNF J. 2011;22(1):9–12.
26. Beck AT, Dozois DJ. Cognitive therapy: current status and future directions. Annu Rev Med. 2011;62:397–409.
27. Bovend'Eerdt TJ, Botell RE, Wade DT. Writing SMART rehabilitation goals and achieving goal attainment scaling: a practical guide. Clin Rehabil. 2009;23(4):352–61.
28. Kugler C, Vlaminck H, Haverich A, Maes B. Nonadherence with diet and fluid restrictions among adults having hemodialysis. J Nurs Scholarsh. 2005;37(1):25–9.
29. Durose CL, Holdsworth M, Watson V, Przygrodzka F. Knowledge of dietary restrictions and the medical consequences of noncompliance by patients on hemodialysis are not predictive of dietary compliance. J Am Diet Assoc. 2004;104:35–41.
30. Tierney P, Hughes C, Hamilton S. Promoting health behaviour change in the cardiac patient. Br J Card Nurs. 2011;6(3):126–30.
31. Karalis M, Wiesen K. Motivational interviewing. Nephrol Nurs J. 2007;34(3):336–8.
32. Rollnick S, Miller WR, Butler CC. Motivational interviewing in health care: helping patients change behavior. New York: Gilford Press; 2008.
33. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005;55:305–12.
34. Russell CL, Cronk NJ, Herron M, Knowles N, Matteson ML, Peace L, et al. Motivational Interviewing in Dialysis Adherence Study (MIDAS). Nephrol Nurs J. 2011;38(3):229–36.

Chapter 27
Outcomes Research

Laura D. Byham-Gray

Key Points

- To define the principles and processes of outcomes research.
- To discuss potential outcomes research projects in nutrition and kidney disease.
- To identify the role of nutrition in patient outcomes among individuals diagnosed with kidney disease.

Keywords Outcomes research • Comparative effectiveness research • Kidney disease • Nutrition • Morbidity • Mortality • Evidence-based practice • Medical nutrition therapy • Dialysis Outcomes and Practice Patterns Study (DOPPS) • Agency for Healthcare Research and Quality (AHRQ)

Introduction and Overview

Despite advances in medicine and technology, clinical outcomes among patients diagnosed with chronic kidney disease (CKD) have remained suboptimal. In the United States, one out of two patients diagnosed with CKD receiving maintenance dialysis (MD) will die within 3 years of initiating renal replacement therapy (RRT), translating to a death risk that is 6.5–7.4 times higher than in the general population [1]. Patients diagnosed with CKD on MD often experience a lower quality of life (QoL), greater risk of morbidity, higher rates for hospitalization, and increased mortality when compared with the general population [2–5]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), which will be discussed later in the chapter, has identified that the annual mortality rate among dialysis patients in the United States is approximately 22 % [6, 7]. Japan and Europe report substantially lower first-year crude mortality rates, 7 % and 16 %, respectively [6, 8]. Although the United States dialyzes patients with higher mean ages (60.5 ± 15.5 years) and a larger number of comorbid diseases, when regression models were adjusted for such case-mix factors, the United States still had higher overall morbidity and mortality rates [7].

Historically, much of the focus in kidney disease had been on the burgeoning end-stage kidney disease (ESKD) population and the respective RRTs necessary for life maintenance; i.e., hemodialysis (HD), peritoneal dialysis (PD), and transplantation. For the first time in decades, the incidence

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of individuals advancing to ESKD has slowed, and may be related to the greater emphasis on early screening for CKD in primary care settings leading to more timely and appropriate intervention [1]. While the rate of individuals diagnosed with CKD has declined, the death rate within this patient population is still reported as high as 147 cases per 1,000 cases [1]. Even though a small percentage of the over 26 million individuals with CKD progress to ESKD, they are more likely to die than to initiate dialysis [9, 10]. Capturing the patient once at stage 5 CKD may be too late to make meaningful changes in the factors associated with poorer outcome [11].

This chapter will give a brief overview of the importance for studying the role that nutrition status has on key clinical outcomes in CKD, a clear description of outcomes research and its related methodology, as well as a thorough discussion of clinical guidelines and their role in reducing practice variation.

Challenges for Nutrition

The importance of nutrition in the treatment and management of CKD is unquestionable. The relationship between nutritional status and morbidity and mortality has been researched extensively. There are a multitude of outcomes across the spectrum of kidney disease that could and should be measured. For example, bone disease, diabetes, dyslipidemias, hypertension, dialysis adequacy, and anemia are all either directly or indirectly related to nutrition intervention. Understanding how nutritional status impacts morbidity and mortality is seemingly more difficult than studying either dialysis adequacy or anemia management [12]. Protein-energy malnutrition or wasting is an independent contributor for mortality risk [13–19]. However, it remains unclear whether the malnutrition or wasting occurs over a period of time or as the result of a suboptimal status at the time of dialysis initiation; i.e., the association between malnutrition and death secondary to changes in nutrition status experienced over time or rather the presence of abnormalities at baseline [20]?

Multiple factors may explain the complexity of defining, treating, and reversing the malnutrition or wasting experienced, and comprise both nutritional and non-nutritional components [20]. Nutritional status can be assessed and "diagnosed" by using anthropometric measures, biochemical indices, clinical symptoms, or dietary intake records separately or together, therein lies the difficulty; the lack of one single measure that provides a good estimate of nutritional status [21]. Compounding these challenges is the impact of metabolic aberrations and hemodynamic imbalances secondary to CKD that may falsely affect nutrition parameters; e.g., non-nutritional factors such as inflammation or hydration status may interfere with the reliability of measuring nutritional status through conventional means. Acknowledging the complexity of protein-energy malnutrition, the International Society of Renal Nutrition and Metabolism (ISRNM) convened an expert panel that has proposed new nomenclature for protein-energy malnutrition with the intent of "systematically defin[ing] the diagnostic criteria" so that it will "clarify communication, enhance the effectiveness of patient care, and promote more incisive research in the field" [22]. The panel members have recommended the term protein-energy wasting (PEW) instead of protein-energy malnutrition since it incorporates a multifaceted explanation for the suboptimal nutritional status often experienced in CKD patients. PEW is further described in the article published by Fouque et al. [22].

Nutrition intervention or medical nutrition therapy (MNT) does make a positive impact on patient health outcomes. Studies have reported the effectiveness of nutrition intervention for a number of clinical outcomes related to disease states/conditions such as diabetes, hyperlipidemia, cancer, unintentional weight loss, as well as outcomes related to cost and health care utilization [23, 24]. Researchers have also explored the impact of nutrition intervention (e.g., counseling, oral supplementation, educational programs, intradialytic parenteral nutrition) on CKD patients [25–41]. Some of these investigations were limited by sample size and study duration and only a few were randomized

controlled trials that have specifically measured the effect of MNT on protein-energy malnutrition or wasting and improved outcomes. Certainly more research is needed to determine how nutrition therapy or dietetic practice patterns may affect outcomes.

Outcomes Research Defined

"The American health care delivery system is in need of fundamental change" is the opening statement to the Institute of Medicine's (IOM) report entitled *Crossing the Quality Chasm*: *A New Health Care System for the 21st Century*, *2001* [42]. It is a provocative beginning for "what works and what doesn't work in health care" [43]. Thus, the goals for outcomes research are really to determine [44]: Which treatments are the most effective? Which providers give the best care? Which health plans are the most efficient? Which delivery systems provide the most patient-centered care? Who produces the best outcomes? Obviously, patients, providers, payers, and policymakers are all interested in the answers to the above questions. Thus, the Agency for Health Care Research and Quality (AHRQ) was formulated with the specific charge to support OR, and thereby improve the quality of health care in the United States. Presently, there are several Evidence-Based Practice Centers organized by the AHRQ with the intent of conducting systematic reviews necessary for developing practice guidelines [14]. For example, five are dedicated to Center for Medicare and Medicaid Services (CMS) and one is for the United States Preventive Services Task Force (USPSTF).

Outcomes research is often referred to as the "third revolution in health care," and is defined as "the process of obtaining data to measure the effect of a particular intervention on patient care" [43]. It has also been termed as "medical effectiveness research (MER)" or "outcomes effectiveness research (OER)." Most recently, the AHRQ has described outcomes research as "comparative effectiveness research" (CER) and is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" [45]. In fact, the American Recovery and Reinvestment Act of 2009 (i.e., the Economic Stimulus Package) provided significant funding for CER through the AHRQ's Effective Health Care Program which focused on key research priorities aimed at improving patient care and outcome. In 2010, with the passing of the Patient Protection and Affordable Care Act, the Patient-Centered Outcomes Research Institute (PCORI), comprising a 21-member board that includes the directors from AHRQ and the National Institutes of Health (NIH), was formally devised to fund and promote CER that will "advanc[e] the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis" [46]. The PCORI includes an independent, federally appointed Methodology Committee who is charged with the mission of formulating the standards for PCOR. The four general areas identified by the committee in which standards will be developed are [47]: (1) prioritizing research questions, (2) using appropriate study designs and analyses, (3) incorporating patient perspectives throughout the research continuum, and (4) fostering efficient dissemination and implementation of results. Regardless of the acronym, outcomes research collects and analyzes data with the intent of aiding patients, health professionals, insurers, and administrators in the selection of suitable medical treatment options and setting health care policy [48].

The benefits for conducting outcomes research are multiple [49, 50]: it identifies best practices and improves the knowledge base of medical and health sciences, quantifies cost-effectiveness of therapeutic interventions, supplies the basis for practice guidelines, formulates methods for continuous quality improvement (CQI), and sets benchmarking thresholds, aids in market decisions, and provides accountability.

There is a distinction to be made between outcomes management and outcomes research; both are equally important for patient care. Outcomes management is the outcomes data routinely collected by practitioners, and lays the groundwork for outcomes research [51]. Outcomes management allows the practitioner to participate in research at a more basic level, and fosters further professional development in research skills. Outcomes research employs controlled research procedures.

Seemingly, CQI or process improvement (PI) interfaces with outcomes management and outcomes research. CQI includes the analysis of the process(es), identification of key quality characteristics of the process, as well as the outcomes of interest. The measurements will often include data collection on key process variables rather than direct clinical care that are hypothesized to influence patient outcomes, such as frequency of contact, length of time between encounters, or when appointment scheduling occurs. Outcomes research, on the other hand, focuses closely on the impact of the treatment on patient outcome. Generally outcomes projects lead to changes in practice standards. Quality of care is then measured according to such standards; this aspect represents CQI.

One example of quality measures that serve as benchmarks is the end-stage renal disease (ESRD) Clinical Performance Measures (CPMs) Project funded by the CMS [52, 53]. This project was completed secondary to the Balanced Budget Act (BBA) which mandated that "CMS develop and implement, by January 1, 2000, a method to measure and report the quality of renal dialysis services provided under the Medicare program" [52]. CMS formulated performance measures based on the National Kidney Foundation's Dialysis Outcome Quality Initiative (DOQI) Clinical Practice Guidelines, and changed the original benchmarks of the ESRD Core Indicators Project to include algorithms that applied the CPMs as well as generated a number of data collection instruments and their respective methodologies. Sixteen ESRD CPMs were rated: five for hemodialysis (HD) adequacy, three for peritoneal dialysis (PD) adequacy, four for anemia management, and four for vascular access [53]. Based on the pilot-testing of the original CPMs, input from content experts, and recommendations of the KDOQI clinical practice guidelines, in 2008, CMS accepted a total of 26 CPMs in order to more comprehensively monitor the quality of care delivery to the ESRD population, and these CPMs are available at the CMS website [53]. In 2010, CMS convened six Clinical Technical Expert Panels (C-TEPs) to obtain further insight and guidance in accordance to new quality measures specific to the management of fluid, anemia, bone and mineral disorders, and vascular access [53]. Such indicators, although measured in the context of outcomes management, can be rich sources of data for potential outcomes research projects [53].

Types of Outcomes

Although categories in the literature may slightly vary, there are generally three "types of outcomes": clinical, patient-oriented, and economic. Clinical outcomes focus on health-status outcomes and can include mortality, risk factors, changes in development or progression of symptoms, disease and its sequelae, and complications from treatment [43, 50]. Some sample types related to nutrition and CKD are provided in Table 27.1 [54]. Patient-oriented outcomes give attention to the consequences of intervention that are of concern to patients/families, such as survival, symptom relief, adverse effects of the condition or its treatment, functional status, QoL, and satisfaction. Economic outcomes are related to indicators that reduce length of stay, minimize care costs, or maximize revenue generation. A number of resources are available on outcomes research that the practitioner may find useful which fully define validated measurements to use for studying these types of outcomes [44, 55–57]. For example, if the practitioner wanted to study the effects of nutrition status on QoL (patient-oriented outcome), she/he would need to consult a number of validated tools to determine which one measured the constructs of interest.

Table 27.1 Main types of outcome measures with nutrition-related examples cited

Clinical outcomes	*Economic outcomes*
Mortality rate	MNT reimbursement
Weight status	Length of stay
Body mass index	Hospitalizations
Subjective global assessment	Delays in CKD progression
Albumin or pre-albumin levels	Cost of enteral versus parenteral nutritional supplementation
Lean body mass	Cost-benefits of MNT versus other adjunctive therapies
C-reactive protein	
Normalized protein catabolic rate	
Interdialytic weight gains	
Patient-oriented outcomes	
Ability to live independently	
Perception of patient care received	
Health-related quality of life	
Symptom relief from early satiety	
Functional status	

Adapted from [54]

Attributes of good outcome variables are "objective, precise, quantitative and translatable" [43]. Dhingra and Laski add that they should be "valid, reproducible, actionable, and comparable over geographic, demographic and temporal boundaries"; allowing for benchmarking to occur [58]. Thus, one way to initiate more outcomes research in clinical practice specifically in kidney disease is to use the outcomes measures published in evidence-based practice guidelines.

Evidence-Based Practice Guidelines

Variances in patient outcome and survival among industrialized countries (e.g., the United States, Europe, Canada, Australia, and Japan) were first recognized in 1989 at the Dallas symposium on morbidity and mortality of dialysis patients [59]. The United States reported the largest number of new patients with ESKD maintained on dialysis but also registered the highest crude mortality rate, ranging from 22 to 24 %. Such results motivated several organizations and regulatory agencies (e.g., National Institutes of Health, Health Care Financing Administration, Kidney Physicians Association) to focus on efforts for improving the quality of care delivered to dialysis patients in the United States. This emphasis on "medical effectiveness" led to the creation of the Dialysis Outcomes Quality Initiative (DOQI) Project of the National Kidney Foundation (NKF) in 1995. To reflect a broader mission of improving the health status of patients across the spectrum of kidney disease, DOQI was later named in 1999 as the Kidney Disease Outcomes Quality Initiative (KDOQI). The first DOQI guidelines were released in 1997 with subsequent updates and topics expanded from dialysis adequacy, vascular access, and anemia to peritoneal dialysis, nutrition, CKD, dyslipidemia, bone disease, hypertension, and diabetes [60].

Concomitantly, other countries initiated their own system for creating and developing practice guidelines [61]. For example, besides the United States, there were four other international guidelines published on nutrition and CKD [62]. Although similar recommendations were established internationally, the target ranges or values for specific outcome measures and how the evidence was rated may be highly variable. A more uniform approach for evidence analysis was needed; therefore, the concept of KDIGO (which stands for Kidney Disease: Improving Global Outcomes) was conceived. Its mission is "to improve care and outcomes of kidney disease patients worldwide through promoting

coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines" [63]. Presently, there are eight international clinical practice guidelines published on critical topic such as transplantation, bone and mineral disorders, hepatitis C, and acute kidney injury, with these and others under constant review and development [63].

Practice Guidelines and Patient Care

There is limited research whether practice guidelines actually affect clinical practice. Nonetheless, successful implementation of evidence-based guidelines can improve outcomes [64, 65]. Sugarman and associates have outlined the methods for making the CPMs measurable indicators of quality; based on the KDOQI evidence-based guidelines [52]. In addition, the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) has published a number of toolkits related to their clinical practice guidelines in nutrition including one on CKD, which provides several reliable indicators for measuring nutritional status and monitoring outcomes [66, 67]. A great initial outcomes research project may be to examine whether integrating such guidelines does impact care. It represents a relatively simple study design, and no investigations of this nature currently exist in nutrition and CKD.

Nonetheless, there are challenges to implementing guidelines into practice; often out of the practitioner's purview. Burrowes et al. [68] surveyed renal dietitians about whether they implemented the KDOQI Nutrition Guidelines. The vast majority (92 %) had integrated at least one guideline into practice, whereas only 5 % had implemented all of them. Dietitians were unable to change their clinical practice according to the best evidence, as a number of barriers existed, such as unavailable equipment or tools (e.g., computers, food models, and calipers), high patient-to-dietitian staffing ratios, or the lack of administrative support for change. In a study published 5 years later by Vergili and Wolfe, it was evident that there was still substantial practice variation among renal dietitians in relation to the KDOQI Nutrition Guidelines [69]. Reasons given by the survey respondents included challenges within the practice setting as well as relevance of the guidelines published in 2000 to current practice. Thus, it is increasingly difficult to determine the impact of practice guidelines on patient outcomes if resources are lacking for their successful implementation. Given such concerns in general clinical practice, the DOPPS has attempted to quantify recommendations published by KDOQI as well as other agencies and organizations [61].

Dialysis Outcomes and Practice Patterns Study

Discrepancies in patient outcomes are believed to be largely related to varying practice patterns. A detailed investigation entitled the Dialysis Outcomes and Practice Patterns Study (DOPPS) was initiated in 1996. The goal of DOPPS was "to increase the longevity of patients on hemodialysis." DOPPS measures a large number of practice patterns to detect new evidence for modifiable treatment factors that are associated with improved outcomes [61]. DOPPS is a large, international, observational, prospective hemodialysis (HD) study which originally involved seven countries (Japan, the United States, and five European countries France, Germany, Italy, Spain, and the United Kingdom) and was expanded to 12 with the addition of Australia/New Zealand, Belgium, Canada, and Sweden [70]. A more detailed discussion of the study is available elsewhere [70, 71]. DOPPS gathers substantial data regarding the patient's demographic characteristics, medical history, laboratory values, drug therapies and prescriptions, dialysis unit practices, and outcomes [72]. It seeks to identify what dialysis practices reduce mortality rates, lower hospitalizations, enhance health-related QoL, and improve

vascular access outcomes after controlling for the effects of comorbid diseases and demographic variables. Over 100 papers have been published using this dataset, with results reported concerning key nutrition indicators [16, 17, 73, 74]. Nutrition-related outcomes associated with increased mortality include low body mass index (BMI), substandard SGA score, and hypoalbuminemia. Poorer nutrition-related outcomes are cited among the US patients in comparison to other countries. In future analyses, DOPPS is expected to supply more insight about therapeutic interventions used at the dialysis facilities that may result in better nutrition-related outcomes, and provide direction towards what variables to study more closely to affect clinical practice changes.

Summary

The incidence of CKD patients is expanding in the United States but sadly, poor outcomes prevail. The complexity of protein-energy malnutrition or wasting impedes its understanding, treatment, and subsequent elimination as a contributor towards the morbidity and mortality experienced in this specific patient population. The generation of evidence-based practice guidelines assists in positively affecting change in practice to optimize outcomes, and serves as sources for measurable indicators in outcomes research. Existing databases have revealed a strong link between nutrition and outcomes in CKD. More research should concentrate on these areas of nutrition intervention in order to improve outcomes, provide direction for future study, and potentially create changes in clinical practice.

References

1. United States Renal Data System. Annual data report 2012. http://www.usrds.org/adr.htm. Accessed 1 Sept 2013.
2. Nicolucci A, Procaccini DA. Why do we need outcomes research in end-stage kidney disease? J Nephrol. 2000; 13:401–4. Accessed 1 Sept 2013
3. Kalantar-Zadeh K, Kopple JD, Block G, et al. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. J Am Soc Nephrol. 2001;12:2797–806.
4. Lopes A, Bragg-Gersham JL, Goodkin DA, Fukuhara S, Mapes DL, Young EW, Gillespie BW, Akizawa T, Greenwood RN, Andreucci VE, Akiba T, Held PJ, Port FK. Factors associated with health-related quality of life among hemodialysis patients in DOPPS. Qual Life Res. 2007;16(4):545–57.
5. Rambod M, Bross R, Zitterkoph J, et al. Association of malnutrition-inflammation score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. Am J Kidney Dis. 2009;53:298–309.
6. Goodkin D, Young EW, Kurokawa K, Prutz K-G, Levin N. Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. Am J Kidney Dis. 2004;44(5 Suppl 2):S16–21.
7. Foley RN, Hakim RM. Why is the mortality of dialysis patients in the United States much higher than the rest of the world? J Am Soc Nephrol. 2009;20(7):1432–5.
8. Goodkin D, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FT, Held PJ, Young EW. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes Practice Patterns Study (DOPPS). J Am Soc Nephrol. 2003;14(12):3270–7.
9. Keith D, Nichols GA, Gullion C, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164:659–63.
10. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038–47.
11. Komenda P, Levin A. Analysis of cardiovascular disease and kidney outcomes in multidisciplinary chronic kidney disease clinics: complex disease requires complex care models. Curr Opin Nephrol Hypertens. 2006;15:61–6.
12. Szczech L. What has outcomes research taught us about evidence-based treatment of end-stage kidney disease? J Clin Outcomes Manage. 2002;9:509–14.
13. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15(5):458–82.
14. Hakim R, Levin N. Malnutrition in hemodialysis patients. Am J Kidney Dis. 1994;21(2):125–37.

15. Kalantar-Zadeh K, Kopple JD, Block G, et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance dialysis patients. Am J Kidney Dis. 2001;38:1251–63.
16. Pifer T, McCullough KP, Fort FK, Goodkin DA, Maroni BJ, Held PJ, Young EW. Mortality risk in hemodialysis patients and changes in nutritional indicators: Dialysis Outcomes Practice Patterns Study (DOPPS). Kidney Int. 2002;62(4):2238–45.
17. Lopes AA, Bragg-Gresham JL, Elder SJ, Ginsberg N, Goodkin DA, Pifer T, et al. Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Ren Nutr. 2010;20(4):224–34.
18. de Araújo IC, Kamimura MA, Draibe SA, Canziani MEF, Manfredi SR, Avesani CM, et al. Nutritional parameters and mortality in incident hemodialysis patients. J Ren Nutr. 2006;16(1):27–35.
19. Leinig CE, Moraes T, Ribeiro S, Riella MC, Olandoski M, Martins C, et al. Predictive value of malnutrition markers for mortality in peritoneal dialysis patients. J Ren Nutr. 2011;21(2):176–83.
20. McClellan W, Rocco MV, Flanders WD. Epidemiologic cohort studies of critical nutritional issues in the care of the dialysis patient. Report of the Epidemiology Work Group. J Ren Nutr. 1999;9:133–7.
21. National Kidney Foundation. Kidney Disease Dialysis Outcome Quality Initiative (KDOQI) clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35 Suppl 2:S1–140.
22. Fouque D, Kalantar-Zadeh K, Kopple JD, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen GA, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391–8.
23. Lemon C, Lacey K, Lohse B, et al. Outcomes monitoring of health, behavior, and quality of life after nutrition intervention in adults with type 2 diabetes. J Am Diet Assoc. 2004;104:1805–15.
24. Franz M, Splett PL, Monk A. Cost-effectiveness of medical nutrition therapy provided by persons with non-insulin-dependent diabetes mellitus. J Am Diet Assoc. 1995;95:1018–24.
25. McGehee M, Johnson EQ, Rasmussen HM, et al. Benefits and costs of medical nutrition therapy by registered dietitians for patients with hypercholesterolemia. J Am Diet Assoc. 1995;95:1041–3.
26. Delahanty L, Sonnenberg LA, Hayden D, et al. Clinical and cost outcomes of medical nutrition therapy in hypercholesterolemia: a controlled trial. J Am Diet Assoc. 2001;101:1012–23.
27. Tosteson A, Weinstein MC, Hunink MGM, et al. Cost-effectiveness of population wide educational approaches to reduce serum cholesterol levels. Circulation. 1997;95:24–30.
28. Pavlovich W, Waters H, Weller W, et al. Systematic review of literature on cost-effectiveness of nutrition services. J Am Diet Assoc. 2004;104:226–32.
29. Isenring E, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. Br J Cancer. 2004;91:447–52.
30. Splett P, Roth-Yousey LL, Vogelzang JL. Medical nutrition therapy for the prevention and treatment of unintentional weight loss in residential healthcare facilities. J Am Diet Assoc. 2003;103:352–62.
31. Campbell KL, Ash S, Zabel R, McFarlane C, Juffs P, Bauer JD. Implementation of standardized nutrition guidelines by renal dietitians is associated with improved nutrition status. J Ren Nutr. 2009;19(2):136–44.
32. Prasad N, Gupta A, Sinha A, Sharma RK, Kumar A, Kumar R. Changes in nutritional status on follow-up of an incident cohort of continuous ambulatory peritoneal dialysis patients. J Ren Nutr. 2008;18(2):195–201.
33. Akers JD, Cornett RA, Savla JS, Davy KP, Davy BM. Daily self-monitoring of body weight, step count, fruit/vegetable intake, and water consumption: a feasible and effective long-term weight loss maintenance approach. J Acad Nutr Diet. 2012;112(5):685–92.e2.
34. Campbell KL, Van Patten CL, Neil SE, Kirkham AA, Gotay CC, Gelmon KA, et al. Feasibility of a lifestyle intervention on body weight and serum biomarkers in breast cancer survivors with overweight and obesity. J Acad Nutr Diet. 2012;112(4):559–67.
35. Krause I, Shamir R, Davidovits M, et al. Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. J Ren Nutr. 2002;12:55–9.
36. Shaw-Stuart N, Stuart A. The effect of an educational patient compliance program on serum phosphate levels in patients receiving hemodialysis. J Ren Nutr. 2000;10:80–4.
37. Wilson B, Fernandez-Madrid A, Hayes A, et al. Comparison of the effects of two early intervention strategies on the health outcomes of malnourished hemodialysis patients. J Ren Nutr. 2001;11:166–71.
38. Beutler K, Park GK, Wilkowski MJ. Effect of oral supplementation on nutrition indicators in hemodialysis patients. J Ren Nutr. 1997;7:77–82.
39. Akpele L, Bailey JL. Nutrition counseling impacts serum albumin levels. J Ren Nutr. 2004;14(3):143–8.
40. Caldeira D, Amaral T, David C, Sampaio C. Educational strategies to reduce serum phosphorus in hyperphosphatemic patients with chronic kidney disease: systematic review with meta-analysis. J Ren Nutr. 2011;21(4):285–94.
41. Małgorzewicz S, Rutkowski P, Jankowska M, Dębska- Ślizień A, Rutkowski B, Łysiak-Szydłowska W. Effects of renal-specific oral supplementation in malnourished hemodialysis patients. J Ren Nutr. 2011;21(4):347–53.
42. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.

43. Splett PL. Outcomes research and cost-effectiveness. In: Monsen E, editor. Research: successful approaches. 2nd ed. Chicago, IL: The American Dietetic Association; 2008.
44. Iezzoni L. Risk adjustment for measuring health care outcomes. Chicago, IL: Health Administration Press; 2003.
45. Agency for Healthcare Research and Quality. Comparative effectiveness research. http://effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/. Accessed 1 Sept 2013.
46. Patient Protection and Affordable Care Act. Publ No. 111-148, 124 Stat 727, 6301 (2010). Accessed 1 Sept 2013.
47. Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) National priorities for research and initial research agenda. JAMA. 2012;307(15):1583–4.
48. August DA. Creation of a specialized nutrition support outcomes research continuum: if not now, when? J Parenter Enteral Nutr. 1996;20:394–400.
49. Inman-Felton AE. The fundamentals of outcomes research: demonstrating the effectiveness of nutrition interventions. Support Line. 1997;3:13–7.
50. Kane R, Radosevich DM. Conducting health outcomes research. Boston, MA: Jones and Bartlett Publishers; 2011.
51. Biesemeier C. Demonstrating the effectiveness of medical nutrition therapy. Top Clin Nutr. 1999;14:13–24.
52. Sugarman J, Frederick PR, Frankenfield DL, et al. Developing clinical performance measures based on the dialysis outcomes quality initiative clinical practice guidelines: process, outcomes, and implications. Am J Kidney Dis. 2003;42:806–12.
53. Center for Medicare and Medicaid Services. Clinical Performance Measures Project. http://www.cms.gov/Medicare/End-Stage-Renal-Disease/CPMProject/index.html?redirect=/CPMProject/. Accessed 1 Sept 2013.
54. Schiller MR, Moore C. Practical approaches to outcomes evaluation. Top Clin Nutr. 1999;14(2):1–12. Accessed 1 Sept 2013.
55. Block DJ. Healthcare outcomes management: strategies for planning and evaluation. Boston, MA: Jones and Bartlett Publishers; 2006.
56. Kane R. Understanding health care outcomes research. Boston, MA: Jones & Bartlett Publishers; 2004.
57. Nolan M, Mock V. Measuring patient outcomes. Thousand Oaks, CA: Sage; 2000.
58. Dhingra H, Laski ME. Outcomes research in dialysis. Semin Dial. 2003;23(3):295–305.
59. Hull A, Parker T. Proceedings from the morbidity, mortality, and prescription of dialysis symposium. Dallas, TX. September 15–17, 1989. Am J Kidney Dis. 1990;15:365–83.
60. National Kidney Foundation. Clinical practice guidelines. http://www.kidney.org/professional. Accessed 1 Sept 2013.
61. Port F, Eknoyan G. The Dialysis Outcomes and Practice Patterns Study (DOPPS) and the Kidney Disease Outcomes Quality Initiative (KDOQI): a cooperative initiative to improve outcomes for hemodialysis patients worldwide. Am J Kidney Dis. 2004;44(5 Suppl 2):S1–6.
62. Kidney Disease-Improving Global Outcomes (KDIGO). Nephrology guideline database. http://www.kdigo.org/nephrology_guideline_database/index.php. Accessed 1 Sept 2013.
63. Kidney Disease-Improving Global Outcomes. Mission. http://www.kdigo.org. Accessed 1 Sept 2013.
64. Collins A, Roberts TL, St Peter WL, et al. United Renal Data System assessment of the impact of the National Kidney Foundation-dialysis outcomes quality initiative guidelines. Am J Kidney Dis. 2002;39:784–95.
65. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362:1225–30.
66. American Dietetic Association. Evidence-based guidelines for critical illness 2008. http://www.adaevidencelibrary.com/topic.cfm?cat=2799. Accessed 16 April 2012.
67. American Academy of Nutrition and Dietetics. Chronic Kidney Disease Evidence Analysis Library. http://www.adaevidencelibrary.com. Accessed 16 April 2012.
68. Burrowes J, Russell GB, Rocco MV. Multiple factors affect renal dietitians' use of the NKF K/DOQI adult nutrition guidelines. J Ren Nutr. 2005;15(4):407–26.
69. Vergili J, Wolf RL. Nutrition practices of renal dietitians in hemodialysis centers throughout the United States: a descriptive study. J Ren Nutr. 2010;20(1):8–16.
70. Pisoni R, Gillespie BW, Dickinson DE, et al. The dialysis outcomes and practice patterns study: design, data elements, and methodology. Am J Kidney Dis. 2004;44 Suppl 2:S7–15.
71. Pisoni R, Greenwood RN. Selected lessons learned from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Contrib Nephrol. 2005;149:58–68.
72. Goodkin D, Mapes DL, Held PJ. The Dialysis Outcomes Practice Patterns Study (DOPPS): how can we improve the care of hemodialysis patients? Semin Dial. 2001;14:157–9.
73. Hecking E, Bragg-Gresham JL, Rayner HC, et al. Haemodialysis prescription and nutritional indicators in five European countries: Results from the Dialysis Outcomes Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2004;19:100–7.
74. Combe C, McCullough KP, Asano Y, et al. Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): nutrition guidelines, indicators, and practices. Am J Kidney Dis. 2004;44 Suppl 2:S39–46.

Chapter 28
Suggested Resources for the Practitioner

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Key Points

- To find information on topics related to kidney disease and related fields.
- To access information in a systematic and well-defined manner.
- To share information and to distribute it to those persons who are in need and will benefit from this knowledge.
- To identify the vast number of resources available.

Keywords Nutrition practice guidelines • Nutritional assessment tools • Nutrition education resources • Potassium sources • Phosphorus sources • Phosphorus additives • Oxalate

Introduction

This chapter was developed with the practitioner in mind. Its primary goal is to be a handy reference for the enumerable resources needed and used by the practitioner in chronic kidney disease (CKD). The chapter's organization includes four basic sections: (1) evidence-based practice guidelines, (2) diet-related resources and food lists, (3) critical tools for conducting nutrition assessments and delivering quality care, and (4) internet websites and applications. Much of what is contained in this chapter may augment topics already presented and discussed in earlier chapters.

Evidence-Based Practice Guidelines

Practitioners in CKD have several evidence-based practice guidelines at their disposal that will assist them in evaluating each patient's status and making appropriate clinical decisions for care delivery. These include those issued by the National Kidney Foundation (NKF) and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association). The following highlight the key nutrition-related guidelines for this population.

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NKF KDOQI Practice Guideline Statements

The NKF and their appointed Work Groups as part of the Kidney Disease Outcomes Quality Initiative (KDOQI) have published a number of practice guidelines related to topics of dialysis adequacy, cardiovascular disease, anemia, bone disease, and, of course, nutrition, as well as many others. The reader is encouraged to consult the NKF website (www.kidney.org) for routine updates and full explanation and details of each practice guideline. Due to space limitations, what are addressed in the next section are the summary practice guideline statements that discuss nutrition management in CKD for adults and children, bone disease, and diabetes only [1–4].

KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (http://www.kidney.org/professionals/kdoqi/pdf/KDOQI2000NutritionGL.pdf). Source: [1], used with permission from Elsevier Limited.

A. Maintenance Dialysis

1. Evaluation of Protein-Energy Nutritional Status

   Guideline 1. Use of Panel of Nutritional Measures
   Nutritional status in maintenance dialysis (MD) patients should be assessed with a combination of valid, complementary measures rather than any single measure alone (*Opinion*).

   Guideline 2. Panels of Nutritional Measures for Maintenance Dialysis Patients
   For MD patients, nutritional status should be routinely assessed by predialysis or stabilized serum albumin, percent of usual body weight, percent of standard (NHANES II) body weight, subjective global assessment, dietary interviews and diaries, and normalized protein nitrogen appearance (nPNA) (*Opinion*).

   Guideline 3. Serum Albumin
   Serum albumin is a valid and clinically useful measure of protein-energy nutritional status in MD patients (*Evidence*).

   Guideline 4. Serum Prealbumin
   Serum prealbumin is a valid and clinically useful measure of protein-energy nutritional status in MD patients (*Evidence and Opinion*).

   Guideline 5. Serum Creatinine and Creatinine Index
   Serum creatinine and the creatinine index are valid and clinically useful measures of protein-energy nutritional status in MD patients (*Evidence and Opinion*).

   Guideline 6. Serum Cholesterol
   Serum cholesterol is a valid and clinically useful measure of protein-energy nutritional status in MD patients (*Evidence and Opinion*).

   Guideline 7. Dietary Interviews and Diaries
   Dietary interviews and/or diaries are valid and clinically useful for measuring dietary protein and dietary energy intake (DEI) in MD patients (*Evidence and Opinion*).

   Guideline 8. Protein Equivalent of Total Nitrogen Appearance (PNA)
   PNA or Protein Catabolic Rate (PCR) is a valid and clinically useful measure of net protein degradation and protein intake in MD patients (*Evidence*).

   Guideline 9. Subjective Global Assessment (SGA)
   SGA is a valid and clinically useful measure of protein-energy nutritional status in MD patients (*Evidence*).

Guideline 10. Anthropometry
Anthropometric measurements are valid and clinically useful indicators of protein-energy nutritional status in MD patients (*Evidence and Opinion*).

Guideline 11. Dual Energy X-Ray Absorptiometry (DXA)
DXA is a valid and clinically useful technique for assessing protein-energy nutritional status (*Evidence and Opinion*).

Guideline 12. Adjusted Edema-Free Body Weight (aBW_{ef})
The body weight to be used for assessing or prescribing protein or energy intake is the aBW_{ef}. For hemodialysis (HD) patients, this should be obtained postdialysis. For peritoneal (PD) patients, this should be obtained after drainage of dialysate (*Opinion*).

2. Management of Acid–Base Status

Guideline 13. Measurement of Serum Bicarbonate
Serum bicarbonate should be measured in MD patients once monthly (*Opinion*).

Guideline 14. Treatment of Low Serum Bicarbonate
Predialysis or stabilized serum bicarbonate levels should be maintained at or above 22 mmol/L (*Evidence and Opinion*).

3. Management of Protein and Energy Intake

Guideline 15. Dietary Protein Intake (DPI) in Maintenance Hemodialysis (MHD)
The recommended DPI for clinically stable MHD patients is 1.2 g/kg body weight/day (*Evidence and Opinion*).

Guideline 16. DPI in Chronic Peritoneal Dialysis (CPD)
The recommended DPI for clinically stable CPD patients is 1.2–1.3 g/kg body weight/day (*Evidence*).

Guideline 17. Daily Energy Intake (DEI) for MD Patients
The recommended DEI for MHD or CPD patients is 35 kcal/kg body weight/day for those who are less than 60 years of age and 30–35 kcal/kg body weight/day for individuals 60 years or older (*Evidence and Opinion*).

4. Nutritional Counseling and Follow-up

Guideline 18. Intensive Nutritional Counseling with MD
Every MD patient should receive intensive nutritional counseling based on an individualized plan of care developed before or at the time of commencement of MD therapy (*Opinion*).

Guideline 19. Indications for Nutrition Support
Individuals undergoing MD who are unable to meet their protein and energy requirements with food intake for an extended period of time should receive nutritional support (*Evidence and Opinion*).

Guideline 20. Protein Intake During Acute Illness
The optimum protein intake for a MD patient who is acutely ill is at least 1.2–1.3 g/kg/day (*Opinion*).

Guideline 21. Energy Intake During Acute Illness
The recommended energy intake for a MD patient who is acutely ill is at least 35 kcal/kg/day for those who are less than 60 years of age and at least 30–35 kcal/kg/day for those who are 60 years of age or older (*Evidence and Opinion*).

Guideline 22. L-Carnitine for MD Patients
There are insufficient data to support the routine use of L-carnitine for MD patients (*Evidence and Opinion*).

B. Advanced Chronic Renal Failure without Dialysis

Guideline 23. Panels of Nutritional Measures for Nondialyzed Patients
For individuals with chronic renal failure (CRF) (GFR < 20 mL/min/1.73 m^2), protein-energy nutritional status should be evaluated by serial measurements of a panel of markers including at least one value from each of the following clusters: (1) serum albumin; (2) edema-free actual body weight, percent standard (NHANES II) body weight, or SGA; and (3) nPNA or dietary interviews and diaries (*Evidence and Opinion*).

Guideline 24. DPI for Nondialyzed Patients
For individuals with CRF (GFR < 25 mL/min/1.73 m^2) who are not undergoing MD, the institution of a planned low protein diet providing 0.60 g protein/kg/day should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate DEI with such a diet, an intake of up to 0.75 g/kg/day may be prescribed (*Evidence and Opinion*).

Guideline 25. DEI for Nondialyzed Patients
The recommended DEI for individuals with CRF (GFR < 25 mL/min/1.73 m^2) who are not undergoing MD is 35 kcal/kg/day for those who are younger than 60 years old and 30–35 kcal/kg/day for individuals who are 60 years of age or older (*Evidence and Opinion*).

Guideline 26. Intensive Nutritional Counseling for CRF
The nutritional status of individuals with CRF should be monitored at regular intervals (*Evidence*).

Guideline 27. Indications for Renal Replacement Therapy
In patients with CRF (GFR < 15–20 mL/min) who are not undergoing MD, if protein-energy malnutrition develops or persists despite vigorous attempts to optimize protein and energy intake and there is no apparent cause for malnutrition other than low nutrient intake, initiation of MD or a renal transplant is recommended (*Opinion*).

KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update (http://www.kidney.org/professionals/KDOQI/guidelines_ped_ckd/index.htm). Source: [2], used with permission from Elsevier Limited.

Recommendation 1. Evaluation of Growth and Nutritional Status

1.1 The nutritional status and growth of all children with CKD stages 2–5 and 5D should be evaluated on a periodic basis (Strength of Recommendation-[A] intervention "should be done").
1.2 The following parameters of nutritional status and growth should be considered in combination for evaluation in children with CKD stages 2–5 and 5D (Strength of Recommendation-[B] intervention "should be considered").

(i) Dietary intake
(ii) Length- or height-for-age percentile or standard deviations scores (SDS)
(iii) Length or height velocity-for-age percentile or SDS
(iv) Estimated dry weight and weight-for-age percentile or SDS
(v) BMI-for-height-age percentile or SDS
(vi) Head circumference-for-age percentile or SDS (≤3 years old only)
(vii) Normalized PCR in hemodialyzed adolescents with CKD stage 5D

1.3 Frequency of monitoring nutritional and growth parameters in all children with CKD stages 2–5 and 5D should be based on the child's age and stage of CKD. In general, assessments should be performed at least twice as frequently as they would be performed in a healthy child of the same age. Infants and children with polyuria, evidence of growth delay, decreasing or low BMI, comorbidities influencing growth or nutrient intake, or recent acute changes in medical status or dietary intake may warrant more frequent evaluation (Strength of Recommendation-[C] intervention "suggested").

Recommendation 2. Growth

2.1 Identification and treatment of existing nutritional deficiencies and metabolic abnormalities should be aggressively pursued in children with CKD stages 2–5 and 5D, short stature (height SDS < −1.88 or height-for-age <3rd percentile), and potential for linear growth (Strength of Recommendation-[A]).
2.2 Serum bicarbonate level should be corrected to at least the lower limit of normal (22 mmol/L) in children with CKD stages 2–5 and 5D (Strength of Recommendation-[B]).
2.3 Recombinant human growth hormone therapy should be considered in children with CKD stages 2–5 and 5D, short stature, and potential for linear growth if growth failure (height velocity-for-age SDS < −1.88 or height velocity-for-age <3rd percentile) persists beyond 3 months despite treatment of nutritional deficiencies and metabolic abnormalities (Strength of Recommendation-[B]).

Recommendation 3. Nutritional Management and Counseling

3.1 Nutrition counseling, based on an individualized assessment and plan of care, should be considered for children with CKD stages 2–5 and 5D (Strength of Recommendation-[B]).
3.2 Nutritional intervention that is individualized according to the results of the nutritional assessment and with consideration of child's age, development, food preferences, cultural beliefs, and psychosocial status should be considered for children with CKD stages 2–5 and 5D (Strength of Recommendation-[B]).
3.3 Frequent reevaluation and modification of the nutrition plan of care is suggested for children with CKD stages 2–5 and 5D. More frequent review is indicated for infants and children with advanced stages of CKD, relevant comorbidities influencing growth or nutrient intake, evidence of inadequate intake or malnutrition, or if acute illness or adverse events occur that may negatively impact on nutritional status (Strength of Recommendation-[C]).
3.4 Nutritional management, coordinated by a dietitian, and in a collaborative effort with the child, caregiver, and the multidisciplinary pediatric nephrology team, is suggested for children with CKD stages 2–5 and 5D (Strength of Recommendation-[C]).

Recommendation 4. Energy Requirements and Therapy

4.1 Energy requirements for children with CKD stages 2–5 and 5D should be 100 % of the EER for chronological age, individually adjusted for PAL and body size. Further adjustment to energy intake is suggested based upon the response in rate of weight gain or loss (Strength of Recommendation-[B]).
4.2 Supplemental nutritional support should be considered when the usual intake of a child with CKD stages 2–5 and 5D fails to meet his or her energy requirements and the child is not achieving expected rates of weight gain and/or growth for age (Strength of Recommendation-[B]).
4.3 Oral intake of energy-dense nutritional supplements should be considered the preferred route for supplemental nutritional support for children with CKD stages 2–5 and 5D. When energy requirements cannot be met with oral supplementation, tube feedings should be considered (Strength of Recommendation-[B]).

4.4 Trial intradialytic parenteral nutrition to augment inadequate nutritional intake is suggested for malnourished children (BMI-for height-age <5th percentile) receiving maintenance HD who are unable to meet their nutrition requirements through oral and tube feedings (Strength of Recommendation-[C]).
4.5 A balance of calories from carbohydrate and unsaturated fats recommended as the AMDR of the DRI is suggested when prescribing oral, enteral, or parenteral energy supplementation to children with CKD stages 2–5 and 5D (Strength of Recommendation-[C]).
4.6 Dietary and lifestyle changes are suggested to achieve weight control in overweight or obese children with CKD stages 2–5 and 5D (Strength of Recommendation-[C]).

Recommendation 5. Protein Requirements and Therapy

5.1 It is suggested to maintain DPI at 100–140 % of the DRI for ideal body weight in children with CKD stage 3 and at 100–120 % of the DRI in children with CKD stages 4–5 (Strength of Recommendation-[C]).
5.2 In children with CKD stage 5D, it is suggested to maintain DPI at 100 % of the DRI for ideal body weight plus an allowance for dialytic protein and amino acid losses (Strength of Recommendation-[C]).
5.3 Use of protein supplements to augment inadequate oral and/or enteral protein intake should be considered when children with CKD stages 2–5 and 5D are unable to meet their protein requirements though food and fluids alone (Strength of Recommendation-[B]).

Recommendation 6. Vitamin and Trace Element Requirements and Therapy

6.1 The provision of dietary intake consisting of at least 100 % of the DRI for thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8), cobalamin (B12), ascorbic acid (C), retinol (A), α-tocopherol (E), vitamin K, folic acid, copper, and zinc should be considered for children with CKD stages 2–5 and 5D (Strength of Recommendation-[B]).
6.2 It is suggested that supplementation of vitamins and trace elements be provided to children with CKD stages 2–5 if dietary intake alone does not meet 100 % of the DRI or if clinical evidence of a deficiency is present (Strength of Recommendation-[C]).
6.3 It is suggested that children with CKD stage 5D receive a water-soluble vitamin supplement (Strength of Recommendation-[C]).

Recommendation 7. Bone Mineral and Vitamin D Requirements and Therapy

7.1 Calcium

7.1.1 In children with CKD stages 2–5 and 5D, it is suggested that the total oral and/or enteral calcium intake from nutritional sources and phosphate binders be in the range of 100–200 % of the DRI for calcium for age (Strength of Recommendation-[C]).

7.2 Vitamin D

7.2.1 In children with CKD stages 2–5 and 5D, it is suggested that serum 25-hydroxyvitamin D levels be measured once per year (Strength of Recommendation-[C]).
7.2.2 If the serum level of 25-hydroxyvitamin D is less than 30 ng/mL, supplementation with vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) is suggested (Strength of Recommendation-[C]).
7.2.3 In the repletion phase, it is suggested that serum levels of corrected total calcium and phosphorus be measured at 1 month after initiation or change in dose of vitamin D and at least every 3 months thereafter (Strength of Recommendation-[C]).
7.2.4 When patients are replete with vitamin D, it is suggested to supplement vitamin D continuously and to monitor serum levels of 25-hydroxyvitamin D yearly (Strength of Recommendation-[C]).

7.3 Phosphorus

7.3.1 In children with CKD stages 3–5 and 5D, reducing dietary phosphorus intake to 100 % of the DRI for age is suggested when serum parathyroid hormone (PTH) is above the target range for CKD stage and serum phosphorus is within the normal reference range for age (Strength of Recommendation-[C]).

7.3.2 In children with CKD stages 3–5 and 5D, reducing dietary phosphorus intake to 80 % of the DRI for age is suggested when serum PTH level is above the target range for CKD stage and serum phosphorus exceeds the normal reference range for age (Strength of Recommendation-[C]).

7.3.3 After initiation of dietary phosphorus restriction, it is suggested that serum phosphorus be monitored at least every 3 months in children with CKD stages 3–4 and monthly in children with CKD stage 5 and 5D. In all CKD stages, it is suggested to avoid serum phosphorus concentrations both above and below the normal reference range for age (Strength of Recommendation-[C]).

Recommendation 8. Fluid and Electrolyte Requirements and Therapy

8.1 Supplemental free water and sodium supplements should be considered for children with CKD stages 2–5 and 5D and polyuria to avoid chronic intravascular depletion and to promote optimal growth (Strength of Recommendation-[B]).

8.2 Sodium supplements should be considered for all infants with CKD stage 5D on peritoneal dialysis therapy (Strength of Recommendation-[B]).

8.3 Restriction of sodium intake should be considered for children with CKD stages 2–5 and 5D who have hypertension or prehypertension (Strength of Recommendation-[B]).

8.4 Fluid intake should be restricted in children with CKD stages 3–5 and 5D who are oligoanuric to prevent the complications of fluid overload (Strength of Recommendation-[A]).

8.5 Potassium intake should be limited for children with CKD stages 2–5 and 5D who have or are at risk of hyperkalemia (Strength of Recommendation-[A]).

Recommendation 9. Carnitine

9.1 In the opinion of the Work Group, there is currently insufficient evidence to suggest a role for carnitine therapy in children with CKD stage 5D.

Recommendation 10. Nutritional Management of Transplant Patients

10.1 Dietary assessment, diet modifications, and counseling are suggested for children with CKD stages 1–5T to meet nutritional requirements while minimizing the side effects of immunosuppressive medications (Strength of Recommendation-[C]).

10.2 To manage posttransplantation weight gain, it is suggested that energy requirements of children with CKD stages 1–5T be considered equal to 100 % of the EER for chronological age, adjusted for PAL and body size. Further adjustment to energy intake is suggested based upon the response in rate of weight gain or loss (Strength of Recommendation-[C]).

10.3 A balance of calories from carbohydrate, protein, and unsaturated fats within the physiological ranges recommended by the AMDR of the DRI is suggested for children with CKD stages 1–5T to prevent or manage obesity, dyslipidemia, and corticosteroid-induced diabetes (Strength of Recommendation-[C]).

10.4 For children with CKD stages 1–5T and hypertension or abnormal serum mineral or electrolyte concentrations associated with immunosuppressive drug therapy or impaired kidney function, dietary modification is suggested (Strength of Recommendation-[C]).

10.5 Calcium and vitamin D intakes of at least 100 % of the DRI are suggested for children with CKD stages 1–5T. In children with CKD stages 1–5T, it is suggested that total oral and/or enteral calcium intake from nutritional sources and phosphate binders not exceed 200 % of the DRI (Strength of Recommendation-[C]).

10.6 Water and drinks low in simple sugars are the suggested beverages for children with CKD stages 1–5T with high minimum total daily fluid intakes (except those who are underweight) to avoid excessive weight gain, promote dental health, and avoid exacerbating hyperglycemia (Strength of Recommendation-[C]).

10.7 Attention to food hygiene/safety and avoidance of foods that carry high risk of food poisoning or food-borne infection are suggested for immunosuppressed children with CKD stages 1–5T (Strength of Recommendation-[C]).

KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (http://www.kidney.org/professionals/KDOQI/guidelines_bone/index.htm). Source: [3], used with permission from Elsevier Limited.

Guideline 3: Evaluation of Serum Phosphorus Levels

3.1 In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (*Evidence*) and no higher than 4.6 mg/dL (1.49 mmol/L) (*Opinion*).

3.2 In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis (HD) or peritoneal dialysis (PD), the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L) (*Evidence*).

Guideline 4: Restriction of Dietary Phosphorus in Patients with CKD

4.1 Dietary phosphorus should be restricted to 800–1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated (>4.6 mg/dL [1.49 mmol/L]) at Stages 3 and 4 of CKD (*Opinion*) and >5.5 mg/dL (1.78 mmol/L) in those with kidney failure (Stage 5) (*Evidence*).

4.2 Dietary phosphorus should be restricted to 800–1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact PTH are elevated above target range of the CKD stage (*Evidence*).

4.3 The serum phosphorus levels should be monitored every month following the initiation of dietary phosphorus restriction (*Opinion*).

Guideline 6: Serum Calcium and Calcium-Phosphorus Product

In CKD Patients (Stages 3 and 4):

6.1 The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used (*Evidence*).

In CKD Patients with Kidney Failure (Stage 5):

6.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4–9.5 mg/dL [2.10–2.37 mmol/L]) (*Opinion*).

6.3 In the event corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that cause serum calcium to rise should be adjusted as follows:

- 6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a non-calcium, non-aluminum, non-magnesium containing phosphate binder (*Opinion*).
- 6.3b In patients taking active vitamin D sterols, the dose should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range (8.4–9.5 mg/dL [2.10–2.37 mmol/L]) (*Opinion*).
- 6.3c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite modification of therapy with vitamin D and/or discontinuation of calcium-

based phosphate binders, dialysis using low dialysate calcium (1.5–2.0 mEq/L) may be used for 3–4 weeks (*Opinion*).

In CKD Patients (Stages 3–5):

6.4 Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day (*Opinion*).

6.5 The serum calcium–phosphorus product should be maintained at <55 mg^2/dL^2 (*Evidence*). This is best achieved by controlling serum levels of phosphorus within the target range (*Opinion*).

6.6 Patients whose serum levels of corrected total calcium are below the lower limit for the laboratory used (<8.4 mg/dL [2.10 mmol/L]) should receive therapy to increase serum calcium levels if:

6.6a There are clinical symptoms of hypocalcemia such as paresthesia, Chvostek's and Trousseau's signs, bronchospasm, laryngospasm, tetany, and/or seizures (*Opinion*).

6.6b The plasma intact PTH level is above the target range for the CKD Stage (*Opinion*).

6.7 Therapy for hypocalcemia should include calcium salts such as calcium carbonate (*Evidence*) and/or oral vitamin D sterols (*Evidence*).

Guideline 8: Vitamin D Therapy in CKD Patients

Guideline 8A: Active Vitamin D Therapy in Patients with Stages 3 and 4 CKD

8A.1 In patients with CKD stages 3 and 4, therapy with an active oral vitamin D sterol (calcitriol, alfacalcidol, or doxercalciferol) is indicated when serum levels of 25(OH)-vitamin D are >30 ng/mL (75 nmol/L), and plasma levels of intact PTH are above the target range for the CKD stage (*Evidence*).

8A.1a Treatment with an active vitamin D sterol should be undertaken only in patients with serum levels of corrected total calcium <9.5 mg/dL (2.37 mmol/L) and serum phosphorus <4.6 mg/dL (1.49 mmol/L) (*Opinion*).

8A.1b Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up (*Opinion*).

8A.2 During therapy with vitamin D sterols, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter (*Opinion*).

8A.3 Dosage adjustments for patients receiving active vitamin D sterol therapy should be made as follows:

8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage, hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing (*Opinion*).

8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to <9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing (*Opinion*).

8A.3c If serum levels of phosphorus rise to >4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy; initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to ≤4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol (*Opinion*).

Guideline 8B. Vitamin D Therapy in Patients on Dialysis (CKD Stage 5)

8B.1 Patients treated with HD or PD with serum levels of intact PTH levels >300 pg/mL (33.0 pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) to reduce the serum levels of PTH to a target range of 150–300 pg/mL (16.5–33.0 pmol/L) (*Evidence*).

8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels (*Evidence*).

8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range, a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol, may be warranted (*Opinion*).

8B.2 When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved (*Opinion*).

8B.3 For patients treated with peritoneal dialysis, oral doses of calcitriol (0.5–1.0 μg) or doxercalciferol (2.5–5.0 μg) can be given 2 or 3 times weekly. Alternatively, a lower dose of calcitriol (0.25 μg) can be administered daily (*Opinion*).

8B.4 When either hemodialysis or peritoneal dialysis patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH (*Opinion*).

Guideline 13. Treatment of Bone Disease in CKD

Guideline 13A. Hyperparathyroid (high-turnover) and mixed (high-turnover with mineralization defect) bone disease

13A.1 In CKD patients (stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (stage 3) or >110 pg/mL (12.1 pmol/L) (stage 4) on more than two consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol (*Evidence*) or one of its analogs [alfacalcidol (*Evidence*) or doxercalciferol (*Opinion*)] should be given to prevent or ameliorate bone disease.

13A.2 In CKD patients (stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol (*Evidence*) or one of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (*Opinion*) should be used to reverse the bone features of PTH overactivity (i.e., high-turnover bone disease), and to treat defective mineralization.

Guideline 13B. Osteomalacia

13B.3 Osteomalacia due to vitamin D_2 or D_3 deficiency or phosphate depletion, though uncommon, should be treated with vitamin D_2 or D_3 supplementation and/or phosphate administration, respectively (*Opinion*).

13B.3a If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (stage 5), treatment with an active vitamin D sterol may be given (*Opinion*).

13B.3b Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved (*Opinion*).

Guideline 13C. Adynamic bone disease

13C.1 Adynamic bone disease in stage 5 CKD (as determined by either bone biopsy or intact PTH <100 pg/mL [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover (*Opinion*).

13C.1a This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy (*Opinion*).

Additional KDOQI commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD) available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDOQI%20CKD-MBD%20commentary.pdf.

KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (http://www.kidney.org/professionals/KDOQI/guideline_diabetes/). Source: [4], used with permission from Elsevier Limited.

Guideline 5. Nutritional Management in Diabetes and CKD

5.1 Target DPI for people with CKD stages 1–4 should be the recommended dietary allowance (RDA) of 0.8 g/kg body weight/day (Strength of Recommendation [B]—It is recommended that clinicians routinely follow the guideline for eligible patients).

Additional KDOQI Clinical Practice Guidelines

Below are links to additional KDOQI clinical practice guidelines that nutrition professionals would find helpful [5–9].

Anemia in Chronic Kidney Disease—http://www.kidney.org/professionals/kdoqi/guidelines_anemia/pdf/AnemiaInCKD.pdf; http://www.kidney.org/professionals/KDOQI/guidelines_anemiaUP/index.htm

Managing Dyslipidemia in Chronic Kidney Disease—http://www.kidney.org/professionals/kdoqi/guidelines_dyslipidemia/pdf/ajkd_dyslipidemia_gls.pdf

Hypertension and Antihypertensive Agents in Chronic Kidney Disease—http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm

Cardiovascular Disease in Dialysis Patients—http://www.kidney.org/professionals/kdoqi/guidelines_cvd/pdf/cvd_%20in_dialysis_composite%20gl.pdf

Academy of Nutrition and Dietetics Chronic Kidney Disease (Non-dialysis) Medical Nutrition Therapy Protocol

As of January 2002, Medicare covers medical nutrition therapy (MNT) for the treatment of CKD (GFR <60 mL/min/1.73 m^2). This was a major breakthrough for the dietetics profession and a boon to the patients who need these services. The recognition of the importance of MNT in the treatment of CKD can make significant progress in the care of many eligible persons. The particulars of coverage can be found at the website for the Centers for Medicare and Medicaid Services (CMS) http://www.cms.gov. The Academy of Nutrition and Dietetics has published evidence-based practice protocols that guide care for non-dialysis kidney disease and can be ordered at http://www.eatright.org. Figure 28.1 provides a summary sheet of these MNT protocols (10). In 2012, the Academy of Nutrition and Dietetics updated and expanded the Chronic Kidney Disease Evidence-Based Nutrition Practice Guideline. The Executive Summary of Recommendations is available at http://andevidencelibrary.com/topic.cfm?cat=3927 with further access to details available to Academy members and subscribers of the Evidence Analysis Library under the Major Recommendations section.

Chronic Kidney Disease (non-dialysis)

Summary Page
Chronic Kidney Disease (non-dialysis)
Medical Nutrition Therapy Protocol

Setting: Ambulatory Care or adapted for other healthcare settings (Adult 18+ years old) **Number of encounters: 3 to 6**

No of Encounters	Length of encounters	Time between encounters
1	60-90 minutes	3-4 weeks
2	45-60 minutes	3-4 weeks
3	30-45 minutes	3-4 weeks
4,5,6	30-45 minutes	6- 8 weeks or as identified by reassessment

Expected Outcomes of Medical Nutrition Therapy

Base Line Evaluation of Outcomes

Outcomes Assessment Factors	1	2	3	4*	Expected Outcomes	Ideal/goal Value
Clinical Assessment						
Laboratory Values:						
• Serum albumin	√		√	√	• Maintain normal range	• Serum Albumin: > 4.0 g/dL (Grade II)
• Serum CO_2	√			√	• Maintain normal range	• Serum CO_2: 24-32 mEq/L (Grade II)
• Serum potassium	√	√	√	√	• Maintain normal range	• Serum Potassium: 3.5-5.5 mmol/L (Grade II)
• Serum calcium	√	√	√	√	• Progress toward goal	• Serum Calcium: 8.5- 10.2 mg/dL (corrected)
• Serum phosphorus	√	√	√	√	• Progress toward goal	• Serum Phosphorus:3.4-5.5 mg/dL (Grade II)
• PTH	√			√	• Progress toward goal	• Intact PTH: 100-300 pg/ml (Grade II)
• Serum glucose (if diabetic)	√			√	• ↓ 10% or at goal	• Random glucose:<140-160 mg/dL (blood); <160-180 mg/dL (plasma); A1C: <7% (Grade I)
• A1C (if diabetic)	√			√		
• Serum lipids	√		√	√	• Within normal range or △ by 10% to 20% if abnormal	• Cholesterol:>160 to <200 mg/dL • LDL-chol:<100 mg/dL;TG:<150 mg/dL • HDL-chol: >45 mg/dL (M) >55 (F)
• Serum Creatinine/GFR	√	√	√	√	• Stabilize creatinine, GFR and urinary albumin excretion	• Serum creatinine/GFR: stabilizes
• Urine albumin	√	√	√	√		• Urine albumin:<30 mg/d or <3 mg/dL
• Hemoglobin	√			√	• Adequate iron, folate for erythropoiesis when rHuEPO is administered	• Hgb: 12 g/L (M); 11 g/L (F) (Grade II)
• Ferritin	√			√		• Ferritin: >100 ng/mL,
• Transferrin saturation	√			√		• Transferrin saturation: >20%
• RBC folate	√			√		• RBC folate: >200 ng/ml
Nutrition/Physical:					• Maintains height, skeletal muscle, weight, fat stores (Weight should be edema free)	• Height: Yearly heights to monitor spinal osteoporosis/bone loss
• Height	√					
• Weight/BMI	√	√	√	√		• BMI: ≥24
• Body composition/SGA	√		√	√		• Blood pressure: <125/75; >1 g proteinuria or diabetic nephropathy; <130/85 without proteinuria (Grade II)
• Blood pressure	√	√	√	√	• Achieves blood pressure goal	
Functional Status:					• Improves/maintains functional status	
• ADLs, IADLs	√	√	√	√		• Optimum functional status
Therapeutic Lifestyle Changes						MNT Goal: Maintain kidney function, ↓ progression; maintain nutritional status
• Food/Meal Plan	√	√	√	√	• Chooses appropriate kinds and amounts of food	• Kcal: BEE (consider stress, dietary protein, weight goals) (Grade I)
	√	√	√	√	• Chooses 50% high biological animal or plant sources of protein	• Protein: 0.6 to 1.0 g/kg/IBW based on GFR, urinary protein excretion, degree of malnutrition, stress, motivation (Grade I)
	√	√	√	√	• Limits total fat, SF, cholesterol to meet serum lipid goals	• Fat: 25-30%, <7% SFA, <200 mg cholesterol
	√	√	√	√	• Eats at consistent times if diabetic	• Carbohydrate: 50 to 60% kcal
	√	√	√	√	• Limits high sodium foods	• Sodium: Individualized, 1-3 g/d
	√	√	√	√	• Consumes potassium per labs	• Potassium: Individualized based on labs
	√	√	√	√	• Limits phosphorus per labs	• Phosphorus: 8-12 mg/kg IBW; phosphate binders/vitamin D analogues may be needed
	√	√	√	√	• Consumes calcium supplements if prescribed, based on labs	• Calcium: Individualized: ~800 to 1200 mg/d
• Food/supplement intake	√	√	√	√	• Maintains adequate appetite	• Consumes >80% meals/supplements • Adequate to maintain weight, body composition
• Food label reading		√	√	√	• Accurately reads food labels	
• Recipe modification	√	√	√	√	• Modifies recipes as needed	
• Food preparation	√	√	√	√	• Uses methods to ↓ sodium	
• Self-monitoring	√	√	√	√	• Records daily food intake	• Dietary intake = prescription >80% of time
• Eating away from home			√	√	• Selects food appropriately	
• Potential food/nutrient/drug interaction	√	√	√	√	• Follows protocols for medications	• Consumes >80% phosphate binders with meals/snacks if prescribed
• Smoking/use of alcohol	√	√	√	√	• Participates in smoking cessation program; limits use of alcohol	
• Physical activity	√	√	√	√	• Participates in physical activity	• Maintains muscle stores/strength

* Print additional copies of this form for additional encounters.

ADA MNT Evidence Based Guides for Practice

Fig. 28.1 Academy of Nutrition and Dietetics Medical Nutrition Therapy Summary Sheet for Non-Dialysis Kidney Disease. © Academy of Nutrition and Dietetics (formerly the American Dietetic Association). Reprinted with permission

Diet-Related Resources and Food Lists

Dietitians assist in translating research in nutrition and CKD to patients and their caregivers. A number of resources are available to help with this process in clinical practice, and a few are provided within this section. The following sections comprise several tables that cover the nutrition composition of foods for various stages of CKD, food sources of potassium, phosphorus, and oxalate, examples of high biologic value protein sources, and renal micronutrient supplements. In addition, *The Journal of Renal Nutrition*, the official journal of the Council on Renal Nutrition of the National Kidney Foundation, includes patient education and product update sections within their publication issues.

Nutrition Composition of Foods

Tables 28.1 and 28.2 present the calories, protein, sodium, potassium, and phosphorus composition of foods for people with CKD stages 3–5 [11].

Food Sources of Potassium

Potassium content of selected foods, sorted by content, can be found on the USDA National Nutrient Database for Standard Reference, Release 24 at http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR22/nutrlist/sr22w306.pdf.

The NKF's Potassium and Your CKD Diet patient education material comprises lists of foods that are both high and low in potassium. This material can be found at http://www.kidney.org/atoz/content/potassium.cfm.

Table 28.1 Nutrition composition of foods (per serving) for people with stages 3 or 4 chronic kidney disease

Foods	Protein (g)	Calories (kcal)	Sodium (mg)	Potassium (mg)	Phosphorus (mg)	Example
Protein						
High	6–8	50–100	20–150	50–150	50–100	1 oz beef, chicken, fish
High phosphorus	6–8	50–100	20–150	50–350	100–300	1 oz organ meats
High sodium	6–8	50–100	200–450	50–150	50–100	¼ c cottage cheese
Vegetable						
Low K^+	2–3	10–100	0–50	20–150	10–70	1 c cabbage
Medium K^+	2–3	10–100	0–50	150–250	10–70	½ c beets
High K^+	2–3	10–100	0–50	250–550	10–70	¼ whole avocado
Fruit						
Low K^+	0–1	20–100	0–10	20–150	1–20	One medium apple
Medium K^+	0–1	20–100	0–10	150–250	1–20	½ c medium peach
High K^+	0–1	20–100	0–10	250–550	1–20	Two apricot halves
Dairy/high phosphorus	2–3	50–200	150–400	10–100	100–200	1 c sherbet
Breads/cereals	2–3	50–200	0–150	10–100	10–70	½ small sweet roll, no nuts
Free calories	0–1	100–150	0–100	0–100	0–100	1 (3 oz) popsicle

Adapted from Renal Practice Group of the American Dietetic Association. National Renal Diet Professional Guide. 2nd ed. Chicago: American Dietetic Association; 2002. With permission © Academy of Nutrition and Dietetics (formerly the American Dietetic Association)

c cup, K^+ potassium, *oz* ounce

Table 28.2 Nutrition composition of foods (per serving) for people with stage 5 chronic kidney disease

Foods	Protein (g)	Calories (kcal)	Sodium (mg)	Potassium (mg)	Phosphorus (mg)	Example
Protein						
Animal	6–8	50–100	20–150	50–150	50–100	1 oz beef, chicken, fish
Animal (with higher Na^{2+} or PO_4^- contents)	6–8	50–100	200–500	50–150	100–300	1 oz sardines
Fruit/vegetable						
Low K^+	0–3	10–100	1–50	20–150	0–70	1 c lettuce OR ½ c grape juice
Medium K^+	0–3	10–100	1–50	150–250	0–70	½ c cooked broccoli OR two Tbsp raisins
High K^+	0–3	10–100	1–50	250–550	0–70	One medium tomato OR one small nectarine
Dairy/high PO_4^-	2–8	100–400	30–300	50–400	100–120	½ c milk
Breads/cereals	2–3	50–200	0–150	10–100	10–70	½ small bagel
Free calories	0–1	100–150	0–100	0–100	0–100	Four pieces hard candy

Adapted from Renal Practice Group of the American Dietetic Association. National Renal Diet Professional Guide. 2nd ed. Chicago: American Dietetic Association; 2002. With permission © Academy of Nutrition and Dietetics (formerly the American Dietetic Association)
c cup, K^+ potassium, Na^{2+} sodium, PO_4^- phosphorus, *oz* ounce, *Tbsp* tablespoon

Food Sources of Phosphorus

Phosphorus content of selected foods can also be found on USDA National Nutrient Database for Standard Reference, Release 24 at https://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR24/nutrlist/sr24a305.pdf.

Listing of foods high in phosphorus and better alternative food choices are provided on the National Kidney Foundation's Phosphorus and Your CKD Diet information health guide at http://www.kidney.org/atoz/content/phosphorus.cfm. Table 28.3 lists the phosphorus and protein content of common foods. Additional literature and listing of dietary phosphorus, protein, and potassium content of food items ranked by phosphorus to protein ratio categories have been published and can be accessed at http://cjasn.asnjournals.org/content/5/3/519.full.pdf+html [12].

Phosphate-based additives can affect the diets of those with CKD and care is taken to limit the intake of foods containing these additives. Table 28.4 displays the most common phosphate additives, their use, and food products in which they are found [13]. Food additives used in fast food restaurant menu items as well as better alternative choices for those menu items can be found on Case Western University's Phos Foods website at http://www.case.edu/med/ccrhd/phosfoods/.

Protein Quality in Foods

Education and monitoring of protein restriction in CRF patients not undergoing maintenance dialysis and adequate protein intake in CKD stages 3–5 patients are important in the care of this population. Table 28.5 presents the biologic values of animal- and vegetable-based foods. Additional biologic values of certain foods can be found in the FAO Amino Acid Content of Foods and Biological Data on Proteins (1970) publication and can be accessed at http://www.fao.org/DOCREP/005/AC854T/AC854T00.htm#TOC [14].

Table 28.3 Phosphorus and protein content of common foods

Food	Amount	Phosphorus (mg)	Protein (g)	Phos (mg)/protein (g)
Beans, legumes, tofu				
Kidney beans, black beans	1 Cup	245	15	16.3
Refried beans, lima beans	1 Cup	215	15	14.3
Navy beans	1 Cup	290	16	18.1
Soybeans, boiled	1 Cup	420	29	14.4
Soybeans, roasted	1 Cup	625	60	10.4
Tofu, firm	100 g	75	6	12.5
Tofu, soft	100 g	55	4	13.8
Cheese				
Cheddar cheese	1 oz	145	7	20.7
Mozzarella cheese	1 oz	140	7	20.0
Swiss cheese	1 oz	170	8	21.3
Cottage cheese, 1 % fat	1 Cup	150	14	10.7
Cottage cheese, 2 % fat	1 Cup	340	31	11.0
Cream cheese	2 Tbsp	30	2	15.0
Cream, milk, yogurt				
Half and half cream	1 Cup	230	7	33.0
Heavy cream	1 Cup	150	5	29.8
Sour cream	2 Tbsp	30	1	30.0
Buttermilk	1 Cup	220	8	27.5
Nonfat milk	1 Cup	250	8	31.3
1 % milk	1 Cup	235	8	29.4
2 % milk	1 Cup	230	8	29.0
Whole milk	1 Cup	230	8	28.7
Low fat yogurt	1 Cup	340	12	28.3
Regular yogurt	1 Cup	215	8	26.9
Fish and seafood				
Blue crab	3 oz	175	17	10.3
Dungeness crab	3 oz	150	19	8.0
King crab	3 oz	240	16	15
Halibut	3 oz	215	23	9.3
Oysters	3 oz	195	13	15
Salmon	3 oz	270	21	12.8
Shrimp	3 oz	115	18	6.4
Meat, poultry, eggs				
Beef liver	3 oz	390	23	17.0
Top sirloin	3 oz	200	25	8.0
Chicken breast	3 oz	195	27	7.2
Chicken thigh	3 oz	150	22	6.8
Egg	1 Large	85	7	12.1
Ham	3 oz	240	19	12.6
Lamb chop	3 oz	190	22	8.6
Pork loin	3 oz	145	22	6.6
Turkey	3 oz	190	27	7.0
Veal loin	3 oz	190	22	8.6
Nuts and nut butters				
Almonds	1 oz	140	6	23.3
Macadamia	1 oz	55	2	27.5
Peanuts, roasted	1 oz	150	8	18.8
Peanut butter	2 Tbsp	110	8	13.8
Walnuts	1 oz	100	4	25.0

(continued)

Table 28.3 (continued)

Food	Amount	Phosphorus (mg)	Protein (g)	Phos (mg)/protein (g)
Fast foods				
Bean/cheese burrito	2 Small	180	15	12.0
Breakfast biscuit (egg, cheese, bacon)	1 Serving	460	16	28.8
Cheeseburger	1 Serving	310	28	11.0
Chicken sandwich	1 Serving	405	29	14.0
Pepperoni pizza	1 Slice	225	16	14.0
Other foods				
Beer	12 oz	40	1	40
Milk chocolate	1 oz	60	2	30
Semi sweet chocolate	1 oz	35	1	35
Coffee	1 Cup	2	0	
Colas	12 oz	45	0	
Lemon lime soda	12 oz	0	0	
Lemonade	1 Cup	5	0.5	10
Root beer	12 oz	0	0	
Tea	1 Cup	2	0	

Adapted from National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(Suppl 3):S1–S201 with permission from Elsevier Limited

Oxalates in Food

For populations where dietary oxalates are of concern, Table 28.6 lists high and moderate oxalate contents of common foods [15].

Vitamin Recommendations and Supplementation in CKD

CKD patients have altered vitamin metabolism and are thought to have increased requirements for some vitamins. Table 28.7 presents the Dietary Reference Intakes for vitamins and their suggested recommendations for various stages of CKD. Table 28.8 lists the micronutrient content of currently available specially formulated renal vitamins.

Assessment Tools

As discussed in a previous chapter on nutrition assessment, there are typically four components to conducting a comprehensive nutrition assessment: (1) Anthropometrics, (2) Biochemical Indices, (3) Clinical Symptomatology, and (4) Dietary Intake Data. The KDOQI Practice Guidelines for Nutrition outline very specifically some of the methods for anthropometry, such as height, frame size, and body circumferences, which should be obtained [1]. The reader is encouraged to consult this resource at http://www.kidney.org/professionals/KDOQI/guidelines_updates/nut_appx07a.html.

Recommendations are also presented by the KDOQI Practice Guidelines on the appropriate use of dietary assessment, and calculations of dietary protein and energy intakes at http://www.kidney.org/professionals/KDOQI/guidelines_updates/nut_appx03a.html.

As reported in the nutrition KDOQI Guideline 9, SGA is a valid and clinically useful measure of protein-energy nutritional status in maintenance dialysis patients. In 1994, SGA was presented at the annual meeting of the American Society of Nephrology. Since that time, it has been used in growing numbers of dialysis clinics as another tool for assessment of the CKD patient's nutritional status. It is simple, subjective, and hands on [22, 23].

Table 28.4 Common phosphate additives in foods

Phosphate additive common name	Uses	Products
Dicalcium phosphate anhydrous	Dough conditioner; mineral source	Bakery mixes; yeast-raised bakery products; cereals; dry powder beverages; flour; food bars; infant food; milk-based beverages; multivitamin tablets; yogurts. Used in powder form as an abrasive in toothpaste
Dicalcium phosphate dihydrous	Leavening agent; mineral source	Bakery mixes; cereals; dry powder beverages; flour; food bars; infant food; milk-based beverages; multivitamin tablets; yogurt
Dipotassium phosphate	Buffer; nutrient in yeast culturing; sequestrant	Casein-based creamers; processed cheese; meat products; mineral supplements; nondairy creamers; starter cultures; yeast-containing products
Disodium phosphate anhydrous	Absorbent; alkalinity source; buffering agent; emulsifier; fortification; pH control agent; protein modifier; sequestrant; stabilizer; thickener Is used to adjust pH of cereal and pasta products to maintain quality color in final product. Accelerates the cook time of pasta and quick cooking cereals	Cereal: cooked and dry breakfast; cheese: imitation and processed; cream; gelatin; half & half; ice cream; infant food; instant cheesecake; instant pudding; isotonic drinks; milk: condensed, evaporated, flavored, and nonfat dry milk powders; pasta; starch; vitamin capsules; whipped topping
Disodium phosphate dihydrous	Same as disodium phosphate anhydrous	Same as disodium phosphate anhydrous
Magnesium phosphate	Dietary supplement; flow aid; nutritional source of magnesium and phosphorous; pH control agent	Magnesium source in infant formulas and diet beverages
Monocalcium phosphate monohydrate	Acidulant for foods and beverages; dietary supplement; firming agent in canning; leavening acid; nutrient; thickener; yeast food dough conditioner. Calcium source for fortification or enrichment	Baking powder; biscuits; cakes; cake mixes; donuts; canned fruit; muffins; pudding; canned and frozen vegetables
Monopotassium phosphate	Acidulant; buffering agent; coloring; leavening agent; nutrient source; pH control agent; stabilizer; whipping properties	Beverages: dry powder and isotonic; bread; dough; egg products; mineral supplements; starter cultures; yeast cultures
Monopotassium phosphate anhydrous	Buffering agent; color enhancer; dry acidulant; emulsifier; flavor enhancer (tartness); gelling agent; leavening agent; protein modifier; sequestrant	Beverages: cola, dry powder, and isotonic; egg: yolks and liquid egg mixtures; gelatin; instant cheesecake; instant pudding
Monosodium phosphate	Color stabilizer; whipping properties	Egg products
Pentasodium triphosphate	Buffering agent; coagulant; curing agent; dispersing agent; emulsifier; flavor enhancer; humectants; moisture retention; pH control; reduces oxidation; sequestrant; stabilizer; texturizer; thickener	Meat; poultry; seafood
Phosphoric acid	Acidulant; buffering agent; flavor enhancer; pH control agent; sequestrant; stabilizer; synergist; thickener	Carbonated and noncarbonated beverages; cottage cheese
Sodium acid pyrophosphate	Acidulant; buffering agent; coagulant; dispersing agent; emulsifier; formulation aid; humectant; leavening agent; pH control agent; protein modifier; processing aid; sequestrant; stabilizer; synergist; texturizer; thickener	Baking powder; cake donuts; cake mixes; canned crab; cheese: imitation and processed; refrigerated dough; icing and frostings; processed meat including bologna, chicken and chicken products, and hot dogs; nondairy creamers; processed potatoes; seafood; canned tuna

(continued)

Table 28.4 (continued)

Phosphate additive common name	Uses	Products
Sodium hexametaphosphate	Buffering agent; color stabilizer; curing agent; deflocculant; dough strengthener; emulsifier; firming agent; flavor enhancer; flavoring agent; humectant; neutral salt; nutrient supplement; processing aid; sequestrant; stabilizer; surface-active agent; synergist; texturizer; thickener	Processed cheese; egg products; meat; poultry; cheese; seafood; sour cream; table syrups; canned and frozen vegetables; vegetable proteins; whey; whipped toppings
Sodium tripolyphosphate	Emulsifier; flavor enhancer; mechanical peeling of shrimp; moisture binding; stabilizer; texture modification	Fish; meats: chicken, corned beef, ham, roast beef, bologna, hot dogs, and sausage; scallops; shrimp; canned or frozen vegetables
Tetrapotassium pyrophosphate	Alkalinity source; antioxidant; buffering agent; coagulant; dispersing agent; nutrient source; pH control agent; protein modifier; sequestrant; texturizer	Processed cheese; milk powders
Tetrasodium pyrophosphate	Buffer; color agent; emulsifying agent; protein modifier; provides "meltability: in processed cheese; quickens cooking time of cooked breakfast cereals; stabilizer; thickener"	Cheese: processed and imitation cheese; isotonic beverages; cooked breakfast cereals; pudding
Tricalcium phosphate	Fortification; prevents caking; reduction in cooking time	Cooked cereal; dry drink mixes; fruit juices; soy beverages
Tripotassium phosphate	Alkalinity source; buffering agent; emulsifier; nutrient; protein modifier; stabilizer	Cereals; processed cheese; bread and dough conditioners; dairy products; isotonic beverages; starter cultures

Source: International Food Additives Council. Phosphates Use in Foods. Retrieved March 31, 2012, from http://www.foodadditives.org/phosphates/phosphates_used_in_food.html

Table 28.5 Biologic values of selected animal and vegetable foods

Foods	Biologic value range[a] (%)
Red beans, lentils	45
Wheat flour, wheat gluten, bean (avg), baker's yeast	50–59
Sesame seed, white rice, black beans, peas, kale, cooked oatmeal, butter beans, wheat (avg), lima beans, brewer's yeast, chick peas, coconut	60–69
Sunflower seeds, cheddar cheese, sardines, brown rice, soybeans, potatoes, wheat germ, beef, veal, chicken, pork, shrimp, fish (avg), rye, buckwheat	70–79
Mushrooms, casein, barley, cod, haddock, milk, lobster	80–89
Egg	>90

Developed by Joni Pagenkemper; *Source*: Food and Agriculture Organization of the United Nations. Amino Acid Content of Foods and Biological Data on Proteins. Rome, Italy: FAO; 1970

[a]Adequate protein quality >60 adults, >70 children

Table 28.6 Food sources of oxalate

High oxalate content (>0.9 % in the food)	Moderate oxalate content (0.2–0.9 %)
Beet greens (and the tuber)	Beans, dried
Chocolate, cocoa	Blackberries
Figs	Carrots
Lamb's quarters	Celery
Pepper, black	Coffee, instant
Poppy seeds	Currants
Purslane	Endive
Rhubarb	Gooseberries
Sorrel	Grapes, concord
Spinach	Green pepper
Swiss chard	Lemon peel
Tea (instant)	Okra
Beer, draft	Onions, green
	Oranges, orange peel
	Raspberries
	Strawberries
	Sweet potatoes
	Tomatoes
	Wheat bran
	Nuts

Source: United States Department of Agriculture, Human Nutrition Information Service. Agriculture Handbook Number 8-11, Composition of Foods: Vegetables and Vegetable Products. Revised August 1984

SGA is a score-based assessment based on a medical history and a physical assessment. Its ratings have been found to be highly predictive of outcome as well as correlate strongly with other subjective and objective measures of nutrition [22–24]. While it was originally used to categorize surgical patients, it is now recognized as a valid and reliable nutritional assessment tool for dialysis patients [25–30]. Studies in CKD patients have also shown the predictive capability of survival outcomes and correlations of SGA with anthropometric and other outcome measures [26–30].

Table 28.7 Daily vitamin recommendations for CKD

Vitamin	Dietary Reference Intakes[a]	Predialysis CKD	Maintenance HD/PD
Vitamin C	75–90 mg/day	60–100 mg/day	60–100 mg/day
Thiamin (B1)	1.1–1.2 mg/day	1.5 mg/day	1.5 mg/day
Riboflavin (B2)	1.1–1.3 mg/day	1.8 mg/day	1.1–1.3 mg/day
Niacin	14–16 mg/day	14–20 mg/day	14–20 mg/day
Vitamin B6	1.3–1.7 mg/day	5 mg/day	10 mg/day
Vitamin B12	2.4 μg/day	2–3 μg/day	2–3 μg/day
Folic acid	0.4 mg/day	1 mg/day	1 mg/day
Pantothenic acid	5 mg/day	5 mg/day	5 mg/day
Biotin	30 μg/day	30–100 μg/day	30–100 μg/day
Vitamin A	700–900 μg/day	700–900 μg/day	700–900 μg/day
Vitamin E	15 mg/day	15 mg/day	15 mg/day
Vitamin K	90–120 μg/day	90–120 μg/day	90–120 μg/day

[a]Dietary Reference Intakes for adults >18 years; *Sources*: see refs. [16–21]

SGA is a score-based assessment centered on a medical history and a physical assessment. Medical history includes progression of weight change, dietary intake, gastrointestinal symptoms, physiological functioning, and a simple analysis of metabolic stress. The physiological assessment includes loss of subcutaneous fat and muscle mass, and edema. Originally, patients were evaluated as (A) well-nourished, (B) mild to moderately malnourished, or (C) severely malnourished [22, 23]. This ABC rating has been changed to a 7-point scale [28]. The scores in the 7 point scale are as follows:

1. 6 or 7 = mildly nutritional risk to well-nourished
2. 3, 4, or 5 = mild to moderately malnourished
3. 1 or 2 = severely malnourished

The KDOQI has recommended the use of this 7-point scale SGA tool for assessing nutritional status of CKD patients. Healthcare professionals should be trained on SGA methods prior to using it in practice. Methods for performing SGA can be found in the nutrition KDOQI Practice Guidelines at http://www.kidney.org/professionals/KDOQI/guidelines_updates/nut_appx06a.html.

Table 28.9 is a sample SGA form based on the 7-point scale. Additional materials that have been published or reviewed are available to assist in performing various nutritional assessments and SGA among CKD patients, including:

SGA Training Materials, Baxter Healthcare Corporation, Renal Division, 1620 Waukegan Road, McGaw Park, IL.

McCann L. Subjective global assessment as it pertains to nutritional status of dialysis patients. Dial Transplant. 1996;25:190–199, 202, 225.

McCann, Yates L, Ezaki-Yamaguchi J, Akiyama P. Forms to monitor and assess nutritional status of renal patients. J Ren Nutr 1995;5:151–155.

Steiber AL, Kalantar-Zadeh K, Secker D, McCarthy M, Sehgal A, McCann L. Subjective Global Assessment in chronic kidney disease: a review. J Ren Nutr 2004;14:191–200.

Table 28.8 Renal micronutrient supplement comparison chart

Product	Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg)	B6 (mg)	B12 (μg)	Folic acid (mg)	Pantothenic acid (mg)	Biotin (μg)	Vitamin D[a] (IU)	Vitamin E (IU)	Zn (mg)	Fe[b] (mg)	Se (μg)
Dialyvite® 800	60	1.5	1.7	20	10	6	0.8	10	300	–	–	–	–	–
Dialyvite® 800 with zinc	60	1.5	1.7	20	10	6	0.8	10	300	–	–	50	–	–
Dialyvite® 800 with zinc 15	60	1.5	1.7	20	10	6	0.8	10	300	–	–	15	–	–
Dialyvite® 800 with iron	60	1.5	1.7	20	10	6	0.8	10	300	–	–	–	29	–
Dialyvite® 800 Ultra D	60	1.5	1.7	20	10	6	0.8	10	300	2,000	30	15	–	70
Dialyvite® Rx	100	1.5	1.7	20	10	6	1	10	300	–	–	–	–	–
Dialyvite® Rx with zinc	100	1.5	1.7	20	10	6	1	10	300	–	–	50	–	–
Dialyvite® 3000 Rx	100	1.5	1.7	20	25	1,000	3	10	300	–	30	15	–	70
Dialyvite® 5000 Rx	100	1.5	1.7	20	50	2,000	5	10	300	–	30	25	–	70
Dialyvite® Supreme D Rx	100	1.5	1.7	20	25	1,000	3	10	300	2,000	30	15	–	70
Nephrocaps®	100	1.5	1.7	20	10	6	1	5	150	–	–	–	–	–
Nephron FA®	40	1.5	1.7	20	10	6	1	10	300	–	–	–	66	–
Nephrovite®	60	1.5	1.7	20	10	6	0.8	10	300	–	–	–	–	–
Nephrovite® Rx	60	1.5	1.7	20	10	6	1	10	300	–	–	–	–	–
NephPlex® Rx	60	1.5	1.7	20	10	6	1	10	300	–	–	12.5	–	–
PS Nephro Aid®	60	1.5	1.7	20	20	1,000	2	5	300	–	–	–	–	–
RenaPlex®	60	1.5	1.7	20	10	6	0.8	10	300	–	–	15	–	–
RenaPlex® D	60	1.5	1.7	20	10	6	0.8	10	300	2,000	35	15	–	70
Rena-Vite®	60	1.5	1.7	20	10	6	0.8	10	300	–	–	–	–	–
Rena-Vite Rx®	60	1.5	1.7	20	10	6	1.0	10	300	–	–	–	–	–

All Dialyvite® supplements are registered trademarks of Hillestad Pharmaceuticals USA, Inc., Woodruff, WI
Nephrocaps® is a registered trademark of Valeant Pharmaceuticals International, Inc., Quebec, Canada
NephronFA®, NephPlex-Rx®, RenaPlex®, and RenaPlex® D are registered trademarks of Nephro-Tech Inc., Shawnee, KS
Nephrovite® and Nephrovite® Rx are registered trademarks of Watson Pharmaceuticals, Inc., Parsippany, NJ
PS Nephro Aid® is a registered trademark of Physician Select Vitamins, Pearland, TX
Rena-Vite® and Rena-Vite® Rx are registered trademarks of Cypress Pharmaceutical, Inc., Madison, MS
[a]Vitamin D in the form of cholecalciferol
[b]Elemental iron

Table 28.9 Sample SGA form using a 7-point scoring system

SUBJECTIVE GLOBAL ASSESSMENT RATING FORM

Patient Name: **ID #:** **Date:**

HISTORY

WEIGHT/WEIGHT CHANGE: ***(Included in K/DOQI SGA)***

1. **Baseline Wt:** _____(Dry weight from 6 months ago)
   Current Wt: _____(Dry weight today)
   Actual Wt loss/past 6 mo: _____ **% loss:**_____(actual loss from baseline or last SGA)
2. **Weight change over past two weeks:** _____No change _____Increase _____Decrease

DIETARY INTAKE No Change_____(Adequate) No Change_____(Inadequate)

1. Change: Sub optimal Intake: _____ Protein _____ Kcal _____ Duration_____
   Full Liquid:_____ Hypocaloric Liquid _____ Starvation_____

GASTROINTESTINAL SYMPTOMS ***(Included in K/DOQI SGA-anorexia or causes of anorexia)***

Symptom:	Frequency:[+]	Duration:[+]
_____ None	_____	_____
_____ Anorexia	_____	_____
_____ Nausea	_____	_____
_____ Vomiting	_____	_____
_____ Diarrhea	_____	_____

[+] Never, daily, 2-3 times/wk, 1-2 times/wk > 2 weeks, < 2 weeks

FUNCTIONAL CAPACITY

Description	Duration:
_____ No Dysfunction	_____
_____ Change in function	_____
_____ Difficulty with ambulation	_____
_____ Difficulty with activity (Patient specific "normal")	_____
_____ Light activity	_____
_____ Bed/chair ridden with little or no activity	_____
_____ Improvement in function	_____

DISEASE STATE/COMORBIDITIES AS RELATED TO NUTRITIONAL NEEDS

Primary Diagnosis_____Comorbidities_____

Normal requirements ____Increased requirements____ Decreased requirements _____

Acute Metabolic Stress: _____None _____Low _____Moderate _____High

PHYSICAL EXAM

_____ Loss of subcutaneous fat (Below eye, triceps, biceps, chest) ***(Included in K/DOQI SGA)*** ____Some areas _____All areas

_____ Muscle wasting (Temple, clavicle, scapula, ribs, quadriceps, calf, knee, interosseous ***(Included in K/DOQI SGA)*** ____Some areas _____All areas

_____ Edema (Related to undernutrition/use to evaluate weight change)

OVERALL SGA RATING

Very mild risk to well-nourished=6 or 7 most categories or significant, continued improvement.
Mild-moderate = 3, 4, or 5 ratings. No clear sign of normal status or severe malnutrition.
Severely Malnourished = 1 or 2 ratings in most categories/significant physical signs of malnutrition.

From Steiber AL, Kalantar-Zadeh K, Secker D, McCarthy M, Sehgal A, McCann L. Subjective Global Assessment in chronic kidney disease: a review. J Ren Nutr 2004; 14:191–200. Reprinted with permission from Elsevier Limited

Internet Sites

There are a plethora of websites that provide resources and online tools that may prove useful for the busy practitioner. Table 28.10 includes a select few.

Tablet and Smartphone Applications

With the increasing use of smartphones and tablets, a growing number of applications are becoming available that both practitioners and clients can utilize to manage their care and treatment. Below are a few with a brief description of the application. As with all print and internet resources available, tablet and smartphone applications should be reviewed and used with appropriate professional and clinical judgment.

National Kidney Foundation-eGFR Calculators: Helps medical professionals estimate kidney function using five separate eGFR calculators.

Table 28.10 Online resources and tools

Academy of Nutrition and Dietetics	www.eatright.org
American Association of Kidney Patients (AAKP)	www.aakp.org
American Diabetes Association	www.diabetes.org
American Kidney Fund	www.akfinc.org
Centers for Medicare and Medicaid Services (CMS)	www.cms.gov
Council of Renal Nutrition (CRN)	www.kidney.org/professionals/CRN/
Council of Nephrology Social Workers (CNSW)	www.kidney.org/professionals/CNSW/
Council of Nephrology Nurses & Technicians (CNNT)	www.kidney.org/professionals/CNNT/
Culinary Kidney Cooks	www.culinarykidneycooks.com
DaVita Healthcare	www.davita.com
Fresenius NA	www.fmcna.com
Hypertension, Dialysis & Clinical Nephrology	www.hdcn.com
Kidney School	www.kidneyschool.org
Life Options Rehabilitation Program	www.lifeoptions.org
National Institute of Diabetes and Digestive and Kidney Diseases	www.niddk.nih.gov
National Kidney Disease Education Program (NKDEP)	www.nkdep.nih.gov
National Kidney Foundation	www.kidney.org
The Nephron Information Center	www.nephron.com
Renal Dietitians Dietetic Practice Group of the American Dietetic Association	www.renalnutrition.org
RenalWEB-Vortex Website of the Dialysis World	www.renalweb.com
USDA Nutrient Database for Standard Reference	http://ndb.nal.usda.gov
United States Renal Data System (USRDS)	www.usrds.org

National Kidney Foundation-Screening for Albuminuria in Patients with Diabetes: A quick pocket tool to help medical professionals assess and treat albuminuria in people with diabetes and other high risk patients.

National Kidney Foundation-Manage CVD Risk in Patients with Reduced GFR: Includes an interactive algorithm to quickly identify patients with high cardiovascular disease risk and apply evidence-based strategies to assess and treat.

National Institutes of Health Office of Dietary Supplements (*ODS*) *MyDS*: Provides an easy way for individuals to keep track of vitamins, minerals, herbs, and other products they take as well as access to science-based, reliable information on dietary supplements, and general information about the ODS.

KidneyDiet: Contains a searchable food list with nutrient content information (i.e., protein, potassium, phosphorus) and ability to enter in food diary that calculates total nutrient intakes and compares it to the patient's physician- and/or dietitian-recommended intake guidelines.

Nutrition Complete: Searchable database of nutrient composition of foods based on the USDA Nutrient Database for Standard Reference.

iFood Diary: Allows the user to enter food diaries and monitor progress with established goals.

Blood Sugar Tracker: Allows user to log blood sugar levels, set target blood glucose ranges, and view history and simple graphs.

Vree for Diabetes: Includes diabetes education resources about Type 2 diabetes, tracking of blood glucose, nutrition, activity, blood pressure and medications, as well as keeping progress charts.

WaveSense Diabetes Manager: Tracks blood glucose results, carbohydrate intake, and insulin doses with features including logbook, trend chart, email reports, color-coded results, video content, and customizable target ranges and mealtime schedules.

Summary

This chapter represents a collection of resources that are required for clinical practice in nutrition and kidney disease. It does not contain an exhaustive list of tools, but should serve to assist the practitioner in locating critical pieces of information necessary for appropriate delivery of care in CKD patients.

References

1. National Kidney Foundation. Kidney Disease Outcomes Quality Initiative clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35 Suppl 2:S1–140.
2. KDOQI Work Group. KDOQI clinical practice guideline for nutrition in children with chronic kidney disease: 2008 update. Am J Kidney Dis. 2009;53 Suppl 2:S11–104.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42 Suppl 3:S1–201.
4. Kidney Disease Outcomes Quality Initiative. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49 Suppl 2:S12–154.
5. Kidney Disease Outcomes Quality Initiative. NKF KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis. 2007;47 Suppl 3:S11–145.
6. Kidney Disease Outcomes Quality Initiative. NKF KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis. 2007;50:471–530.
7. Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. NKF K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Dis. 2003;41 Suppl 3:S1–91.
8. Kidney Disease Outcomes Quality Initiative (K/DOQI). NKF KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43 Suppl 1:S1–290.
9. K/DOQI Work Group. NKF KDOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 Suppl 3:S1–154.
10. American Dietetic Association. Medical nutrition therapy evidence based guides for practice. Chronic kidney disease (non-dialysis) medical nutrition therapy protocol CD-ROM. Chicago: American Dietetic Association; 2002.
11. Renal Practice Group of the American Dietetic Association. National renal diet professional guide. 2nd ed. Chicago: American Dietetic Association; 2002.
12. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson AR, Kopple JD. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5:519–30.
13. International Food Additives Council. Phosphates use in foods. http://www.foodadditives.org/phosphates/phosphates_used_in_food.html. Accessed 31 March 2012.
14. Food and Agriculture Organization of the United Nations. Amino acid content of foods and biological data on proteins. Rome: FAO; 1970.
15. U.S. Department of Agriculture, Agricultural Research Service. Composition of foods: vegetables and vegetable products; raw, processed, prepared. Agriculture Handbook 8–11;1984.
16. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academies Press; 1998.
17. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: The National Academies Press; 2000.
18. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: The National Academies Press; 2001.
19. Kopple JD, Massry SG, editors. Nutritional management of renal disease. Philadelphia: Lippincott Williams & Wilkins; 2004.
20. Mitch WE, Klahr S, editors. Handbook of nutrition and the kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
21. Steiber AL, Kopple JD. Vitamin status and needs for people with stages 3–5 chronic kidney disease. J Ren Nutr. 2011;21:355–68.
22. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment? JPEN J Parenter Enteral Nutr. 1987;11:8–13.

23. Jeejeebhoy KN, Detsky AS, Baker JP. Assessment of nutritional status. JPEN J Parenter Enteral Nutr. 1990;14: 193S–6.
24. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewa J, Langer B, Jeejeebhoy KN. Nutritional assessment: a comparison of clinical judgment and objective measurements. N Engl J Med. 1982;306:969–72.
25. Young GA, Kopple JD, Lindholm B, Vonesh EF, De Vecchi A, Scalamogna A, Castelnova C, Oreopoulos DG, Anderson GH, Bergstrom J, DiChiro J, Gentile D, Nissenson A, Sakhrani L, Brownjohn AM, Nolph KD, Prowant BF, Algrim CE, Martis L, Serkes KD. Nutritional assessment of continuous ambulatory peritoneal dialysis patients: an international study. Am J Kidney Dis. 1991;17:462–71.
26. Enia G, Sicuso C, Alati G, Zoccali C. Subjective global assessment of nutrition in dialysis patients. Nephrol Dial Transplant. 1993;8:1094–8.
27. Fenton SSA, Johnston N, Delmore T, Detsky AS, Whitewall J, O'Sullhan R, Cattran C, Richardson RMA, Jeejeebhoy KN. Nutrition assessment of continuous ambulatory peritoneal dialysis patients. Trans Am Soc Artif Intern Organs. 1987;33:650–3.
28. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol. 1996;7:198–207.
29. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Reliability of the 7-point subjective global assessment scale in assessing nutritional status of dialysis patients. Adv Perit Dial. 1999;15:222–5.
30. Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, Sehgal AR, Kalantar-Zadeh K. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. J Ren Nutr. 2007;17: 336–42.
31. Steiber AL, Kalantar-Zadeh K, Secker D, McCarthy M, Sehgal A, McCann L. Subjective Global Assessment in chronic kidney disease: a review. J Ren Nutr. 2004;14:191–200.

Index

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