A Case-Based Guide to Clinical Endocrinology

Terry F. Davies
Editor

Third Edition

Springer

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Preface to the Third Edition

I write in June 2021. What a year 2020 was and so far 2021 is not so easy. The COVID epidemic has been beyond the imagination of all of us including the infectious disease epidemiologists. As I write, the USA is pushing full steam ahead with widespread immunizations and the economy is beginning to roar. I just cannot believe how, in such difficult times, our authors have managed to put together such a marvelous collection of Endocrine Cases. Some of them will keep you on the edge of your chair if you do not cheat and read the diagnosis first! You will also see that some of my colleagues have contributed to the first, the second, and now the third edition and I am so grateful for their support. We also have a cadre of new authors, both young and not so young, and I look forward to their joining us again for the fourth edition! In the last preface I see that I realized how little free time we all have for writing cases and chapters and I cannot decide whether the increased time working at home has really given us more time to work or just more time to walk the dogs and help with housekeeping. I thank my wife Susan for putting up with my extra computer and Zoom time! Nevertheless, we have all managed to get the job done and mainly because we all believe that teaching is second only in importance to the care of our patients. And these books have been really successful. When I last looked, there had been over 60,000 downloads from the second edition published in 2015 and the reach was international. I have little doubt that this edition will be just as popular thanks to the variety of cases and the simplicity of the presentation. I want to send special thanks to Ms. Pinky Sathishkumar from our publisher Springer Nature without whom this collection would never have been finished. Lastly, I warn you that some of the questions after each case are really difficult so concentrate well!

New York, NY, USA — Terry F. Davies

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Part I
Pituitary Disorders

Chapter 1
Preface: Pituitary Tumors Are More Frequent Than Previously Thought

Maria Fleseriu

Introduction

The prevalence of clinically significant pituitary tumors is increasing (up to 1/1000 people) and comprises approximately 16% of all primary cranial neoplasms. Although the natural history of pituitary adenomas (PA) is not completely described, most microadenomas (lesions <10 mm) have a benign course, whereas macroadenomas (≥10 mm) require careful monitoring. Macroadenomas present a higher risk for hormonal abnormalities (either excess or deficits) and mass effects, including vision loss.

Pituitary masses that are detected incidentally, so-called pituitary incidentalomas, are also increasing in frequency, as a result of an increase in the availability of brain imaging worldwide. The most relevant detected incidental lesions are those that fulfill the radiological criteria of a PA (or tumor) in asymptomatic patients or in patients with subclinical diseases. Differential diagnosis is essential as pituitary hyperplasia or imaging artifacts could look similar on pituitary magnetic resonance imaging (MRI).

Prolactinomas (PRL-omas) and non-functioning pituitary adenomas (NFPA) are the most common PA types, followed by somatotroph (growth hormone; GH), corticotroph (adrenocorticotropic hormone; ACTH), and thyrotroph (thyroid stimulating hormone; TSH) adenomas. Almost all gonadotroph adenomas are clinically NFPA, and < 1% are hormonally active.

Over the last several years, there have been significant advances in the field of pituitary tumors. The 2017 World Health Organization (WHO) classification attempts

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to reduce imaging monitoring of both non-functioning and functioning PA. There are novel medical therapies and new combination regimens for functioning PA and new insights into rare, but serious psychological effects of dopamine agonists (DA).

Updates in the World Health Organization Classification

In 2017 the WHO introduced significant PA classification changes, from the concept of "a hormone-producing PA" to a pituitary adenohypophyseal cell lineage description with subsequent histological classification based on type of hormonal content and specific histological and immunohistochemical markers. From a clinician's point of view, several tumors are highlighted as potentially more aggressive and thus require closer follow-up and/or multimodal therapy: sparsely granulated somatotroph adenoma, lactotroph adenoma in men, Crooke's cell adenoma, silent corticotroph adenoma, and plurihormonal Pit-1-positive adenoma (previously called silent subtype III pituitary adenoma) [1].

Tumor proliferation, by both mitotic count and Ki-67 labeling index, and tumor invasion evaluation should still be offered on an individualized case basis to identify clinically aggressive adenomas. Importantly, the 2017 WHO classification does not require a routine ultrastructural examination, which is expensive and difficult for most centers to perform.

A new definition, null cell adenoma requires immuno-negative results for pituitary transcription factors and adenohypophyseal hormones. Furthermore, the definition "atypical adenoma," based on highly proliferative characteristics to predict poor prognosis, has been removed due to the lack of evidence.

Timeline for Follow-Up Imaging

Pituitary MRI (with and without contrast) remains the ideal imaging modal to delineate PAs. A study in 2019, indicated that while consensus exists among pituitary endocrinologists and neurosurgeons that long-term repeated imaging is recommended for most patients, imaging timing varied depending on the specialist group and the specific clinical context of the adenoma [2].

Furthermore, data has shown gadolinium deposits in post-mortem human brain as well as bone, skin, and other tissues even in patients with intact kidney function. Macrocyclic agents (as gadoteridol, gadobutrol, gadoterate) appear to be more stable and thus have less potential for accumulation than linear agents [2].

Non-functioning pituitary adenomas when diagnosed as pituitary incidentalomas have fairly rare complications that may be more common when lesions are large (>10 mm) and solid. Of note, a meta-analysis was associated with significant heterogeneity. There is a need for increased awareness of pituitary disease, as many patients still have *mass effect* signs at presentation. Several attempts have been

made, but there is no uniform protocol for monitoring NFPAs [3]. Endocrine Society (ES) guidelines recommend that patients with incidentalomas who do not undergo surgery be followed clinically and with pituitary MRI, at 6 months for macroadenomas, and at 1 year for microadenomas [4]. Subsequently, timing can be less frequent if the incidentaloma is stable in size. Visual field tests for tumors close to the optic chiasm are recommended at 6 months and then yearly. Follow-up endocrine tests are also needed. Another novel follow-up strategy is based on assessment of initial tumor volume and volume growth rate. It has been suggested that in patients with microadenomas, the next MRI can be performed at 3 years and for macroadenomas a second MRI should be performed at 6 months–1 year to assess tumor growth rate and determine further needs within 2–4 years [5].

A recent study by Freda et al. showed that incidentalomas comprised 48.7% (incidental group) at presentation and 51.3% were due to tumor symptoms (symptom group). Interestingly, 58.7% and 27.4% of patients had hypopituitarism in the symptom and incidental groups, respectively [6]. Additionally, 25% of patients with microadenomas had hypopituitarism, highlighting a need for hypopituitarism screening for tumors of all sizes. Furthermore, many patients had unrecognized signs and symptoms of pituitary disease. Men were older and had larger tumors in both groups, and notably patients in the incidental group were older also.

For *prolactinomas*, the ES guidelines recommend for microadenomas repeating a pituitary MRI in 1 year [7]. Recommendations for macroprolactinomas after DA initiation are repeating a pituitary MRI in 3 months or repeating if prolactin levels increase on treatment or if a patient develops new vision changes, headaches, galactorrhea, or new hypopituitarism. Serial follow-up should be determined on a case-by-case basis. Notably, there are cases with discordant findings: either prolactin normalization without substantial tumor shrinkage or tumor shrinkage without complete prolactin normalization (albeit a major decrease). Data that T2 WI signal intensity is a possible predictor of prolactinoma DA response in some patients is limited. It is now recognized that prolactinomas in males are more aggressive, independent of histologic subtype, and closer follow-up is required in such cases [8].

Pearls: Screening, Differential Diagnosis, and Localization of Cushing's Syndrome

Cushing's syndrome remains one of the most difficult in the field of endocrinology to diagnose. Testing has many inherent pitfalls with numerous false positives and negatives [9]. Dynamic testing is also available; however, pre-test probability values are essential for accurate interpretation. Salivary cortisol [10], in >1 sample, remains a good screening test for Cushing's disease (CD); Interestingly, it has been shown that salivary cortisol is of less value in cases of CS that are due to an adrenal adenoma. Patients with non-tumor-related hypercortisolemia (*pseudo* CS) may have clinical features similar to CS patients, and close attention is needed to differentiate such cases. Adrenocorticotropic hormone levels as assessed by Immulite assays can

be falsely increased, and other assays are needed if laboratory and clinical pictures do not match.

High-accuracy localization testing for ACTH-dependent disease is facilitated by use of inferior petrosal sinus sampling (IPSS) [11]. However, IPSS requires specialized centers, normal anatomy, and good bilateral catheterization. Tumor identification in cases of ectopic CS (ECS) can prove more complicated despite ample imaging resources and nuclear scans. In cases of severe disease, some patients will require treatment before localization, as is evident in the patient described in the chapter by Fernandez et al., Abrupt Weight Gain, Hypertension, and Severe Hypokalemia in a Young Male.

Of note, over the last several years, awareness with regard to high rates of CD recurrence has increased, approaching 3–35% over an individual's lifetime [12]. Numerous studies have shown that a recurrence diagnosis remains difficult. Salivary cortisol levels can be abnormal for a year before urinary free cortisol (UFC) levels are noted as abnormal. In Fig. 1.1 sequential testing in an evaluation for CD recurrence is suggested.

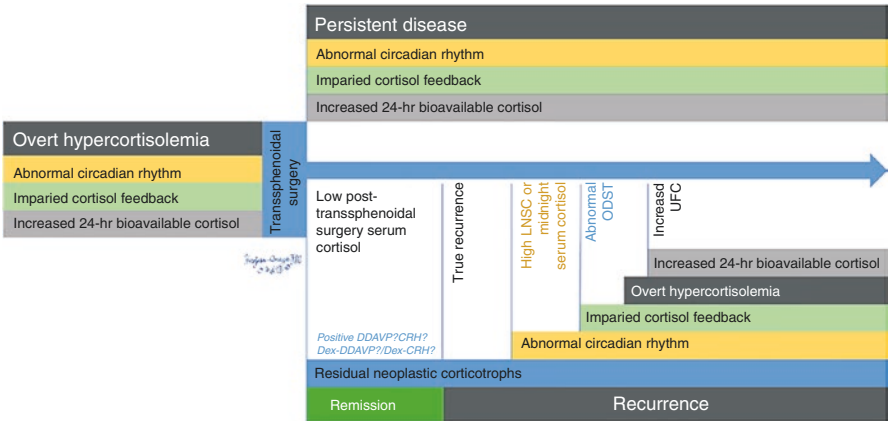

Fig. 1.1 Chronological changes of recurrent hypercortisolemia in Cushing's disease. Overt hypercortisolemia is characterized by abnormal circadian rhythm which can be assessed by LNSC, impaired feedback shown by lack of suppression of ACTH/cortisol after dexamethasone, and increased levels of bioavailable cortisol measured by UFC. After TSS, patients with persistent disease will retain these abnormalities while they will resolve in the ones who experience remission, who will also have low post-TSS serum cortisol (remission) or normalized during the first ~25 days post-op (delayed remission). Residual neoplastic corticotrophs may be identified during remission or early recurrence by DDAVP/Dex-DDAVP and potentially by CRH/Dex-CRH. Abnormal circadian rhythm is the first abnormality that appears after recurrence, followed by impaired cortisol feedback and finally by overt hypercortisolemia. DDAVP testing for hypercortisolemia is rarely performed in the United States. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone stimulation test; DDAVP, desmopressin stimulation test; Dex-DDAVP, desmopressin stimulation test after low-dose dexamethasone suppression test; Dex-CRH, corticotropin-releasing hormone stimulation test after low-dose dexamethasone suppression test; LNSC, late-night salivary cortisol; ODST, overnight dexamethasone suppression test; UFC, 24-h urinary free cortisol; TSS, transsphenoidal surgery. (From Hinojosa-Amaya et al. [9])

Medical Therapy for Functioning Pituitary Adenomas

Frequently, treatment for functioning PA is comprised of surgery, medical therapy, and/or radiation [13]. While medication is the primary treatment for prolactinomas in most patients, transsphenoidal surgery (TSS), preferably by an experienced neurosurgeon, is the first-line treatment for other functioning PA. However, many patients with CS or acromegaly require multimodal treatment for biochemical and clinical control, when surgery is not curative or when medical therapy fails. Several drugs have been US Food and Drug Administration (FDA) approved recently for CD (osilodrostat) [14] and acromegaly (oral octreotide) [15]. Other novel, medical treatments for functioning PA are in clinical trials. Many investigators using study and registry data have tried to elucidate predictive factors for response to medication and devise individualized treatment(s) based on pathology tumor type, imaging characteristics, clinical presentation, and patient preference.

For *prolactinomas*, an important controversy remains as to if and when *DA treatment can safely be withdrawn*. The main candidates are patients with no visible or small tumors and prolactin levels that are controlled on low-dose DA. Hage and Salvatori found that approximately one-third of patients could reach conditions for withdrawal after 2 years of DA therapy. As expected tumor size was smaller for patients in which withdrawal was attempted. Prolactin levels that changed immediately after DA initiation and parasellar invasiveness were predictors of reaching withdrawal conditions [16].

Another more recent focus in prolactinoma treatment is the *psychologic effect of DAs*. An increasing number of reports highlighted DAs' psychological side effects, either de novo or in patients with a history of prior psychiatric disease. There are a few prospective studies and many cross-sectional studies with controls consisting of healthy volunteers or patients with NFPAs. Patients with hyperprolactinemia were found to have decreased quality of life (QoL), depression, anxiety, and certain personality traits. Impulse control disorders (ICDs) were reported in both sexes, with hyper-sexuality reported mostly in men. Multiple ICDs were sometimes reported in the same patient, usually, but not always this was reversible after discontinuation of DAs. Furthermore, patients treated with DAs had higher impulsivity scores than normo-prolactinemic controls. Dopamine agonists induced severe depression, manic episodes, or psychosis, which improved after discontinuation and/or administration of psychiatric medications [17]. In most studies, neither DA type, dose and duration of therapy, nor sex correlated with new psychiatric pathology [18]. This data shows that increased awareness with regard to these adverse events is needed while still working to further delineate prevalence, risk stratification, and management. Further discussion of psychological effects of DAs is illustrated in a patient in the chapter by Capatina et al., Dopamine Agonist-Induced Impulse Control Disorders.

Treatment of CS requires normalization of hypercortisolemia, tumor control, but also improvement in signs and symptoms of CS and QoL [12]. Medical treatment comprises steroidogenesis inhibitors, agents that act at the pituitary or

glucocorticoid receptor level, and novel agents in development. Drugs are mostly used as adjuvant therapy after failed surgery (though rarely used as primary therapy), pending effects of radiation, or in severe cases for adrenalectomy planning. Though data is limited, patients treated with medical therapy who achieve both normal UFC and salivary cortisol levels achieve better clinical control in blood pressure and weight. Furthermore, recognition, prevention, and/or treatment of complications, including infections and thromboembolism, is also essential [19]. Odds risk ratio of venous thromboembolism in CS is almost 18 times higher than in the normal population; thus selected patients will need to take thromboprophylaxis prevention and balance any advantages with bleeding risk. Patient clinical course where prevention of several complications, including thromboembolism and infection is needed, is discussed in the chapter by Fernandez et al., Abrupt Weight Gain, Hypertension, and Severe Hypokalemia in a Young Male.

New research in patients with acromegaly highlights sex presentation, comorbidities, and mortality in acromegaly (Table 1.1) [20]. Growth hormone (somatotroph) adenomas

Table 1.1 Presentation, monitoring, and outcomes: summary points

Presentation, comorbidities, and mortality
Although men present at a younger age than women, women may show both increased incidence and mortality risk. (MQ, DR) Biochemical control remains the strongest predictor of patient outcomes, reflecting improvements in glucose metabolism, OSA, cardiovascular disease, and VFs. However, structural heart and joint changes are unlikely to resolve. (MQ, DR) The observed decline in reported mortality among acromegaly patients is likely due to more effective therapies, which, in turn, yield higher biochemical control rates and reduce the likelihood of developing respiratory and cardiovascular comorbidities that increase mortality. Rate of thyroid malignancies is not greater among acromegaly patients than among those without the condition. After a screening colonoscopy at diagnosis, further testing should be performed similar to the general population, as per previous recommendations. (LQ, DR)
Assays
Reference GH nadir levels after OGTT using the IDS-iSYS assay accounting for BMI, sex, and ethinylestradiol-containing oral contraceptive use confirm the importance of these factors as confounders in GH measurements. (MQ, SR) IGF-I levels measured 6 weeks postoperatively can be used in most patients to assess remission, although patients with mildly elevated IGF-I may yet normalize by 3–6 months. (MQ, SR)
Sex, age, and surgical outcomes
Women, especially when postmenopausal, may exhibit lower surgical remission rates from TSS, as they tend to have larger and more invasive tumors that are less amenable to total resection. (LQ, DR) Patient age is likely not a predictor of surgical outcomes, nor does age impact the favorable effects of postsurgical remission on alleviating disease comorbidities. (LQ, DR)
Radiotherapy outcomes
Long-term follow-up of patients treated with SRS and FRT show that approximately half achieve and maintain biochemical control. However, up to one-third of patients with normal pituitary function develop hypopituitarism, confirming the need for ongoing monitoring. (LQ, SR)

From Fleseriu et al. [20]
BMI body mass index, *DR* discretionary recommendation, *FRT* fractionated radiotherapy, *GH* growth hormone, *IGF-I* insulin-like growth factor I, *LQ* low-quality evidence, *MQ* medium-quality evidence, *OGTT* oral glucose tolerance test, *OSA* obstructive sleep apnea, *SR* strong recommendation, *SRS* stereotactic radiosurgery, *TSS* transsphenoidal surgery, *VF* vertebral fracture

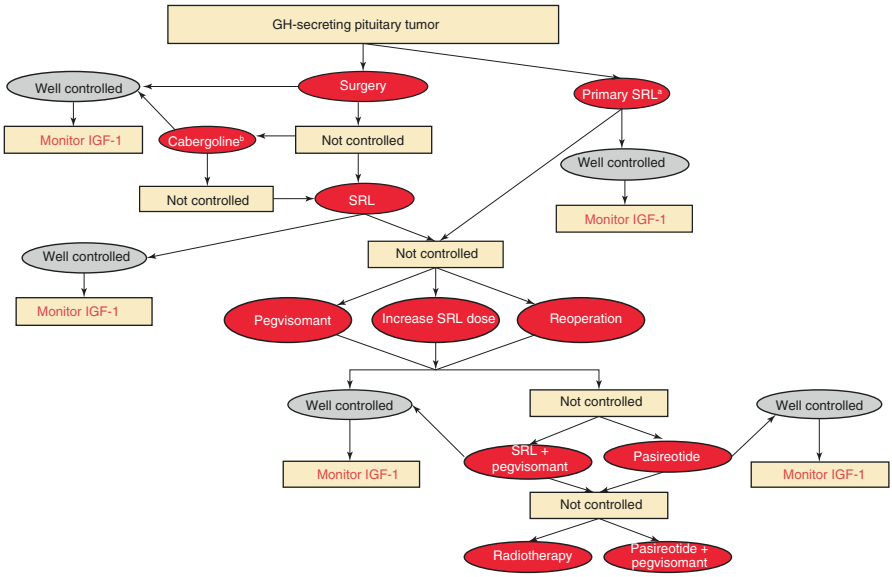

Fig. 1.2 Algorithm for the Multidisciplinary Management of Acromegaly. (**a**) If curative surgery is not feasible; (**b**) Consider in cases of mild postoperative GH/IGF-I elevations. Well controlled defined as normalized GH/IGF-I; not controlled defined as other than well-controlled. Abbreviations: IGF-I, insulin-like growth factor-I; SRL, somatostatin receptor ligand octreotide or lanreotide. (From Giustina et al. [22]. Adapted/Translated by permission from Springer: Springer Rev Endocr Metab Disord. Multidisciplinary management of acromegaly: a consensus. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al., 2020;21(4):667–78.)

have distinctive histologic subtypes, which can predict clinical course and/or treatment response. Subtypes include densely granulated (DG), sparsely granulated (SG) or intermediate-type somatotroph adenomas, mixed GH- and prolaction (PRL)-secreting adenomas, mammosomatotroph (MS) adenomas, and plurihormonal adenomas. As illustrated in the chapter by JM Hinojosa-Amaya and D Cuevas-Ramos, Tumor Behavior and Disease Severity in Patients with Acromegaly, Can We Predict Outcomes?, SG adenomas have been associated with more aggressive behavior and reduced somatostatin receptor ligand response versus DG. Imaging characteristics have been also shown useful to distinguish GH adenoma type, with SG usually appearing as hyperintense on T2-weighted MRI, while DG adenomas are more commonly described as hypo- or isointense. Furthermore, acromegaly patients with cystic tumors may have lower rates of biochemical remission after surgery, regardless of histological subtype [21]. An algorithm for treatment that was developed by a recent acromegaly consensus and is illustrated in Fig. 1.2 [22].

Conclusion

In conclusion, PA patients, especially those who have large complex, invasive, or recurrent tumors and hypersecretory syndromes, such as acromegaly or CD, would benefit from clinical work-up and specialized treatment [23] in a Pituitary Center of Excellence.

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Chapter 2
Pituitary Tumor Behavior and Disease Severity in Patients with Acromegaly

José Miguel Hinojosa-Amaya and Daniel Cuevas-Ramos

Objectives

- To highlight the diverse clinical presentation and tumor behavior in patients with acromegaly.
- To review the potential pitfalls in the diagnosis of acromegaly.
- To learn the screening methods and follow-up of the potential comorbidities of acromegaly.
- To review available treatment options and medical treatment response according to different clinical settings.

Overview

Acromegaly is a chronic and debilitating disorder characterized by abnormal somatic growth as a consequence of increased growth hormone (GH) levels, secreted by a somatotroph cell pituitary adenoma [1]. Research to uncover the pathophysiological mechanisms underlying somatotroph tumor cell proliferation and GH synthesis and release has shown different tumor behavior, disease activity, and response to treatment [2].

Somatotroph adenomas have been classified depending on their granulation density, hormone content, and cytogenesis [3]. Densely granulated (type 1) GH cell adenomas can be identified either by electronic microscopy or a perinuclear pattern

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of low-molecular-weight cytokeratin staining (CAM 5.2 or CK18). These tumors hold abundant large GH-containing secretory granules, meaning a decreased rate of GH secretion, which is reflected as a milder clinical and biochemical disease activity. In contrast, sparsely granulated adenomas show higher cell proliferation and invasiveness and cause greater disease activity, commonly unresponsive to multiple therapeutic modalities [2]. The mechanisms explaining such different tumor behavior, the current and novel therapeutic approaches, and related comorbidities of acromegaly are summarized in this chapter with the description of three clinical representative cases.

Case Presentation

Case 1

An 84-year-old woman diagnosed with acromegaly at the age of 64 presented for fatigue, muscle weakness, and weight gain. At the time of diagnosis, her symptoms were headache, prognathism, and acral growth. She received medical care after 7 years of symptoms onset. GH and insulin-like growth factor type 1 (IGF-1) levels were found increased, and a right-side, hypointense, pituitary microadenoma of 7 mm was present (Table 2.1 and Fig. 2.1). She refused neurosurgery and, therefore, was treated medically with once monthly octreotide LAR 20 mg and primary stereotactic radiosurgery with Gamma Knife. GH and IGF1 levels were normalized after treatment and remained under medical control for the following 20 years. Therapy was withdrawn after 2, 5, and 10 years to evaluate if in remission, however, increased GH levels were identified after oral glucose tolerance testing (OGTT), confirming persistent disease activity. Octreotide LAR 20 mg every 28 days was resumed, but developed symptoms of GH deficiency are confirmed by low IGF-1 levels. The medication was adjusted to every 45 and then every 60 days with resolution of symptoms. Seven years later, the patient died at 91 years due to a stage IV bladder adenocarcinoma.

Case 2

A 27-year-old man has an 8-year long evolution of acral growth, frontal bossing, nose widening, and prognathism. He also complained of arthralgia in hands and knees and increasing shoe size. Physical examination was positive for skin tags, goiter, and obesity. GH and IGF-1 levels were increased at diagnosis (Table 2.1), and pituitary MRI showed a non-invasive, intrasellar, macroadenoma (Fig. 2.1).

Table 2.1 Clinical presentation and laboratory results during follow-up of three patients with different types of acromegaly presentation

	Case 1	Case 2	Case 3
First evaluation after first symptom	7 ys	8 ys	4 ys
Age at diagnosis	64 years	27 years	37 years
Gender	Woman	Man	Man
Clinical syndrome at first evaluation	Headache, prognathism, and acral growth	Frontal bone, nose, maxillary growth, arthralgias, and goiter	Headache, visual impairment, involuntary hits in extremities
MRI	Microadenoma	Non-invasive macroadenoma	Invasive macroadenoma
GH (ng/ml)	7.7	16	17.5
IGF-1 (ng/ml)	638	683	823
IGF-1 index	2.9	3.0	3.9
Prolactin	12	23	71
Treatment	Refused TSS. Gamma-Knife radiosurgery and octreotide LAR 20 mg per month	TSS. Lanreotide autogel 90 mg per month + cabergoline 2 mg/week. Then LiNAC radiotherapy	Lanreotide autogel 120 mg per month + cabergoline 1 mg/week
Follow-up	20 years	10 years	1 week
Clinical syndrome at last evaluation	Fatigue, weakness, and weight gain	Asymptomatic	Dyspnea, orthopnea, peripheral edema, sleep apnea, macroglossia, diaphoresis
Last GH (ng/dl)	1.5	0.8	21
Last IGF-1 (ng/dl)	71	211	723
Last IGF-1 index	0.8	0.8	3.5
Treatment	Octreotide LAR 20 mg every 60 days	Lanreotide autogel 90 mg per month + cabergoline 2 mg/week	Patient died night before neurosurgery
Comorbidities	Bladder carcinoma	Malocclusion, multinodular goiter, obesity	Heart failure, diabetes, systemic and pulmonary hypertension

Transsphenoidal surgery (TSS) was performed with no complications; however, the patient had persistent disease activity, and lineal accelerator (LiNAC) stereotactic fractionated radiotherapy was used for the residual tumor. Lanreotide autogel 120 mg every 28 days and cabergoline 2 mg per week were also added with good tolerance and response. Such therapy persisted until last follow-up.

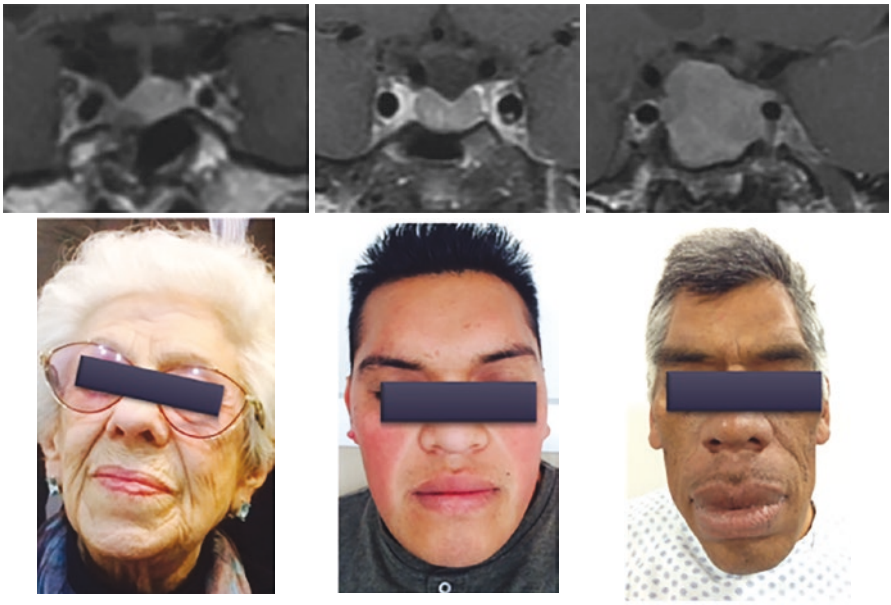

Fig. 2.1 Pituitary MRI and clinical picture of three cases with different acromegaly presentation and outcomes

Case 3

A more symptomatic 37-year-old man has a 4-year history of headache and temporal visual field impairment (manifested by multiple involuntary collisions with furniture and doors with his shoulders, arms, and knees). Physical examination was relevant for a typical acromegalic facies with macroglossia (Fig. 2.1), with significant growth of the soft tissue on his hands and feet, hypertension, tachypnea, tachycardia, and peripheral edema. The patient was hospitalized for urgent treatment and diagnosis. GH and IGF1 confirmed of acromegaly (Table 2.1). Also, prolactin was moderately high, explained by compression of the pituitary stalk. An invasive macroadenoma was found on MRI (Fig. 2.1). The patient also had hyperglycemia (285 mg/dl) corrected with an insulin analog therapy. TSS was scheduled, and primary medical treatment with lanreotide autogel 120 mg and cabergoline 1 mg per week was started to improve the patient's condition. Cabergoline was planned to be titrated to 2 mg per week gradually; however, the patient developed acute heart failure and cardiogenic shock and unfortunately died the night before surgery.

How Does the Clinical Presentation of Acromegaly Relate to Tumor Behavior?

Every organ can be affected by the excessive systemic effect of GH and IGF1 in acromegaly, from local tumor effects (headache and visual field defects) to acral enlargement and musculoskeletal, skin, gastrointestinal, cardiovascular, endocrine, pulmonary systems morbidity [1]. However, a better understanding of acromegaly clinical presentation is emerging from recent studies [2, 4, 5]. Men are significantly younger than women at diagnosis by about 4.5 years [6]. Microadenomas in acromegaly are usually densely granulated tumors with lower disease activity and complications and more easily controlled with current therapy than sparsely granulated macroadenomas. Patients with microadenomas are usually less symptomatic and may have long-term remission without needing therapy (case 1). Despite no treatment, some patients with >65 years harbor small adenomas, with low invasion rates and a high probability of surgical remission (73%) [7]. Therefore, age is not a good predictor of remission [8]. On the other hand, invasive macroadenomas cause more symptomatology, requiring prompted evaluation and therapy. Despite earlier evaluation and treatment, remission is difficult, and multiple therapeutic modalities are commonly required [2].

Which Mechanisms Determine the Diverse Tumor Aggressiveness and Disease Activity Among These Patients?

Pituitary somatotroph cell adenomas exhibit a heterogeneous behavior ranging from small and difficult-to-detect tumors, with limited biochemical activity (case 1), to large, invasive, and highly active adenomas (case 3). Although some of the molecular mechanisms are shared by the different pituitary tumor lineages, somatotroph cell adenomas develop on a specific background of chromosomal instability with overexpression of the pituitary tumor-transforming gene protein (PTTG), which is a securin molecule that regulates chromatid segregation [9]. Then, cell cycle disruption leads to tumor growth without malignant transformation in most of all somatotroph cell adenomas, thanks to the senescence pathway [9–11]. PTTG overexpression leads to p53 pathway induction, increasing expression of cyclin-dependent kinase (CDKs) inhibitors such as p21, p57, and p16, which leads to irreversible cell cycle arrest [11, 12]. GH-secreting carcinomas are extremely rare cases in which p21 expression is lost [11]. When SSTR2 expression is low, it also correlates with decreased somatostatin-mediated inhibition of cell proliferation, leading to tumor growth, aggressive tumor behavior, and impaired response to treatment [13, 14]. GH secretion is lower in densely granulated cells (likely to be senescent) than in

sparsely granulated somatotroph cells (likely to have higher proliferation rate) [15]. In summary, patients with densely granulated tumors are likely to show microadenomas with lower biochemical activity, higher p21 and SSTR2 expression, and more feasible to reach surgical remission or control with medical therapy. In contrast, sparsely granulated tumors are highly active and invasive and have lower p21 and SSTR2 expression and higher probability to persist with active disease despite multimodal treatment [2]. This somatotroph adenoma subtype requires close clinical surveillance and an individualized therapeutic approach.

Which Are the Pitfalls in the Diagnostic Workup of Acromegaly?

The diagnosis of acromegaly may be challenging in patients with very mild or recent-onset disease in which clinical features may not be as evident as in more active disease, which may be not related with disease duration in all cases. On the other hand, certain acromegalic features may be present in certain ethnic groups in which "acromegaloidism," or pseudoacromegaly, is more prevalent. Pseudoacromegaly is a differential diagnosis of acromegaly and is defined in patients who have an acromegalic facies as a consequence of physiologic or pathological causes, other than increased GH or IGF-1 levels [16].

An important pitfall is the biochemically discordant acromegaly at diagnosis, previously called "micromegaly" or "small acromegaly," and has been found not to differ from acromegaly. Between 2.4% and 13.7% of patients with acromegaly will have this biochemical discordance at diagnosis, with elevated IGF-1 levels and normal GH-nadir levels after an OGTT [17].

Pitfalls can also be found in laboratory assays. It is important for the clinician to know the details of GH and IGF-1 measurements when interpreting results. As GH has many isoforms, it is crucial to know whether the assay measures the most common variant (22 kD) GH (monoclonal) or other isoforms (polyclonal) and if it is a sensitive assay or ultra-sensitive assay [18]. In the interpretation of the OGTT, GH-nadir <1 μg/L is appropriate for sensitive assays, while 0.4 μg/L is for ultra-sensitive ones [19]. Random GH measurement is not recommended for initial diagnosis, since it is extremely variable, due to its pulsatile nature [20]. Changes in the levels of the GH-binding protein may also affect the measurement of GH [21].

Although IGF-1 is a molecule much more stable than GH, IGF-1 assays have a considerable (~ 20%) intraindividual variation to be taken into account for interpretation [19–21]. IGF-1 has six binding proteins (IGFBP), mainly IGFBP-3. For this reason, an IGF-1/IGFBP-3 ratio is considered as a surrogate marker of free IGF-1, which may be used when the biochemical result is discordant to the clinical picture [21].

GH and IGF-1 are the assessments of choice for diagnosis and follow-up. When further confirmation at diagnosis is necessary, an OGTT using the

immunodiagnostic systems (IDS-iSYS) chemiluminescence GH assay may be required [5]. IGF-1 measurement should be adjusted for body mass index (BMI), age, and gender. Also, estrogen-containing oral contraceptives may be considered for test interpretation and to avoid false-positive results [22]. IGF-binding protein 3 (IGFBP3) and acid-labile subunit are not routinely necessary. To evaluate remission, IGF-1 should be measured at least 6 weeks post-operatively, and if they are mildly elevated, they may yet normalize by 3–6 months [5].

Which Therapeutic Options Are Currently Available for Acromegaly?

First-line therapy for acromegaly is pituitary adenoma resection through TSS. However, depending on country practices, some patients are treated with SRLs for tumor volume reduction before surgery, particularly those with invasive tumors without optic chiasm compression. Surgical and pharmacological outcomes in acromegaly are highly dependent on tumor size and invasiveness. Patients with microadenomas (case 1) achieve higher remission rates than non-invasive macroadenomas (case 2), and both show better outcomes than invasive macroadenomas (case 3) [23]. Somatostatin receptor ligands, octreotide LAR and lanreotide acting as SSTR2 agonists and the multiligand pasireotide LAR directed to SSTR5 > SSTR2 > SSTR3 > SSTR1 [24], have shown >20% tumor volume reduction [25, 26]. If the disease does not reach remission, combination therapy with the D2 dopamine receptor agonist cabergoline [27] and/or the GH receptor antagonist pegvisomant has shown improved efficacy than monotherapy [28–30]. One study found low-dose octreotide LAR (10 mg) or lanreotide (60 mg) combined with once weekly pegvisomant (40–160 mg/week) was a cost-effective option, showing a 96% biochemical control rate [31]. Stereotactic radiotherapy or radiosurgery has also demonstrated good efficacy and safety as an adjuvant therapy in patients with persistent disease and tumor residual [32, 33]. Medical therapy should be continued until reaching remission after a complete radiotherapy effect. Oral octreotide capsules (40–80 mg/day) have been recently approved by the US Food and Drug Administration for long-term maintenance treatment after proving non-inferiority in patients with adequate response and tolerance to first-generation SSTR agonist therapy (octreotide or lanreotide) [5, 34–36]. Potential therapies in the near future include octreotide fluid crystal (CAM2029) [37] and blocking GH receptor through antisense oligonucleotide therapy (ATL1103) [38].

These novel strategies aim to improve acromegaly disease control which is crucial to prevent excess mortality [39]. Before 2008, studies reporting higher mortality in acromegaly than general population were more commonly published ($n = 17$) [40]. Recent studies show normalization of mortality risk over time in disease-controlled patients when compared with the general population (SMR 1.3, 95% CI 0.9–1.8) [40, 41]. Extended dosing intervals may be an effective weaning therapy in patients under good biochemical control with SRLs and suspected remission [42].

How Should Patient Comorbidities Be Screened, Treated, and Followed?

Excess mortality in patients with acromegaly is mainly related to cardiovascular and cerebrovascular disease [41]. Comorbidities leading to this excess mortality risk are secondary diabetes mellitus, hypertension, and obstructive sleep apnea (OSA). Some patients will also develop acromegalic cardiopathy and valvular disease, leading to heart failure (case 3).

Blood pressure should be assessed every visit, while screening glucose abnormalities and electrocardiogram may be performed every 6 months to 1 year. If an impaired fasting glucose is found, an OGTT and glycated hemoglobin (HbA1c) may be performed and followed every 6 months.

OSA screening with validated scales as the Epworth sleepiness scale may be a practical option, but none of the known OSA scales has been validated as screening tools for acromegaly, and a sleep study (polysomnography) is still the study of choice for ruling out OSA at diagnosis [5]. A recent meta-analysis found significant improvement after surgical or medical treatment of acromegaly [43] and 69% OSA cure rate with disease control [44].

A clear role for echocardiography (ECHO) in acromegaly is yet to be defined [45, 46]. The Acromegaly Consensus Group suggests a baseline ECHO for screening valve disease or acromegalic cardiopathy, and repeat it yearly thereafter as needed [45].

Malignancy as an effect of chronically increased GH and IGF-1 is also a potential risk but has a lower effect on mortality. Currently, controlled acromegaly patients will have similar or longer life expectancy, increasing the chance for comorbidities that lead to death like in case 1. The most common malignancies associated with acromegaly are colorectal and thyroid cancer [46, 47]. Physical examination of the thyroid and a screening colonoscopy are therefore important. Benign neoplasms are more frequent than malignant. Therefore, follow-up colonoscopy or thyroid ultrasound is indicated similar to patients without acromegaly. If the disease remains active, surveillance can be performed more frequently individualizing each case [45].

Acromegaly has shown lower femoral neck bone mineral density (BMD) and higher risk of vertebral fractures (VF) related with lower trabecular bone score (TBS). A baseline dual-energy X-ray absorptiometry (DEXA) is therefore recommended [48]. Although acromegaly patients may have normal BMD by DEXA, they may still have fragility fractures because of lower TBS. BMD does not correlate with fracture risk as disease control does. A proactive evaluation of VF risk, with a morphometric approach, is therefore recommended [42].

Pituitary function might be followed in an individualized fashion and is frequently assessed every 6 to 12 months. Evaluation of quality of life scores with approved questionnaires may be performed annually [49].

Conclusions

Disease control is the strongest predictor of favorable outcomes in acromegaly. Somatotroph adenoma subtypes are likely to be related to the patient's clinical manifestations of the disease. Aggressive subtypes are less likely to reach remission or biochemical control. When disease control is achieved (cases 1 and 2), comorbidities such as DM, OSA, hypertension, cardiopathy, and valvular disease are likely to be prevented, disappear, or have better response to treatment. This in turn decreases the risk of cardiovascular events, which are the most common cause of morbidity and mortality in acromegalic patients. However, chronic somatic and visceral changes are unlikely to be reversed; therefore, early diagnosis and treatment are quite important to reduce the likelihood of developing respiratory and cardiovascular complications which may lead to death (case 3). As novel treatment options continue to emerge, it is likely to achieve better outcomes for patients with acromegaly.

Lessons Learned

- Diagnosis of acromegaly may be challenging in patients with mild symptoms, due to several pitfalls found in the interpretation GH or IGF-1 assays or discordant results at diagnosis.
- The first-line treatment for acromegaly is transsphenoidal surgery; however, some patients with severe disease and comorbidities may benefit from primary medical therapy. Some studies report improvement in surgical remission after pretreatment, but data are conflicting.
- Surgical and pharmacological outcomes in acromegaly are highly dependent on tumor size and invasiveness.
- Treatment responsiveness in acromegaly may vary depending on the structural and functional characteristics of the somatotroph cell adenoma subtype.
- As emerging medications for treating acromegaly are being approved, it is likely to achieve disease control with subsequent reduction of morbidity and mortality.

Multiple-Choice Question

1. Which of the following factors are associated with somatotroph cell adenoma aggressiveness?

   (a) Number of mitosis
   (b) p21 expression
   (c) Granulation
   (d) (a) and (b)
   (e) (b) and (c)

Answer (e) = PTTG overexpression leads to p53 pathway induction, increasing expression of cyclin-dependent kinase (CDKs) inhibitors such as p21, which leads to irreversible cell cycle arrest and cell senescence [11, 12]. Somatotroph

cell adenomas with high p21 levels are less invasive microadenomas with better disease control and prognosis. Also, GH secretion is lower in densely granulated cells (likely to be senescent) than that in sparsely granulated somatotroph cells (likely to have higher proliferation rate) with better disease control and outcomes [15]. Since usual are benign tumors, number of mitosis is low and not related with aggressiveness.

2. Which of the following statements is correct regarding somatostatin receptor ligands (SRLs)?

   (a) Longer periods of SRL injection are not recommended despite good disease control.
   (b) Parenteral octreotide (IM, SC) is the only FDA-authorized route of administration in acromegaly.
   (c) SRLs should not be combined with other FDA-approved therapies for active acromegaly.
   (d) Expression of SSTR2 at somatotroph cells has a good correlation with SRL responsiveness.
   (e) None of the SRLs has shown tumor volume reduction >20% when used before surgery.

Answer (d) = When SSTR2 expression is low, it also correlates with decreased somatostatin-mediated inhibition of cell proliferation, leading to tumor growth, aggressive tumor behavior, and impaired response to treatment [13, 14]. Extended dosing intervals may be an effective weaning therapy in patients under good biochemical control with SRLs and suspected remission [42]. Since there are novel treatment options with different mechanisms of action, combination therapy is increasingly employed [42]. All SRLs have shown tumor volume reduction [42].

3. Which factors are highly associated with surgical and pharmacological outcomes in acromegaly?

   (a) Age and gender
   (b) Neurosurgeon experience and access to stereotactic radiotherapy
   (c) Tumor size and invasiveness
   (d) Disease duration before diagnosis
   (e) IGFBP3 and acid-labile subunit serum levels at diagnosis

Answer (c) = Despite no treatment, some patients with >65 years harbor small adenomas, with low invasion rates and a high probability of surgical remission (73%) [7]. Therefore, age is not a good predictor of remission [8]. First-line therapy for acromegaly is pituitary adenoma resection through TSS. However, if cavernous sinus invasion is positive, neurosurgery is more difficult with lower successful rates, and it is not related with neurosurgeon experience. Therefore, surgical and pharmacological outcomes in acromegaly are highly dependent on tumor size and invasiveness. Disease duration depends on clinical and biochemical activity [2].

4. How should the patient risk of comorbidities be followed?

   (a) Colonoscopy every year or every 5 years in patients in remission
   (b) Fine-needle thyroid aspiration every year when thyroid nodules are palpable
   (c) Echocardiography only when symptomatology is present
   (d) Proactive evaluation of VF with a morphometric approach
   (e) Acromegaly Quality of Life Questionnaire (AcroQoL) every 6 months

Answer (d) = Acromegaly has shown lower femoral neck bone mineral density (BMD) and higher risk of vertebral fractures (VF) related with lower trabecular bone score (TBS). A baseline dual-energy X-ray absorptiometry (DEXA) is therefore recommended [48]. Otherwise, follow-up colonoscopy or thyroid ultrasound is indicated similar to patients without acromegaly. If the disease remains active, surveillance can be performed more frequently individualizing each case [45]. A clear role for echocardiography in acromegaly is yet to be defined [45, 46]. Evaluation of quality of life scores with approved questionnaires (AcroQoL) may be performed annually [49].

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Chapter 3
Abrupt Weight Gain, Hypertension, and Severe Hypokalemia in a Young Male

Stuti Fernandes, Elena V. Varlamov, and Maria Fleseriu

Objectives

- To recognize clinical presentation of Cushing's syndrome (CS).
- To appropriately work up and diagnose CS.
- To select optimal treatment of CS.
- To manage comorbidities/risks associated with CS.

Case Presentation

A 29-year-old male presented to a hospital clinic with weakness, edema, and weight gain. Past medical history was significant for recently developed hypertension and diabetes. Weight gain of 70 pounds over 6 months was noted. Recently developed painful purple stretch marks on the abdomen and chest and easy bruising were reported by the patient. The patient also reported that he had an active job and had experienced recent difficulty with lifting boxes and going up stairs. The patient denied use of alcohol or glucocorticoids.

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Physical examination (Fig. 3.1) was remarkable for hypertension (blood pressure; BP 146/107 mm Hg), obesity (body mass index; BMI 35), moon facies, facial plethora, mild acne, dorsocervical and supraclavicular fat pads, decreased skin fold thickness, abdominal bruising, and purple striae. Based on clinical presentation, it was suspected that this patient had excess cortisol production or Cushing's syndrome (CS).

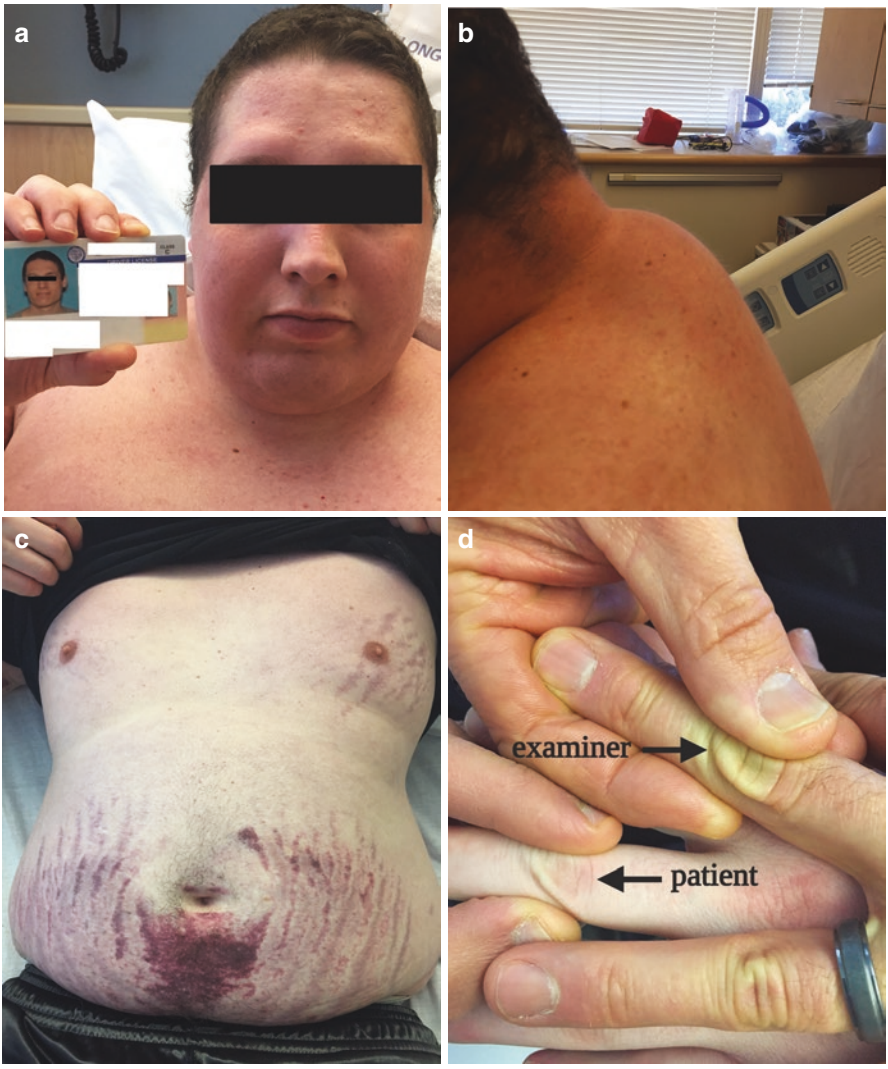

Fig. 3.1 Physical exam (photographs). Moon facies and facial plethora (**a**). Dorsocervical and supraclavicular fat pads (**b**). Abdominal bruising and purple striae (**c**). Finger decreased skin fold thickness; patient compared with examiner (**d**). Obtained with patient consent/permission. (Provided by Andre Mansoor, M.D., Department of Medicine, Division of Hospital Medicine, Oregon Health & Science University)

Does This Patient Have Cushing's Syndrome?

Cushing's syndrome (CS) can be difficult to differentiate from metabolic syndrome and obesity. Fatigue, weight gain, obesity, hypertension, decreased libido, menstrual abnormalities, hirsutism, dorsocervical fat pad, supraclavicular fullness, and peripheral edema are features of CS that are also common in the general population [1]. Signs and symptoms that have a higher specificity for diagnosing CS include easy bruising, facial plethora, proximal myopathy or muscle weakness, reddish purple striae >1 cm, osteoporosis, and decreased skinfold thickness (measured over the proximal phalanx of the middle finger of the non-dominant hand; Fig. 3.1) [1, 2]. These more specific signs are a result of increased protein breakdown caused by the underlying catabolic state in hypercortisolism [3].

Other laboratory findings in CS include hypokalemia (due to action of excess cortisol on mineralocorticoid receptor) [4], hyperglycemia [5], leukocytosis with higher percentage of polymorphonuclear cells [6], elevated liver enzymes [7], and secondary hyperparathyroidism [8]. A summary of pertinent patient laboratory results is provided in Table 3.1. Based on the laboratory results, it was determined that this patient had hypokalemia, hyperglycemia, mildly elevated liver function tests, and leukocytosis.

It is possible for patients to present with alterations in other endocrine hormone levels. Patients with pituitary CS (Cushing's disease, CD) may have hypopituitarism from a pituitary adenoma, mostly resulting in growth hormone (GH) deficiency and/or hypothyroidism [8–10]. Patients with both pituitary and non-pituitary CS often have functional central hypogonadism and hypothyroidism [8]. In the case of this patient, there was central hypogonadism and a slightly suppressed thyroid-stimulating hormone (TSH) level with normal free T4 level. Insulin-like growth factor 1 (IGF-1) and prolactin levels were in the normal range.

Once CS is suspected, exogenous corticosteroid exposure (the most common etiology) should be excluded through history and medication review. If endogenous CS is suspected, the patient should undergo several tests to confirm the presence of

Table 3.1 Patient laboratory results

Laboratory	Units	Normal range	Patient result	Patient range result
Potassium	mmol/L	4.5–5.0	3.1	Low
Hemoglobin A1c	%	<5.7	6.1	High
Alanine transaminase	U/L	<60	103	High
White blood cell count	K/mm^3	3.5–10.80	12	High
Testosterone (total)	ng/dL	>250	172	Low
Follicle-stimulating hormone	mIU/L	1.3–19.3	0.2	Low
Luteinizing hormone	mIU/L	1.2–8.6	<0.2	Low
Thyroid-stimulating hormone	mIU/L	0.4–3.98	0.32	Low
Free T4	ng/dL	0.6–1.2	0.7	In range
Insulin-like growth factor 1	ng/mL	84–250	233	In range
Prolactin	ng/mL	2.1–17.7	14.4	In range

cortisol excess. The three main tests used are 24-hour urinary free cortisol (UFC), late night salivary cortisol (LNSC), and dexamethasone suppression testing. These tests have a high sensitivity but not high specificity in diagnosing CS [1]. Urinary free cortisol measures cortisol not bound to cortisol-binding globulin (CBG) and therefore is not affected by conditions or medications that alter CBG, such as pregnancy and oral estrogen-containing contraceptive use [1]. Urinary free cortisol may be falsely high in patients with high fluid intake or falsely low in those with chronic renal insufficiency [3]. Late night salivary cortisol is reported to have high sensitivity (92–100%) and specificity (85–100%); however, this varies by assay characteristics and technique. False positives may occur due to smoking, oral bleeding, oral infections, and depression or shift work. It is recommended to collect at least two samples because of test variability [3]. Low-dose dexamethasone suppression test (LDT) is conducted by the patient taking a bed time dose of 1 mg dexamethasone with blood collection the following morning for cortisol (>1.8 μg/dL is consistent with CS) and dexamethasone serum levels. False positives can occur in women on oral contraceptives or medications that increase metabolism of dexamethasone (e.g., carbamazepine, phenytoin). Inaccurate results may also occur in patients with renal or liver insufficiency who have reduced dexamethasone clearance [3, 11]. It is not recommended to use random serum cortisol, adrenocorticotropic hormone (ACTH) levels, and/or urine 17 ketosteroids to diagnose CS [1]. Pseudo-Cushing's states, caused by physiological activation of the hypothalamic-pituitary adrenal axis, should be ruled out. Common causes of this include obesity, eating disorders, poorly controlled diabetes, chronic alcoholism, and depression [12]. Clinicians should use the results of several screening tests and clinical judgment to determine if any given patient has CS.

In the case presented, 24-hour UFC was significantly elevated as determined by repeated measures (7950 μg/24 h; a normal value is <60 μg/24 h). This information, along with the details of clinical presentation, confirmed a diagnosis of CS.

The next step was to determine if CS was ACTH dependent (ACTH >20 pg/mL) or independent (ACTH <5 pg/mL) [13]. The patient's ACTH was elevated at 480 pg/mL, confirming ACTH-dependent CS.

How to Determine an ACTH Source?

This step should not precede confirmation of cortisol excess as patients may have pituitary or adrenal incidentalomas that can lead to unnecessary treatment [1]. If the patient has ACTH-independent CS (15–20% of CS patients), the next step would be to perform adrenal imaging to determine if there is an adrenal adenoma, which commonly requires surgical therapy [8, 14]. Since this patient had ACTH-dependent CS, the differential was an ACTH-producing pituitary adenoma (80% of cases) or ectopic ACTH secretion (EAS; approximately 20% of cases) [14, 15]. Tumors that cause EAS include most commonly carcinoid tumors of the lung, islet cell tumors

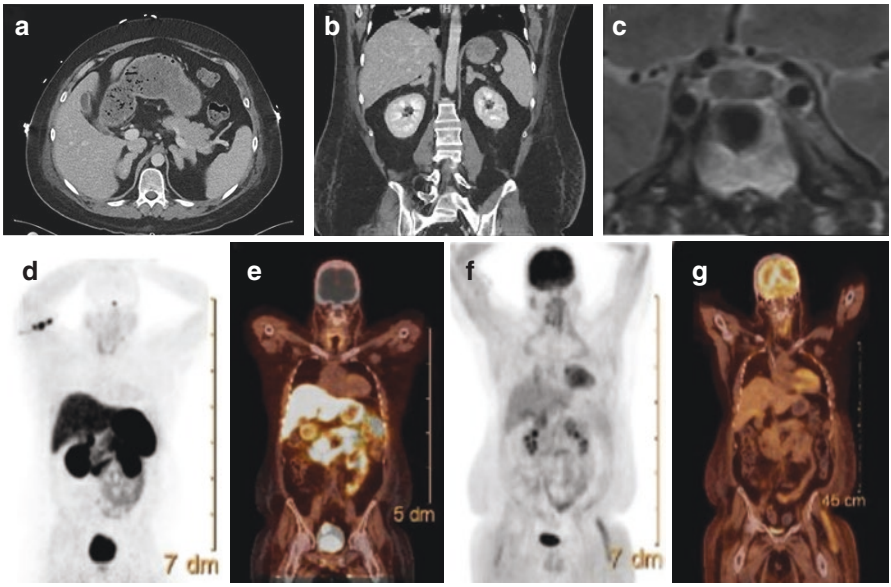

Fig. 3.2 Imaging. Abdominal axial (**a**) and coronal (**b**) computed tomography (CT), showing bilaterally enlarged adrenal glands. Pituitary coronal T2 magnetic resonance imaging without contrast (**c**), showing a 3 × 4 mm T2 hyperintense mass in the posterior superior aspect of the pituitary gland. Functional positron emission tomography; PET imaging gallium-68 somatostatin receptor (^{68}Ga-SSTR) PET/CT (**d** and **e**) and 2-deoxy-2-fluorine-18-fluoro-D-glucose (^{18}F-FDG)-PET (**f** and **g**), only physiologic uptake is observed

of the pancreas, medullary carcinoma of the thyroid, small cell tumors of the lung, and tumors of the thymus [16]. In the case presented, pituitary magnetic resonance imaging (MRI) revealed a 3 × 4 mm pituitary lesion (Fig. 3.2).

However, this did not confirm pituitary CS (CD) since 10% of healthy adults have pituitary lesions <6 mm. Additionally, 12% of patients with EAS have abnormal pituitary imaging [8]. Given that this patient's tumor was <6 mm, inferior petrosal sinus sampling (IPSS) to localize the ACTH source was performed. Inferior petrosal sinus sampling is the gold standard for ACTH source localization (sensitivity 82–100%; specificity 100%), and serious complications are rare [14]. However, IPSS is a technically challenging procedure, one that should be conducted at specialty centers by an experienced interventional radiologist [8, 14]. Asymmetric venous drainage, improper catheter placement, or treatment with cortisol-lowering therapies may result in false-negative results [17]. It is important to note that this procedure has poor accuracy in lateralizing ACTH source to one side of the pituitary gland, nor can it distinguish normal or pseudo-Cushing's patients from those patients with CS [8, 15, 18]. In the case presented, IPSS results (Table 3.2) [19] were consistent with EAS, and venography confirmed appropriate catheter placement and normal venous anatomy. If the patient had a pituitary ACTH source, they would have been referred for transsphenoidal resection.

Table 3.2 Patient inferior petrosal sinus sampling (IPSS) results

	Adrenocorticotropic hormone (pg/mL)			Cortisol (μg/dL)	ACTH petrosal sinus: peripheral
	Peripheral	Left petrosal sinus	Right petrosal sinus	Peripheral	Ratio[a]
Pre-CRH	451	480	499	95.2	1.11
Post CRH	1303	1514	1496	–	1.15

[a]Ratio ≥ 2 pre-CRH and ≥ 3 post-CRH indicates a pituitary source; *ACTH* adrenocorticotropic hormone; *CRH* corticotropin-releasing hormone

Once EAS is confirmed, the next step is to localize the ectopic ACTH-producing tumor, evaluate tumor extension, and determine surgical candidacy. Degree of hypercortisolism does not correlate with tumor aggressiveness [16]. Spiral thin slice computed tomography (CT) of cervical, thoracic, abdominal, and pelvic regions is recommended initially and may be performed in conjunction with pituitary MRI if the patient is deteriorating rapidly. Most thymic tumors, small cell pulmonary neuroendocrine carcinomas, pancreatic neuroendocrine tumors (NETs), ACTH-secreting medullary thyroid cancers and ACTH-secreting pheochromocytomas, and paragangliomas are detected by this imaging. However, bronchial carcinoids, one of the main causes of EAS, may be overlooked due to small size and proximity to pulmonary vessels. If the tumor remains occult, then it is recommended to proceed with functional imaging. Octreoscan detects tumors based on expression of somatostatin receptor 2 (SSTR2). However, sensitivity is low (64%), and hypercortisolism may cause downregulation of SSTR2 and SSTR5, resulting in false negatives. False positives may occur with pulmonary infections or physiologically higher uptake in the pancreatic uncinate process [16]. Positron emission tomography (PET)-CT using gallium-68 (^{68}Ga)-labeled SSTR ligands can also be used. Gallium-68-radiolabeled ligands have a higher affinity for the SSTR2 than those used in the octreoscan. Additionally, this imaging may offer better spatial resolution and anatomical detail than an octreoscan. The sensitivity of ^{68}Ga-SSTR PET/CT is not well established (64-100%); EAS is rare and statistics are based on case reports and small case series [20]. False positives may occur due to physiological uptake in the adrenal medulla, pancreatic uncinate process, and inflammatory lesions. False negatives may occur due to downregulation of receptors in response to high cortisol; medical treatment may lower cortisol levels and result in positive imaging [16, 20]. ^{18}F-labeled fluoro-2-deoxyglucose (^{18}FDG) and CT (^{18}FDG-PET/CT) utilize the high consumption of glucose by cancer cells and therefore higher uptake of ^{18}FDG to detect tumors. However, NETs may be slow growing, and thus ^{18}FDG-PET imaging may not aid in revealing such tumors [16]. If a small, localized tumor is found, then it is likely to be a well-differentiated NET with an excellent prognosis after surgical resection. If metastatic disease is found, then chemotherapy should be started urgently along with treatment of hypercortisolism. Radiofrequency ablation and chemoembolization have been used in patients with non-resectable tumors [16].

The patient underwent CT of the abdomen and chest, which did not identify an ectopic ACTH-secreting tumor but showed bilaterally enlarged adrenal glands consistent with ACTH-dependent bilateral adrenal hyperplasia in the setting of intense ACTH stimulation (Fig. 3.2). ^{68}Ga-DOTATATE PET/CT and ^{18}F-DG-PET/CT imaging was also unrevealing (Fig. 3.2).

Treatment in Severe Cases with Rapid Clinical Deterioration

In severe cases with rapid clinical deterioration, treatment should be prioritized over etiologic workup [16]. Thus, the patient was prescribed ketoconazole (US Food and Drug Administration; FDA off-label use), which was up titrated to a dose of 600 mg/twice daily. Ketoconazole is an imidazole anti-fungal drug that inhibits steroidogenesis by blocking CYP11 and CYP17. Other adrenal steroidogenesis inhibitors that are used to treat CS are detailed in Table 3.3 [8, 21–23]. Of note, etomidate is the only adrenal steroidogenesis inhibitor available intravenously.

Ketoconazole, etomidate, metyrapone, mitotane, and levoketoconazole (in clinical trials) are not FDA approved for use in treating CS but, however, are often used off-label [22]. Levoketoconazole is an enantiomer of ketoconazole that has greater potency compared to ketoconazole in vitro. In the SONICS clinical trial, levoketoconazole was shown to be efficacious and appears to have a lower risk of severe transaminitis as compared with ketoconazole (though no direct comparison was made) [23].

While taking ketoconazole, the patient's UFC reduced to 73.3 μg/24 h, but unfortunately he developed transaminitis (5 times the upper limit of normal; ULN) and ketoconazole was discontinued.

Metyrapone, a potent inhibitor of CYP11B1, can also be used to treat CS and has rapid action. Side effects include hypertension and hypokalemia (due to aldosterone precursors), hirsutism, and adrenal insufficiency.

Mitotane, an insecticide derivative, inhibits steroidogenic acute regulatory protein (StAR) and CYP11 enzymes and is approved for use in adrenal carcinoma [22]. Mitotane has a slow onset of action and is not useful to quickly control hypercortisolism [16]. Side effects include dizziness, altered cognition, gastrointestinal distress, and adrenal insufficiency [22].

Osilodrostat is an US FDA- and European Medicines Agency (EMA)-approved treatment for CD and inhibits CYP11B1 and aldosterone synthase. Efficacy is high, and in a phase III trial, more patients maintained a complete response with osilodrostat versus placebo at 34 weeks (31 [86%] vs 10 [29%]; odds ratio 13:7, $p < 0.0001$) [21]. Though not FDA approved for this indication, osilodrostat has been used more recently to treat other forms of CS, including severe EAS and adrenal carcinoma. In one case series, patients who could not tolerate other CS medications were started on high dose of osilodrostat and achieved rapid control of hypercortisolism (<2 weeks) without significant adverse events [24]. Potential side effects include nausea, diarrhea, hypertension, hypokalemia, hirsutism, and adrenal insufficiency [21].

Table 3.3 Medical treatment of Cushing's syndrome

Medication	Dosing	Mechanism of action	Side effects	US FDA approved for CD or hyperglycemia associated with CS
Adrenal steroidogenesis inhibitors				
Osilodrostat	4–60 mg (2× daily)	Inhibits CYP11B1 and aldosterone synthase	Nausea, diarrhea, asthenia, hypertension, hypokalemia, hirsutism, hyperkalemia, adrenal insufficiency	Yes
Ketoconazole	400–1200 mg (2× daily)	Inhibits steroidogenic acute regulatory protein (StAR), CYP11A1, CYP11B1, CYP17	Transaminitis, gastrointestinal distress, hypogonadism, adrenal insufficiency	No
Fluconazole	200 mg (1× daily)	Inhibits CYP17	Transaminitis	No
Etomidate	Bolus 5 mg (one time) followed by intravenous 0.02–0.3 mg/kg/h	Inhibits StAR, CYP11A1, CYP11B1, CYP17	Sedation, propylene glycol toxicity, adrenal insufficiency	No
Metyrapone	0.5–4.5 g (3× or 4× daily)	Inhibits mainly CYP11B1, Inhibits also CYP17, CYP11B2, CYP19	Hypertension, hypokalemia, hirsutism, gastrointestinal distress, adrenal insufficiency	No
Mitotane	2–5 g (1× daily)	Inhibits StAR, CYP11A1, CYP11B1, CYP11B2, 3β-HSD adrenolytic	Dizziness, altered cognition, gastrointestinal distress, teratogenic, cytopenia, low T4, hyperglycemia, adrenal insufficiency	No

(continued)

Table 3.3 (continued)

Medication	Dosing	Mechanism of action	Side effects	US FDA approved for CD or hyperglycemia associated with CS
Levoketoconazole (in phase 3 clinical trials)	150–1200 mg (2× daily)	Inhibits StAR, CYP11A1, CYP11B1, CYP17 Inhibits also CYP21A2	Nausea, headache, edema, transaminitis, adrenal insufficiency	No
Pituitary directed drugs				
Pasireotide	600–900 μg (2× daily)	Somatostatin receptor agonist	Nausea, gallstones, transient diarrhea, prolonged QT_c, hyperglycemia is very frequent	Yes
Pasireotide long-acting release; LAR	10–30 mg (monthly)	Somatostatin receptor agonist	Nausea, gallstones, transient diarrhea, prolonged QT_c, hyperglycemia is very frequent	Yes
Cabergoline	0.5–7 mg (weekly)	Dopamine receptor agonist	Nausea, dizziness, psychological symptoms, valvular disease at higher doses	No
Temozolomide (aggressive pituitary tumors and carcinomas)	150–200 mg/m^2/day (for 5 days) Repeat at 28-day cycles	DNA alkylation	Fatigue, hearing loss, urinary tract infection, transaminitis, cytopenias	No
Glucocorticoid receptor blocker				
Mifepristone	300–1200 mg (daily)	Glucocorticoid receptor antagonist	Hypertension, hypokalemia, adrenal insufficiency, vaginal bleeding, endometrial hyperplasia, nausea, fatigue, edema, arthralgias	Yes

Mifepristone is approved for treatment of hyperglycemia associated with CS and if used in high doses has glucocorticoid receptor (GR) and progesterone receptor antagonist properties. There is no biochemical marker to follow efficacy of mifepristone; therefore, clinical evaluation is key. Adrenocorticotropic hormone and cortisol levels may increase, and excess cortisol can activate mineralocorticoid

receptors, resulting in hypokalemia and hypertension. Vaginal bleeding and endometrial hyperplasia in women can also occur. If adrenal insufficiency occurs, high doses of dexamethasone are needed to overcome the GR blockade [22].

In severe CS, combination therapy is frequently used to lower cortisol to allow more time for diagnostic workup and optimize surgical candidacy. A combination of metyrapone and ketoconazole has been used in patients with EAS and adrenal cortical carcinoma (ACC). The result was a dramatic UFC reduction within 1 week [25]. Another study using mitotane, metyrapone, and ketoconazole combination drastically reduced patients' UFCs within 24–48 hours [26]. The principle behind this approach was to use two fast-acting steroidogenesis inhibitors (ketoconazole and metyrapone) to rapidly control hypercortisolism in the lag period before mitotane exerted its action. A block and replace regimen with oral hydrocortisone was used in those patients to prevent adrenal insufficiency [26]. In both cases, reduction in cortisol resulted in localization of previously occult EAS-producing tumors in some patients and optimized surgical conditions in other patients, while some patients were also able to avoid bilateral adrenalectomy (BLA) [25, 26].

If the patient had CD, then medical treatment options would have also included pasireotide, cabergoline, and temozolomide (very rarely used in ACTH-secreting carcinoma).

Pasireotide is a SSTR ligand that works to decrease ACTH secretion and cell proliferation. Side effects include nausea, gallstones, transient diarrhea, hyperglycemia, and prolonged QTc.

Cabergoline is a dopamine receptor agonist that can sometimes, but not in all cases, decrease ACTH secretion. Side effects include nausea, dizziness, and impulse control disorders.

Temozolomide causes DNA methylation and tumor regression. Side effects include fatigue, hearing loss, urinary tract infections, transaminitis, and cytopenias [22].

In cases of occult, metastatic EAS, or life-threatening and severe ACTH-dependent disease unable to be controlled by medical therapy, guidelines recommend removal of the adrenal glands [8].

The patient presented here was deteriorating rapidly, and treatment options were limited by side effects and pharmacy availability. Thus, he underwent a bilateral laparoscopic adrenalectomy (BLA), which is highly effective in treating hypercortisolism with an immediate effect. Surgical failure is rare but can occur due to difficulty identifying the adrenals or ectopic adrenocortical tissue (accessory adrenals) that are missed by the surgeon [16]. The patient's serum cortisol dropped to 0.7 μg/dL post-operatively, indicating a good surgical outcome.

Patients with EAS have higher rates of complications (myocardial infarction, internal bleeding, poor wound healing, infections, hematomas, and post-operative thromboembolic events) after BLA than those with less severe CS [16]. Patients with CD who undergo BLA are at risk of Nelson's syndrome (NS), corticotroph adenoma progression associated with increasing ACTH levels. Treatment options for NS include surgery, radiotherapy, chemotherapy, pasireotide, or temozolomide [27].

Evaluation and Treatment of Complications

Complications of severe hypercortisolism include hypertension, hypokalemia, hyperglycemia, thombosis/thromboembolism, infection, *Pneumocystis* pneumonia, and steroid psychosis [16]. The patient presented here was treated with insulin and oral antihypertensives. Cushing's syndrome results in hypercoagulability and increased risk of thromboembolic events; therefore, the patient was prescribed enoxaparin 40 mg/day for prophylaxis. The risk of thromboembolism remains elevated even after surgery, and the patient continued to take enoxaparin for 28 days post-discharge; guidelines do not provide recommendations on duration, and an individualized approach is needed [28]. The patient also developed respiratory distress requiring supplemental oxygen. Infectious workup was negative, except for elevated serum 1,3-β-d-glucan (188 pg/mL; normal range <80 pg/mL), which was concerning for a fungal infection. Chest CT (Fig. 3.3) showed bilateral ground glass opacities highly suspicious for *Pneumocystis jiroveci* pneumonia (PJP).

The patient declined bronchoscopy to confirm diagnosis and was empirically treated with trimethoprim-sulfamethoxazole and prednisone with rapid improvement in respiratory status [29]. Patients with CS are at high risk of opportunistic infection. Cortisol excess results in depressed immune function, allowing PJP to colonize the lungs. Treatment of CS leads to recovery of T cells, which can result in an inflammatory reaction to PJP, analogous to immune reconstitution syndrome in human immunodeficiency virus patients [30]. The risk of PJP is associated with EAS and high cortisol levels, and thus these patients should be considered for PJP prophylaxis prior to initiation of cortisol-lowering therapy [16, 30].

At 2 months follow-up, the patient had lost 30 pounds, hypertension had resolved, and he was no longer taking insulin. He was transitioned from prednisone to replacement hydrocortisone and fludrocortisone. He was provided with sick day instructions and emergency injectable steroids for use in the event of an adrenal crisis.

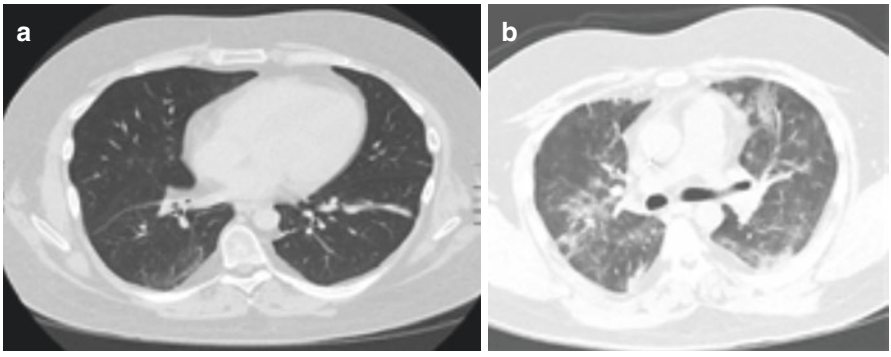

Fig. 3.3 Chest axial computed tomography. Images (**a**) and (**b**) showing bilateral ground glass opacities concerning for *Pneumocystis jiroveci* pneumonia

Later in recovery, hypogonadism and hypothyroidism resolved. The patient is scheduled to undergo repeat imaging for localization of the ACTH-secreting neuroendocrine tumor.

Conclusions

Cushing's syndrome can be a difficult diagnosis to ascertain. Clinicians must have a high index of suspicion and be able to identify more specific features of CS to distinguish from more common metabolic syndrome. Even when a patient presents with classic symptoms, confirmation of CS takes time and multiple tests (e.g., 24-hour UFC, LDT, and salivary free cortisol). It is important to confirm diagnosis before attempting to localize a source; skipping ahead in disease workup can lead to unnecessary treatment and surgery. Once cortisol excess is confirmed, it is important to determine whether the disease is ACTH-dependent or ACTH-independent. Computed tomography adrenal imaging is used to locate an ACTH-independent tumor source. Inferior petrosal sampling is used to determine an ACTH-dependent tumor source. Magnetic resonance imaging is used to locate pituitary adenomas. A combination of CT and functional imaging can locate ectopic tumors. While this diagnostic workup is ongoing, it is important to keep in mind the patient's clinical picture and progression. In rapidly deteriorating patients, it is more important to treat the high cortisol with either medication or BLA than to delay treatment while looking for a source. It is also important to be aware of and manage the complications associated with CS, including PJP and cardiovascular and deep vein thrombosis risks.

Lessons Learned

- Diagnosis of CS remains difficult in most situations and could be more challenging in a severely ill patient; it is important to screen and confirm the diagnosis in a timely manner. Cortisol is usually high in all patients with severe illness. A next step should be determining ACTH dependence or independence.
- Once ACTH dependence is confirmed, in patients where IPSS has ruled out a pituitary source, functional imaging plays an important role in identifying an ectopic ACTH-producing tumor. However, a tumor will not be found in some patients, and treatment should be started while looking for a cause.
- Medications for treating hypercortisolemia have different targets and mechanism of action, and combination therapy is sometimes used in patients with severe CS; side effects could be occasionally a limiting factor in properly up-titrating doses to maximum efficacy. Bilateral laparoscopic adrenalectomy remains the treatment of choice in severe CS with no definite source and clinical deterioration, while on medical therapy.
- Cushing's syndrome has many complications in general, but patients with severe CS have risk of *Pneumocystis jiroveci* pneumonia and deep vein thrombosis, and prophylaxis should be started immediately after diagnosis.

Multiple-Choice Question

A 50-year-old male presents with a 30 pound weight gain in 8 months, easy bruising, and new stretch marks and fatigue.

Physical Exam

The patient appears to be well and is friendly, however, they have difficulty rising from the chair to greet you. Upon examination, they have central abdominal obesity with multiple bruises on their abdomen >1 cm, violaceous abdomen and chest stretch marks, and increased dorsocervical fat pad deposition.

Other Details

Vital signs	Patient result
Blood pressure (mm Hg)	152/85 bilaterally
Heart rate (beats per minute)	70
Temperature (°F)	98.2
Respiration (breaths per minute)	16
Body mass index (kg/m^2)	33

Laboratory	Normal range	Patient result
Sodium (mmol/L)	136–145	143
Potassium (mmol/L)	3.4–5.0	3.4
Glucose (mg/dL)	97–108	120
Hemoglobin A1c (%)	5.7	6
Creatinine (mg/dL)	0.6–1.1	1.2
Urinary free cortisol (μg/24 h)	≤ 45.0	225 and 300
Cortisol (μg/dL) [after overnight 1 mg dexamethasone suppression test]	1.8	4.0
Adrenocorticotropic hormone (pg/mL)	6–50	2

Imaging	Patient result
Pituitary magnetic resonance	4 mm pituitary adenoma
Chest computed tomography	2 mm left lung nodule 3 mm right lung nodule and 3 cm right adrenal adenoma

Given the collective laboratory results, this patient has been diagnosed with Cushing's syndrome.

1. What is the best next step in the management of this patient?

   (a) Obtain functional imaging (^{68}Ga-SSTR PET/CT)
   (b) Refer for pituitary surgery
   (c) Refer for inferior petrosal sinus sampling

(d) Refer for adrenal vein sampling
(e) Refer for right adrenalectomy

2. What is the most important pre-operative consideration in this patient?

(a) Toxoplasmosis gondii prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX)
(b) Diabetes management with metformin
(c) Deep vein thrombosis prophylaxis with enoxaparin
(d) Prophylactic radiation to prevent Nelson's syndrome

Answers
1. (e)
2. (c)

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Chapter 4
Dopamine Agonist-Induced Impulse Control Disorders

Cristina Capatina, Catalina Poiana, and Maria Fleseriu

Objectives

- To highlight the possible occurrence of an underestimated adverse effect of dopamine agonists in treatment of prolactinoma patients and ICD.
- To review possible improvements in endocrine clinical practice, from patient information at drug initiation to monitoring and management of a possible ICD adverse effect.

Overview

Prolactinomas represent the most frequent type of pituitary adenoma encountered in endocrine clinical practice, and the first-line treatment is with dopamine agonists (DA). Dopamine agonists used to treat prolactinomas are typically cabergoline and to a lesser extent bromocriptine (quinagolide is now available in a few countries). Dopamine agonists are highly effective in controlling prolactin secretion and tumor growth [1]. They are also used in the treatment of certain neurological conditions (mainly Parkinson's disease (PD) but also restless leg syndrome (RLS) typically at high doses). In neurology clinical practice, the most frequently used DA are, however, pramipexole, ropinirole, or rotigotine, not cabergoline.

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Dopamine agonist treatment is generally well-tolerated with minor side effects such as gastrointestinal symptoms, dry mouth, hypotension, and dizziness. Contrary to the higher doses used in PD and RLS, the lower doses used in the treatment of prolactinomas do not increase the risk of valvular heart disease [2]. During DA treatment some patients develop new psychiatric symptoms or complain of worsening of preexisting symptoms. In a recent study, moderate depression was significantly more frequent among patients with pituitary tumors under DA treatment, while severe depression was only present in this subgroup and not in DA-naïve patients. Routine screening of depression during follow-up visits is recommended in pituitary adenoma DA-treated patients [3].

An increased frequency of impulse control disorders (ICD) has been reported in patients with PD or RLS undergoing DA treatment [4]. Impulse control disorders are a group of heterogeneous psychiatric disorders characterized by the inability of a patient to control an urge to repeatedly engage in excessive or harmful behaviors (to themselves or others). The most common presentations of DA-associated ICD in PD are pathological gambling, compulsive sexual behavior, compulsive buying, and binge eating. Other presentations are also possible (e.g., punding-repetitive purposeless mechanical activities, pyromania, kleptomania, trichotillomania, and intermittent explosive disorder) [5, 6]. There are numerous descriptions of ICD in patients with PD or RLS being treated with DA. Reports in prolactinoma DA-treated patients are rare. As a result of the difference in doses used (much higher in PD) and/or the type and receptor specificity of the DA used, the incidence of ICD in endocrinological patients treated with DA is commonly perceived as being much lower. However, ICD in endocrinological patients treated with DA is not so rare per se. The relative lack of awareness of this potential side effect is only partially the result of a lower incidence compared to that in neurological patients. Increased awareness among endocrinologists is essential. More so, because the intimate nature of these ICD presentations, could mean that patients may be reluctant to report, unless actively asked. Improvements in current clinical practice and specific recommendations about this potential side effect in current guidelines are needed. Formal evaluation for ICD should be incorporated into the care of all endocrine DA-treated patients.

Case Presentation

A 51-year-old female diagnosed with a microprolactinoma at age 34 years presented for secondary amenorrhea and bilateral galactorrhea. These symptoms appeared after interruption of long-term treatment with bromocriptine. At the time of initial diagnosis, the patient's prolactin level was increased at 136 ng/mL (normal 3.3–26.7 ng/mL). A pituitary microadenoma of 8–9 mm was also present. She had been treated for 17 years with 7.5 mg/day bromocriptine. Under the daily bromocriptine treatment regimen, prolactin level was suppressed, regular menses resumed, and the tumor remained stable.

There was a family history of metabolic disturbances (three sisters with diabetes mellitus (DM) and one sister and mother with obesity and hypertension). In the

17 years from the initial prolactinoma diagnosis, the patient exhibited a number of comorbidities. At the time of presentation in our department at age 51 years, she had severe metabolic syndrome (arterial hypertension, dyslipidemia, obesity, and type 2 DM) and ischemic heart disease and had experienced a few episodes of atrial fibrillation. She also had primary hypothyroidism, on adequate levothyroxine replacement. In addition to L-thyroxine, she was being treated with oral anticoagulant, rilmenidine, sartan, fibrate, statin, amiodarone, and long-acting insulin. No previous psychiatric history could be elicited. Six months before presentation, a decision was made to stop the bromocriptine by the primary local endocrinologist. After stopping bromocriptine, secondary amenorrhea and bilateral galactorrhea reoccurred.

On clinical examination the patient was obese (weight 94 kg, height 162 cm, body mass index 36.71 kg/m^2), heart rate is 62 beats/min, blood pressure is 140/80 mmHg, and minimal galactorrhea was noted on breast exam. No other significant features were noted at the initial examination. Routine laboratory tests revealed uncontrolled DM (HbA1c 9.9%). Endocrine evaluation revealed slightly increased prolactin (167 ng/dL), increased follicle-stimulating hormone (FSH; 14.6mIU/mL) serum level, and normal estradiol (55 pg/mL) levels (Table 4.1). Pituitary MRI revealed a stable microadenoma compared to previous imaging (Fig. 4.1). Treatment with cabergoline 0.5 mg twice a week was initiated. During treatment normal menses resumed initially, in parallel with good biochemical response. Over the next 6–12 months, menstrual irregularities reappeared, and eventually secondary amenorrhea occurred, this time as a clinical sign of menopause (revealed by the low estradiol and increased gonadotropin concentrations) (Table1). Repeat pituitary MRI after 6 months showed a stable microadenoma.

During the first months of treatment with cabergoline, hypersexuality became an issue for the patient and her family. She progressively began to experience increased libido, episodes of increased sex drive, and recurring sexual thoughts. No symptoms or signs of depression were present. She became unhappy with her marital sexual life and insisted on having her husband evaluated by endocrinologist to rule out

Table 4.1 Clinical and hormonal data during patient follow-up

Timeline	Clinical signs and symptoms	Prolactin (ng/dL)	Follicle-stimulating hormone (mIU/mL)	Estradiol (pg/mL)	Treatment
First presentation	Secondary amenorrhea. Galactorrhea.	167	14.6	55	Start cabergoline at 1 mg/week
After 6 months	Oligomenorrhea. No galactorrhea. Hypersexuality.	1.37	44.9	31	Continue cabergoline at 1 mg/week
After 12 months	Amenorrhea. No galactorrhea. Hypersexuality.	0.33	60	19	Stop cabergoline
After 18 months	Amenorrhea. No galactorrhea.	–	45.3	15	–

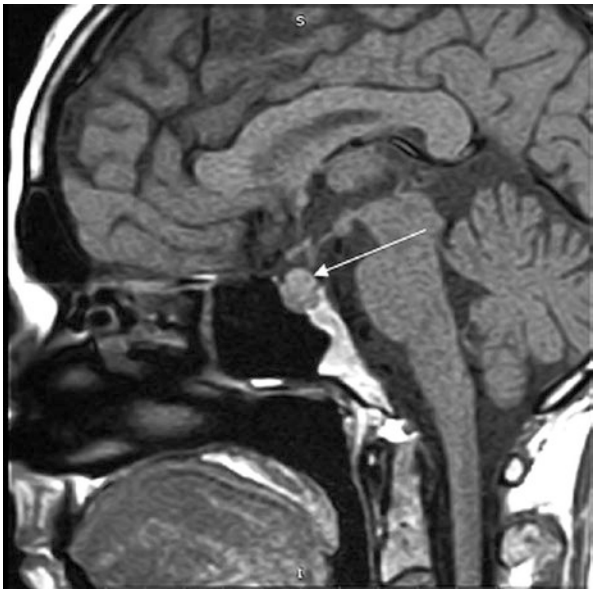

Fig. 4.1 Pituitary MRI sagittal section showing pituitary microadenoma (arrow)

possible hypogonadism (which was ruled out). Socially, strong religious beliefs prevented her engagement in inappropriate sexual behavior outside of marriage or purchase of specific sex-related materials. However, the newly developed symptomatology brought severe distress to the marital relationship.

After 12 months of cabergoline treatment, and taking into account the clear biochemical evolution toward menopause, the distressing symptomatology related to hypersexuality (likely related to cabergoline), and the fact that microprolactinoma treatment after menopause does not provide proven clinical benefit [7], we recommended stopping the DA treatment (Fig. 4.1).

At 6 months after stopping cabergoline, the hypersexuality symptomatology was completely resolved. The patient noted symptomatology improvement in the first month after stopping cabergoline. A decision was made to observe the patient without further DA treatment.

What Are Impulse Control Disorders and How Common Are They in the General Population?

Impulse control disorders are described as "failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or others" according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) fifth edition [8]. Accordingly, ICDs are a heterogeneous group of diseases characterized by

repetitive behaviors with a potential to harm the person affected or others and the inability of the affected person to resist the drive to engage in these behaviors. These include, among others, pathological gambling (PG), compulsive shopping, and hypersexuality disorder. Patients report experiencing tension prior to engaging in the compulsive behavior and a release of tension after [9]. There is reduced control over the behavior despite the acknowledged adverse consequences.

The epidemiology of ICDs is not yet fully understood. As reviewed in Dell'Osso et al. [9], the reported prevalence in different general population age groups is 0.4–1.6% for PG, 0.5–3.9% for trichotillomania, 1% for pyromania, 4–7% for intermittent explosive disorder, 0.38% for kleptomania, 5.8% for compulsive shopping, and 3.7% for hypersexuality disorder.

How Common Are Dopamine Agonist-Related Impulse Control Disorders?

In PD patients treated with DA, the prevalence of ICD is considerably higher than that in the general population. A large epidemiological multicenter study looking at the incidence of ICD in PD in the USA and Canada (DOMINION study) reported a global prevalence of 13.6%. Dopamine agonist treatment was associated with 2–3.5-fold increased ICD risk. Impulse control disorders occurred also in PD patients not treated with DA but with a significantly lower frequency (6.9% vs 17.1%) [6]. In a recent meta-analysis, DA-induced ICD prevalence in PD was reported as 2.6%–34.8% [10]. A longitudinal study of patients with PD revealed an increasing ICD prevalence from 19.7% at baseline to 32.8% after 5 years [11]. While DA-induced ICD has been assessed in a large number of PD patient studies, there is a limited number of studies in prolactinoma patients; this is discussed below [12–16].

One of the first studies (a cross-sectional study) conducted in 20 consecutive patients with a DA-treated prolactinoma, published in 2011, noted a 10% prevalence of DA-induced ICD [15]. However, the study was small and lacked a control group.

In the only case-control study, patients with prolactinomas with current or previous DA treatment and patients with non-functioning pituitary adenomas (NFPA) without DA treatment were compared [12]. The study included postal survey, review of electronic medical records, and telephonic interviews [12]. The total prevalence of at least one ICD was significantly higher in patients with prolactinomas (24.6%) compared to the NFPA group (17.14%) or the general population of Sao Paulo, Brazil (8.4%) [17]. Pathologic hypersexuality was the main ICD among patients with prolactinoma (12.99%), significantly higher than in the control group (2.87%). No relationship was reported between ICD development and the type of DA and duration or dose of DA treatment (however, most patients were on low doses of cabergoline) [12].

In a small mixed cohort of patients with prolactinoma or acromegaly treated with DA, 7.5% of prolactinoma patients and 5% of those with acromegaly were diagnosed with an ICD; also in this study, no correlation was reported between ICD development and DA treatment dose or duration [18].

However, impulsivity assessed by using validated psychometric tests (Barratt Impulsiveness Scale) revealed higher scores in DA-treated hyperprolactinemic patients compared to untreated patients with hyperprolactinemia or normoprolactinemic subjects [13]. A direct correlation between high impulsivity score and weekly cabergoline dose was reported [13]. Similarly, cumulative DA dose was associated with significantly higher scores for a number of psychiatric abnormalities [14]. In the aforementioned study, Celik et al. prospectively evaluated 88 patients (25 prolactinoma, 31 NFA, and 32 healthy controls subjects followed for 1 year) for the presence of ICDs and other psychiatric disorders. An ICD (hypersexuality only) was diagnosed in two cases (8%) of DA-treated prolactinoma. Symptoms of ICD improved or disappeared after DA discontinuation [14].

The largest study to date is a recent multicenter study that aimed to assess the prevalence of ICD in patients with prolactinoma receiving DA therapy. This study revealed an overall ICD prevalence of 17% [16].

These results described above may appear surprising, given the clinical perception is that these side effects are rare in patients who have a prolactinoma. However, it must be considered that due to ICD being perceived as a rather sensitive topic, symptoms that are suggestive of one are likely underreported by patients.

Male sex appears to be a risk factor for ICD development in both patients with PD and those with a prolactinoma [12, 16, 19] especially for hypersexuality disorder [10, 16]. Males with a prolactinoma and past or present DA treatment had a significantly increased frequency of ICD (27.7%) when compared to male patients with NFPA (3.7%) [12]. The risk of ICD development is 2.4 times higher in males compared to that in females [16].

Current smoking and alcohol use [16], younger age [10, 11], and single status [6] have also been described as risk factors for ICD development. The same is true for positive personal or family psychiatric history as well as specific personality traits [10], but, in order to minimize bias, many studies have excluded such patients. However, it is reasonable to conclude that DAs should be prescribed with caution in subjects with previous or current psychiatric diagnosis and possibly also in those with positive psychiatric family history [10].

What Is the Mechanism of Dopamine Agonist-Related Impulse Control Disorders?

The etiology of this ICD is thought to be related to dopamine excess in specific brain regions. Initially described in PD patients, ICD were thought to develop as a result of an interaction between DA and an inherent neurological vulnerability, possibly associated with PD [20]. This hypothesis is strengthened by the observation

that ICD occur even in PD patients not being treated with DA, with higher incidences compared to the general population [11]. However, the significantly higher incidence of ICD in DA-treated cases [6] as well as the rapid disappearance of symptoms in many cases after drug discontinuation or dose reduction [21] suggests a significant contribution of DA in the development of ICD. Additionally, the fact that similar reactions also occur in prolactinoma patients suggests that PD-specific brain abnormalities are not a prerequisite for these reactions to occur. The disappearance of ICD symptoms after stopping DA administration in many cases [22] strongly suggests a causal relationship.

Selective D3 receptor stimulation in the mesolimbic system has been suggested as the major mechanism of DA-associated ICD [23]. Dopamine receptors are widely expressed in the brain, and DA do not generally exhibit receptor-type specificity. The endocrine effects are exerted by binding to D2 receptors in the tuberoinfundibular system [24]. The degree of specificity of individual drugs for the D3 receptor appears to be correlated with the risk of ICD development [25]. In addition, certain gene polymorphisms involved in the functioning of the dopamine pathways are associated with decreased impulse control in adults. The genetic basis of ICD development needs further study, and in future genotyping might prove useful in predicting the development of DA-induced ICD [26].

For certain types of ICD, alternative explanations have been discussed. For example, hypersexuality in DA-treated prolactinoma patients has been viewed as the possible result of correction of hypogonadism under treatment [27]. However, this is unlikely as hypersexuality also appears in male patients with eugonadism at diagnosis and in females [16]; in addition, increased levels of testosterone are not achieved under DA therapy [16], in sufficient levels to contribute to hypersexuality.

How Should Dopamine Agonist-Related Impulse Control Disorders Be Managed?

The most effective treatment of a drug-related adverse effect is usually discontinuation of the offending drug. Therefore, despite the fact that psychiatric medications and psychotherapy are frequently used to treat ICD in the general population, whenever DA are the presumed cause of ICD, drug discontinuation should be taken into consideration. This is generally associated with a very rapid disappearance of the behavior. However, this is not always possible, for example, in PD patients discontinuing DA can be associated with worsening motor symptoms or DA withdrawal syndrome [21]. In addition, a long-lasting effect cannot be fully disregarded in PD patients, as patients who used DAs in the previous 12 months still have more than twice the risk of an ICD compared to “never”-users [11].

A strong dose-effect relationship for both increasing duration and dose of DA treatment has been described in PD [11]. In prolactinoma patients some authors [12, 16] reported no correlation between DA dose and ICD development. In contrast, others reported that cabergoline dose was associated with increased impulsivity

[13]. Individual case reports of ICDs, as reviewed by Ioachimescu et al. [22], suggest that in DA-treated prolactinoma cases, ICD symptoms disappear after interrupting DA administration or after lowering the dose (sometimes adding psychotherapy or psychiatric medications). In conclusion, lowering the DA dose or even stopping DA administration in patients with a prolactinoma should be considered whenever it is considered safe.

Changing the DA drug type could be associated with reoccurrence of an ICD; current data do not allow for differentiation of the risk associated with each particular DA drug [22]. However, in some published cases, including this one, ICD symptoms only occurred with one DA drug and not with another [22]; this approach also should be considered.

Treatment with aripiprazole (an antipsychotic approved for major psychoses that has partial DA activity acting on the D2 receptors) has been used in selected prolactinoma patients with psychiatric disease. Subsequently this has led to biochemical control of hyperprolactinemia and improvement in psychiatric symptoms [28, 29] and has therefore been viewed as a potential alternative in DA-intolerant patients. However, aripiprazole itself has been associated with PG [19], and efficacy and safety studies in the setting of DA-induced ICD are lacking.

Therefore, increased awareness of the potential of DA to induce ICD is needed among endocrinologists. Treatment with the lowest dose of DA to control tumor hypersecretion and volume in patients with prolactinoma is recommended. Switching to another DA approved for hyperprolactinemia can be attempted. However, this is not always successful, as ICD have been reported with both cabergoline and bromocriptine [15]. Irrespective of the particular approach, the patient should be carefully monitored by an endocrinologist and a psychiatrist.

Conclusions

In conclusion, DA-induced ICDs are more frequent than previously thought in patients with prolactinoma who are receiving DA therapy. Before offering a DA, a thorough patient and family history of psychiatric disease should be elicited. A discussion with the patient about this possible adverse effect of these otherwise very well-tolerated drugs should be conducted. Close monitoring is required, and patients should be encouraged to report any new psychiatric side effects at each care visit. If an ICD is diagnosed, drug discontinuation, dose lowering, switching to a different DA, and/or adding psychological or psychiatric care should be discussed with the patient. Patients should be under continuous multidisciplinary care (endocrinologist and psychiatrist).

Lessons Learned

- Dopamine agonist use can be associated with the development of psychiatric adverse effects collectively referred to as ICD.
- Dopamine agonist-related ICD in patients with endocrine disorders are not so rare as previously thought; in clinical practice the incidence might be artificially lowered by patient reluctance to report symptoms suggestive of an ICD.

- Depending on the behavioral manifestation and severity of ICD, devastating personal and/or social consequences for patients and their families can ensue.
- Assessing individual risk (e.g., prior or current history of psychiatric disease) and informing the patient about the possible occurrence of an ICD should be undertaken at the initiation of DA treatment.
- The lowest effective DA dose should always be used.
- At each follow-up visit, patients should be directly questioned about changes in mood and behavior.
- If behavioral changes are reported, psychiatric assessment is recommended.
- Drug discontinuation should be considered; if this is not possible, further dose lowering or a change in DA drug should be attempted.
- Psychotherapy and/or psychiatric drugs can be added (at the indication of the psychiatrist), if previous measures are ineffective or cannot be administered.

Questions

1. A 36-year-old male with erectile dysfunction is diagnosed with a large macroprolactinoma (4.5 cm, largest diameter) with a PRL level of 9420 ng/mL and hypogonadotropic hypogonadism (low testosterone, FSH, and LH levels). Treatment with cabergoline (2 mg weekly) is initiated. After 6 months the patient reports hypersexuality symptoms. Prolactin and testosterone levels have normalized.

   What is true in this situation?

   (a) Hypersexuality is associated with restoration of eugonadism.
   (b) Hypersexuality is a beneficial effect of controlling tumor hypersecretion.
   (c) Drug discontinuation is mandatory.
   (d) Dose reduction should be attempted.

2. A 25-year-old male with a history of pathological gambling is diagnosed with a 2.2 cm macroprolactinoma.

   The following is true:

   (a) Dopamine agonist treatment is contraindicated.
   (b) Dopamine agonist treatment can be initiated with caution.
   (c) The highest tolerated dose of DA should be used.
   (d) The risk of DA-related ICD is lower than in a patient with no previous history of ICD.

3. A 35-year-old female under treatment with cabergoline 1 mg weekly for a prolactinoma reports at a follow-up visit that she experienced episodes of compulsive shopping and her financial and marital status declined as a consequence.

   You should:

   (a) Recommend psychiatric assessment.
   (b) Immediately stop cabergoline administration.
   (c) Not tell the patient this can be a drug-related problem.
   (d) Recommend surgery for prolactinoma.

Answers

1. (d) Restoration of eugonadism is clearly a beneficial effect of prolactin normalization, but hypersexuality can rarely be explained by this mechanism. A clear evaluation of the reported symptoms should be undertaken; if pathological hypersexuality is suggested, then obviously this is not an expected or wished effect, and cabergoline dose reduction should be attempted. Given the tumor size and magnitude of tumor hypersecretion, it would be dangerous to discontinue the drug completely.
2. (b) Male sex and previous history of ICD are risk factors for the development of DA-related ICD. Dopamine agonist treatment is not contraindicated but should be initiated with caution, after providing detailed information to the patient and under close supervision.
3. (a) If the patient being treated with DA reports symptoms compatible with DA-related ICD, psychiatric assessment should be performed. Endocrine reevaluation should also be undertaken to assess the possibility of dose lowering, changing DA drug, or even interruption of administration but only after carefully weighing the risks and potential benefits and after fully informing the patient about the process.

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Part II
Thyroid Overactivity

Chapter 5
Introduction to Thyroid Overactivity

Terry F. Davies

Introduction

Hyperthyroidism is a common clinical disorder with the vast majority of cases consisting of either toxic multinodular goiter or Graves' disease (Table 5.1). The introduction of the thyroid sonogram into many endocrinologist's examination rooms has made the distinction between these two common conditions almost immediate on seeing the patient.

The terms hyperthyroidism and thyrotoxicosis are now used interchangeably although in the past the latter term referred to the clinical presentation. But since the symptoms and signs of thyroid dysfunction are generally non-specific, unless the thyroid is enlarged or the eyes show clinical changes of orbitopathy, then we often have to rely on thyroid function tests to detect thyroid disease. Although serum T4 and T3 are poor tests for many patients with thyroid disease, because of their wide normal ranges, the introduction of the sensitive TSH immunoassays allowed hyperthyroidism to be defined as the presence of a suppressed TSH with or without detectable increases in serum T4 or T3 and with or without clinical signs and symptoms. When there is no detectable increase in T4 and T3, then the term "subclinical" is often used (first coined by David Evered [1]) although I now prefer to use the term "mild" thyroid dysfunction. We then enter the discussion of how suppressed does the TSH have to be to call it hyperthyroidism and when is such suppression pathological rather than a physiologic adjustment? A suppressed TSH is below the accepted normal range in the local population, usually around 0.3 uU/mL. In significant disease the TSH is generally more suppressed and often unmeasurable. In my practice a TSH below 0.2 generally requires treatment depending on the clinical situation. For example, the normal TSH rises with age [2], and a TSH of 0.5 in a

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Table 5.1 Causes of hyperthyroidism

Cause	TSHR autoantibodies	RAIU Scan pattern	Thyroid ultrasound Color flow Doppler	Thyroglobulin
Graves' disease	Positive	Normal or high Diffuse	Hypoechoic High or normal flow	High
Toxic multinodular goitre	Negative	Normal or high Patchy	Multiple nodules	High
Destructive thyrotoxicosis	Negative	Nil	Hypoechoic Low flow	High
Toxic adenoma	Negative	Normal or high Unifocal	Single nodule	High
Factitious thyrotoxicosis	Negative	Nil	Normal	Undetectable
Struma ovarii	Negative	Nil	Normal	High

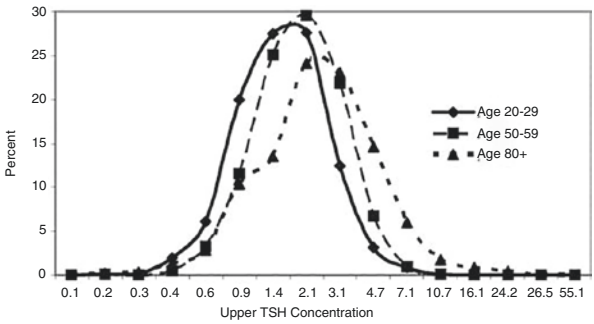

Fig. 5.1 The distribution of TSH in the NHANES III population. (From Ref. [2])

95 year old patient may be highly abnormal (Fig. 5.1). In the presence of atrial fibrillation, that patient may benefit from methimazole.

The epidemiology of Graves' disease (GD) has been well studied and affects ~2% of women and 0.2% of men globally (with a female to male ratio of ~10:1) [3], but as in all diseases the incidence of GD varies depending on the areas surveyed and methods applied. In contrast multinodular goiters are mostly non-toxic, but with age the finding of a mild toxic state is common. The degree of hyperthyroidism is generally much milder than with Graves' disease. In previous versions of this collection, we have dealt with a variety of both common and unusual causes of thyroid overactivity, but it is important to remember that as a practicing consultant endocrinologist, it is the unusual cases that more often arrive at your door. The most important aspect of these cases is the message that a diagnosis must be made. Hyperthyroidism is not a diagnosis. The cause must be determined because this may not only determine the most appropriate treatment but is also a reminder that medicine is a science and science is the art of measurement. We, therefore, must document the evidence for the diagnosis so that subsequent physicians will have no

doubt about the history of the patient. In multinodular goiter this may include a thyroid sonogram, a TSH, and negative thyroid antibodies, and a thyroid scan and uptake may be needed if a suppressed TSH is found. In Graves' disease this documentation of the diagnosis would include a measure of TSH receptor antibodies and a thyroid ultrasound to exclude nodules. In subacute thyroiditis an absent radioactive iodine uptake will clinch the diagnosis.

In this third edition of the Case-Based Guide, we have included three new cases of thyroid overactivity including the controversial topic of subclinical hyperthyroidism where the TSH is suppressed, but thyroid hormone levels remain very normal, an unusual case of Graves' orbitopathy with an IgG4 autoantibody and a patient with gestational hyperthyroidism which can often be misdiagnosed.

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Chapter 6
Immunoglobulin G4 and Graves' Orbitopathy

Katharina A. Ponto and George J. Kahaly

Overview Graves' orbitopathy (GO), also known as thyroid-associated orbitopathy or thyroid eye disease, is the most common extra thyroidal manifestation of Graves' disease [1–3]. At the onset of GO, most patients are hyperthyroid, while cases of euthyroid and hypothyroid are rare [4]. The clinical spectrum of GO reaches from complete absence of symptoms to signs-to-sight-threatening conditions. Dysthyroid optic neuropathy (DON) is a major sight-threatening complication affecting 4–8% of patients with GO [5]. It is defined as neuropathy caused by compression or stretch of the optic nerve associated with edema and volume increase and inflammation of orbital tissue due to deposition of excess glycosaminoglycans. In most patients, specific autoantibodies that bind to the thyrotropin receptor are present in the serum of these subjects (TSH-R-Ab). In particular, thyroid-stimulating immunoglobulins (TSI), assessed with a cell-based bioassay, bind to the thyrotropin receptor (TSH-R) and transmit signals for cyclic adenosine monophosphate (cAMP)-dependent activation of luciferase gene expression. The cAMP/cAMP response element-binding protein/cAMP-regulatory element complex induces luciferase that is quantified after cell lysis. TSI show more significant association with clinical features of GO than binding TSH-R-Ab and are regarded as functional biomarkers for GO [6, 7]. Furthermore, serum TSI levels identify patients with DON of recent onset requiring urgent therapy [8].

On the other hand, immunoglobulin G4-related orbital disease (IgG4-ROD) is characterized by lymphocytoplasmatic infiltration and tissue fibrosis within the orbit. Orbital manifestations of IgG4-ROD may include unilateral or bilateral

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proptosis, cicatricle extraocular muscle myopathy, and orbital inflammation and pain which may mimic GO. No pathognomonic clinical findings for GO or IgG4-ROD have been reported, but some key features can help distinguish the conditions [9]. GO is likely if thyroid-specific autoantibodies or typical clinical (lid retraction/lid lag) and radiological signs (enlarged extraocular muscles with typical tendon-sparing morphology) are present. Furthermore, a history of intrinsic asthma and progressive orbital disease in patients with previous diagnosis of GO, disproportionately large lateral rectus muscles, and enlarged infraorbital nerves are suggestive of IgG4-ROD. Increased serum IgG4 level and biopsy showing >10 IgG4+ plasma cells/high-power field and IgG4:IgG ratio > 40% will support the diagnosis of IgG4-ROD.

Here we describe the challenging course of a patient with a rare combination of autoimmune thyroid-related orbital disease and the presence of high serum levels of IgG4.

Objectives

1. To review the presentation of severe Graves' orbitopathy
2. To try and distinguish GO from IgG4-ROD
3. Examine the role of TSH receptor autoantibodies
4. Learn how to pursue the appropriate treatment for each individual patient

Case Report

A 55-year-old male patient was referred to the multidisciplinary ORPHAN disease orbital center, in Mainz, Germany. This academic referral center offers a joint thyroid-eye clinic at the Johannes Gutenberg University Medical Center. The patient had Graves' disease and had previously received radioactive iodine therapy, which led to the deterioration and exacerbation of eye signs and symptoms. He was a heavy smoker. His GO was severely active and inflammatory (Clinical Activity Score of the European Group on Graves' Orbitopathy, EUGOGO, CAS 7/7; (Fig. 6.1). He had elevated serum levels of binding TSH-R-Ab (8.7 IU/l; cut-off or reference <1.8 IU/l) and TSI (563 SRR%; cut-off <140 SRR %), respectively. Thyroid-related hormone levels were increased, and the patient was biochemically hyperthyroid. Serum levels of IgG4 were 2.26 g/l at initial presentation (reference <1.3 g/l). Orbital imaging showed enlargement of all extraocular muscles and of the lacrimal gland. Antithyroid drugs and intravenous glucocorticoid pulses were administered according to the joint guidelines of the European Thyroid Association and EUGOGO [10–13] with 750 mg methylprednisolone IV once weekly for 6 weeks followed by 500 mg once weekly for further 6 weeks. Unfortunately, 2 weeks after starting therapy, his clinical signs and symptoms of GO deteriorated (Fig. 6.2). His visual acuity had decreased from 0.00 log MAR to 1.60 log MAR on the right eye and from 0.00 log MAR to 0.40 log MAR on the left eye. A relative afferent pupillary deficit was present on the right side, as well as a significant visual field defect. Magnetic resonance imaging showed enlarged extraocular muscles and

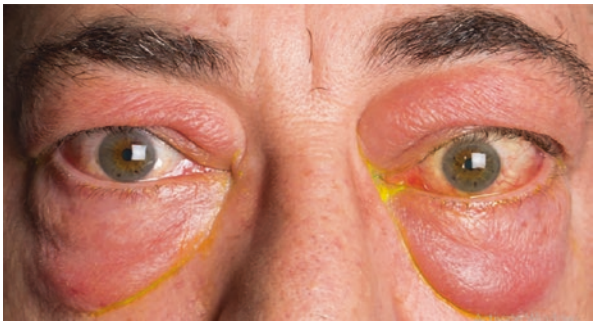

Fig. 6.1 Initial presentation of a 55-year-old patient with Graves' disease and Graves' orbitopathy (GO). At this visit the patient was biochemically hyperthyroid, GO was clinically active, but no signs of dysthyroid optic neuropathy (DON) were present. We measured elevated values of total or binding TSH-R-Ab (8.7 IU/l; reference <1.8 IU/l) and TSI (563 SRR %; cut-off <140 SRR %), respectively. Serum levels of IgG4 were 2.26 g/l at initial presentation (reference <1.3 g/l)

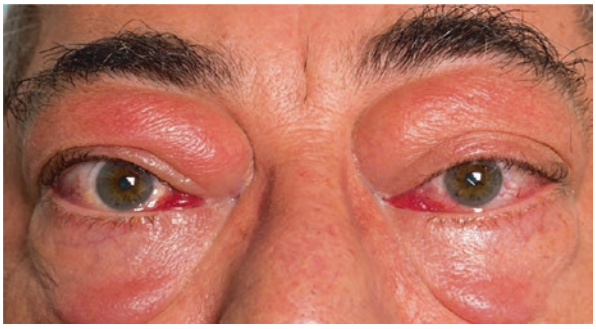

Fig. 6.2 Deterioration of Graves' orbitopathy (GO) during steroid treatment. The patient did not respond to intravenous glucocorticoids and developed signs of dysthyroid optic neuropathy (DON)

a *crowded* orbital apex. According to the EUGOGO recommendations [6, 7], the patient was admitted as inpatient where he received 750 mg methylprednisolone intravenously every second day. Because of a further deterioration in visual acuity, we then performed bony decompression surgery of the lateral orbital wall combined with orbital fat resection from both eyes via a trans-conjunctival approach. Because of elevated serum levels of IgG4, biopsies of the lacrimal gland and of the retrobulbar adipose tissue were also performed. A local infiltration of IgG4-positive plasma cells into the orbit could not be detected in the intraoperatively removed adipose tissue. A muscle biopsy was not performed. After surgery, visual acuity quickly improved to 0.00 log MAR in both eyes, and both the relative afferent pupillary deficit and the visual field defects disappeared.

Because of the aggressiveness of the disease before surgery, we decided to administer post-op weight-adapted oral steroids. Parallel to the improvement in the clinical findings, serum levels of TSH-R-Ab, TSI, and IgG4 decreased from 13.2 IU/l to 0.3 IU/l, from 600 SRR% to 402 SRR%, and from 2.26 g/dl to 0.9 g/dl,

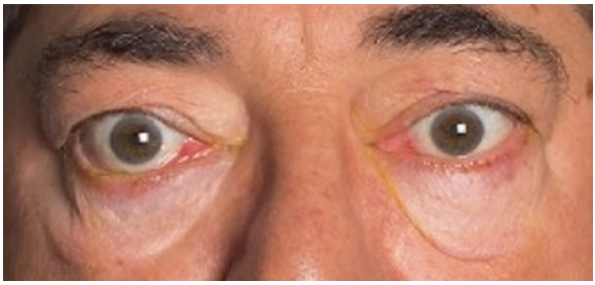

Fig. 6.3 Inactivation of GO after transconjunctival bony decompression of the lateral orbital wall and orbital fat resection. All signs for dysthyroid optic neuropathy had disappeared. At this follow-up visit, the serum levels of binding TSH-R-Ab were 5.5 IU/l, of TSI 783 SRR%, and of IgG4 1.71 g/l, and the clinical findings had further improved (visual acuity 0.00 logMAR on both eyes)

respectively. At a follow-up visit (Fig. 6.3), the levels of binding TSH-R-Ab, TSI, and IgG4 were 5.5 IU/l, 783 SRR%, and 1.71 g/l, respectively, and the clinical findings had further improved (visual acuity 0.00 log MAR on both eyes).

Review of How the Diagnosis Was Made

This novel case report describes the sequential clinical and serological course of severe and active GO with high serum levels of IgG4. Furthermore, this patient developed sight-threatening disease, which required both high doses of intravenous steroid pulses and subsequent urgent bony decompression surgery. Hence, it is justified to speculate that the combination of orbital disease and elevated serum IgG4 may have led to this unfortunate exacerbation of orbital inflammation, severe swelling of the orbital tissue, and finally compressive signs of the optic nerve. In other words, high serum IgG4 and suspected IgG4-related orbital disease might be regarded as a sign or additional parameter of severe GO. Furthermore, the patient had extremely high serum levels of TSI, which were both associated with the clinical phenotype of GO and the response to specific treatment. GO and IgG4-ROD are complicated inflammatory processes affecting the orbit, and that may occur together in the same patient. It has been shown previously that serum IgG4 levels may be increased in a few patients with Graves' disease and that there is a possible relationship between IgG4 and GO [14]. In line with this, Takeshima et al. found elevated serum IgG4 levels in 5 of 109 patients with Graves' disease [15].

Based on the obtained data and potential complications of this combined disease, we recommend the measurement of serum levels of IgG4 and orbital biopsy in patients who do not follow the usual clinical course of GO or have clinical characteristics of IgG4-ROD. Warranted prospective studies will answer the pending question whether the coexistence of GO and high serum levels of IgG4 always suggests a more severe course of the autoimmune thyroid-related orbital disease.

Lessons Learned

In the normal course of severe GO, it is reasonable to expect an early response to IV corticosteroids [3]. When the patient fails to respond and the clinical situation remains threatening, then there should be no hesitation in proceeding to decompression surgery. In experienced hands this approach can be highly successful as in the case described. Can a failure to respond to such therapy be predicted? It would be fair to say that even patients with high levels of TSH receptor antibodies may respond, but as clinicians we learn to recognize patients who we think will do poorly, but some type of immunosuppression should be attempted before surgery unless sight is imminently threatened. New drugs now available, such as teprotumumab, may replace corticosteroids in the treatment of many GO patients, but in the most severe patients, such as this one, an early response would be needed, and it is unclear at this time whether such a drug should replace emergency IV corticosteroids.

Multiple-Choice Questions (There May Be More than One Answer)

1. In hyperthyroid patients with signs of GO, the recommended approach to control their thyroid function is:

   (a) Iodine blockade of the thyroid gland
   (b) Methimazole blockade of thyroid synthesis
   (c) Radioiodine destruction of the thyroid gland
   (d) Total thyroidectomy

2. Patients with deteriorating and inflamed eye signs of Graves' disease require:

   (a) Orbital decompression surgery
   (b) IV corticosteroids
   (c) Selenium supplementation
   (d) Full ophthalmological assessment

3. Stimulating TSH receptor antibodies in Graves' disease:

   (a) Correlate poorly with severity of GO
   (b) Increase after a total thyroidectomy
   (c) Indicate the need for continued antithyroid drugs
   (d) Can distinguish the GO disorder from IgG4-retroorbital disease

4. What is not true about pain behind the eyes in a patient with GO?

   (a) The need for ibuprofen analgesia
   (b) Is secondary to retroorbital tissue swelling
   (c) Is yet another sign of the patients' state of stress
   (d) Should be taken as a warning sign of significant disease

Answers

1. (b) and (d)
2. (b) and (d)
3. (c) and (d)
4. (c)

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Chapter 7
Subclinical Hyperthyroidism: Case Report and Review of the Literature

Karen Tsai and Angela M. Leung

Objectives

- Appropriately diagnose and evaluate the underlying potential causes of subclinical hyperthyroidism.
- Understand the risks of adverse outcomes related to cardiovascular risks, bone health, and possibly cognitive decline associated with subclinical hyperthyroidism.
- Determine the necessity and type of treatment that may be recommended in some individuals with subclinical hyperthyroidism.

Case Presentation

A 66-year-old female presents after an incidental finding of abnormal serum thyroid function tests obtained following a routine visit with her primary care doctor. Her medical history consists of hypertension, atrial fibrillation, systemic lupus erythematous, pre-diabetes, and osteoporosis. She has had prior cesarean section for identical twins in her early 20s. Her family history is notable for Hashimoto's thyroiditis in her mother. She currently lives with her husband and drinks socially during the weekends and denies any smoking history or illicit drug use. Her medications include metoprolol, rivaroxaban, plaquenil, mycophenolate mofetil, and an over-the-counter calcium and vitamin D combination pill. She has been post-menopausal since age 51. Upon further review of systems, she notes unintentional weight loss of

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5 pounds over the past 2 months, anxiety, insomnia, heat intolerance, hand tremors, and palpitations, all of which she initially attributed to aging. She denies any symptoms of loose stools, vision changes, proptosis, or eye swelling.

On physical exam, her vitals showed a temperature of 37 °C, heart rate of 80 beats per minute, blood pressure of 120/80 mmHg, respiratory rate of 18 breaths per minute, 100% oxygen saturation on room air, and body mass index of BMI 25.0 kg/m^2. Her exam was notable for mildly pressured speech, fine bilateral hand tremors of her outstretched hands, and a diffusely enlarged, nontender thyroid gland. Her biochemical workup revealed a thyroid-stimulating hormone (TSH) of 0.09 mIU/L (reference range, 0.3–4.7 mIU/L), free thyroxine (FT4) of 1.6 ng/dL (reference range, 0.8–1.7 ng/dL), and free tri-iodothyronine (FT3) of 400 (reference range, 222–383 pg/dL). These blood tests remained persistent on repeat assessment 3 months later. Previous thyroid function tests over the last 5 years were all within their mid-normal ranges. Serum thyroid peroxidase (TPO), thyroid-stimulating immunoglobulin (TSI), and TSH receptor antibody (TRAb) were all negative.

A thyroid radioactive iodine uptake and scan showed three dominant hot nodules in the superior, middle, and inferior poles of the right thyroid lobe with overall increased radioiodine uptake at 6 (28%, normal 6–18%) and 24 hours (54%, normal 15–30%). A thyroid ultrasound showed three discrete solid, isoechoic nodules in the right superior, middle, and inferior poles of the thyroid gland, all measuring slightly less than 1.0 cm each and with well-defined borders, no calcifications, no increased Doppler flow, and no extrathyroidal extension. A bone dual-energy X-ray absorptiometry (DXA) performed the previous year showed a T score of −2.6 in lumbar spine, −2.5 in left femoral neck, and −2.7 in left total hip, consistent with osteoporosis.

The patient was diagnosed with subclinical hyperthyroidism arising from a multinodular goiter and started on propranolol 10 mg three times a day as needed for hyperthyroid symptoms. Due to her underlying risk factors including older age (greater than 65 years), cardiac history with atrial fibrillation, osteoporosis, symptoms of hyperthyroidism, and serum TSH <0.1 mIU/L, a recommendation was made to treat the patient. Given her autonomous thyroid nodules, definitive therapy was desired. She successfully received radioactive iodine therapy with 21.6 mCi of ^{131}I. Over the next several months, her symptoms resolved, and her weight normalized to that of her baseline. Repeat serum thyroid function tests 3 months later showed normal TSH, FT4, and FT3 concentrations. A repeat bone DXA scan 2 years later showed an approximate 5% gain of bone mineral density at each site to the osteopenic range.

Discussion

Subclinical hyperthyroidism was first described in the 1970s upon the advent of the TSH immunoassay. Over the past couple of decades, increased understanding on this topic has allowed refined recommendations on how diagnosed patients should

best be monitored and treated. The condition is a biochemical diagnosis that is defined by a decreased serum TSH and normal serum T4 and T3 concentrations. In contrast, overt hyperthyroidism is defined by a decreased TSH in the setting of elevated serum T3 and/or T4 levels. Furthermore, a proposed grading system distinguishes mild from severe subclinical hyperthyroidism, according to the degree of TSH reduction (mild, TSH 0.1–0.4 mIU/L; severe, TSH <0.1 mIU/L) [1].

The clinical presentation of subclinical hyperthyroidism is variable and can range from the absence of symptoms to mild or even pronounced symptoms of hyperthyroidism such as arrhythmias, heat intolerance, insomnia, increased appetite, diarrhea, weight loss, hair loss, diaphoresis, abnormal menses, and hand tremors. The diagnosis of subclinical hyperthyroidism should be confirmed by repeating thyroid function tests in 3–6 months, as the entity can be transient due to thyroiditis, lab error, or other causes [2]. Due to the ubiquity of thyroid function tests which are now available in most major laboratories, and an increase in ordering of these tests by clinicians, it is important to understand the pathophysiology of the disease and current societal guidelines to help identify those who would require treatment and those who can be closely monitored.

From the TEARS Scottish population study, the annual incidence of subclinical ranges from 17.5% to 56.1% per 100,000 persons with increasing annual prevalence from 0.05% seen in 1994 to 0.63% in 2008 [1]. In this cohort, very few patients (0.5–0.7%) developed overt hyperthyroidism at 2, 5, and 7 years of follow-up, and an increasing number of cases reverted back to the euthyroid state over longitudinal monitoring (17.2% at 2 years of follow-up, compared to 35.6% at 7-year follow-up), especially in those with baseline TSH levels between 0.1 and 0.4 mIU/L and those of younger age [1]. Contributing factors to the diagnosis of subclinical hyperthyroidism include older age, female sex, and higher socioeconomic status [1]. Thyroid autoimmunity with either thyroid peroxidase (TPO) or TSH receptor antibodies (TRAb) does not appear to be a risk factor of conversion from subclinical hyperthyroidism to the euthyroid state [1].

Several studies have shown that particularly severe subclinical hyperthyroidism (i.e., TSH <0.1 mIU/L) is negatively associated with adverse effects on cardiovascular health, particularly arrhythmias such as atrial fibrillation, strokes, and bone health, including increased risk of fractures [2–4]. With correction of the subclinical hyperthyroidism, these negative adverse events and risks are reversible, thus stressing the importance of clinicians to identify those who would benefit from treatment [2–4]. In addition, some studies have also assessed the potential associations between subclinical hyperthyroidism, dementia, and cognitive decline, but the results are equivocal [5, 6].

When evaluating the underlying cause of subclinical hyperthyroidism, it is recommended to group causes based on endogenous versus exogenous etiologies, as well as transient versus persistent sources. Diagnostic workup may include the ascertainment of serum thyroid antibodies including thyroid-stimulating immunoglobulin (TSI), TSH receptor antibody (TRAb), thyroid peroxidase (TPO) titers, thyrotropin-binding inhibitory immunoglobulin (TBII), serum thyroglobulin, thyroid ultrasound with Doppler flow, and radioactive iodine uptake scan [2].

Endogenous causes include toxic thyroid nodule(s), toxic multinodular goiter (TMNG), and Graves' disease. Toxic nodule(s) and TMNG are the most common causes of persistent subclinical hyperthyroidism especially in older individuals, whereas Graves' disease is the second most common cause that is seen more commonly in younger individuals [2]. Exogenous causes include intentional use of a supraphysiologic thyroid hormone dose to manage postoperative hypothyroidism such as in patients with differentiated thyroid cancers, as well as iatrogenic overestimation of thyroid hormone replacement for hypothyroidism and the surreptitious use of thyroid hormone for weight loss. Transient forms of subclinical hyperthyroidism can be seen during the course of treatment of hyperthyroidism with radioiodine therapy or antithyroid medications and in various forms of thyroiditis such as subacute thyroiditis, postpartum thyroiditis, and thyroiditis due to lithium, amiodarone, or immune checkpoint inhibitor use. Furthermore, it is important to also rule out other clinical scenarios which can cause a low serum TSH value. These include pregnancy, acute or chronic iodine load from iodine-rich medications or radiologic contrast media, psychiatric disorders, non-thyroidal illness, hypothalamic or pituitary dysfunction, and spurious laboratory assays due to interfering antibodies, paraproteins, or medications such as biotin [2].

Once a diagnosis of subclinical hyperthyroidism has been confirmed and is found to be persistent, the goal is to identify the individual's risk factors to determine if treatment would be beneficial. If warranted, the goal of treatment is to normalize serum thyroid function, in order to achieve a euthyroid state and reduce cardiac, bone, and other complications. The American Thyroid Association (ATA) recommends treatment in patients age <65 years with subclinical hyperthyroidism if the serum TSH is <0.1 mIU/L, especially if the individual has hyperthyroid symptoms (Table 7.1) [2]. The guidelines also advocate treatment in those age ε 65 years if the serum TSH is <0.1 mIU/L; if there are cardiac risk factors or known heart disease

Table 7.1 American Thyroid Association recommendations for the management of subclinical hyperthyroidism (*Adapted from* Ref. [2])

		TSH 0.1–0.4 mU/L[a] (mild subclinical hyperthyroidism)	TSH < 0.1 (severe subclinical hyperthyroidism)
Age < 65 years old[b,c]	Asymptomatic	Monitor	Consider treating
	Asymptomatic with risk factors[d]	Consider treating	Consider treating
	Symptomatic	Consider treating	Treat
Age ε65 years old[b]	Asymptomatic	Consider treating	Treat
	Asymptomatic with risk factors[d]	Consider treating	Treat
	Symptomatic	Consider treating	Treat

[a]TSH of 0.4 mU/L is the lower limit of most reference ranges
[b]Ensure persistence of subclinical hyperthyroidism by repeating labs in 3–6 months
[c]In pregnant patients, treatment of subclinical hyperthyroidism is not recommended
[d]Risk factors: cardiac disease, osteoporosis, menopausal women not on estrogens or bisphosphonates

or osteoporosis; in postmenopausal women who are not taking estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms [2]. For those who have a TSH between 0.1 and 0.4 mU/L and have underlying risk factors (i.e., heart disease, osteoporosis, menopausal state not on hormonal or bisphosphonate therapy) or hyperthyroid symptoms, treatment may also be appropriate [2]. Monitoring without treatment is appropriate for those age < 65 years who have a TSH value between 0.1 and 0.4 mU/L and are asymptomatic (Table 7.1) [2].

Options for treatment of subclinical hyperthyroidism will be dependent on the underlying cause and follow the same principles as overt hyperthyroidism. These include thionamides such as methimazole or propylthiouracil, thyroid surgery, and/or radioactive iodine therapy. Beta-blockers such as propranolol, atenolol, or metoprolol may be additionally used to mitigate hyperthyroid symptoms if present.

Learning Points

- Accurate diagnosis of subclinical hyperthyroidism is important, due to the many mimickers of the biochemical pattern that defines this entity.
- Serum thyroid function tests should be repeated in 3–6 months after an initial abnormal set to confirm their persistence and thus a diagnosis of subclinical hyperthyroidism.
- The presentation of subclinical hyperthyroidism can vary from the lack of symptoms to the presence of mild or pronounced symptoms of hyperthyroidism.
- Subclinical hyperthyroidism is associated with increased risks of cardiovascular-related adverse outcomes, bone loss, and, in some studies, cognitive decline**.**
- Appropriate evaluation of an individual's risk factors is needed to correctly differentiate between patients who can be monitored with serial serum thyroid function tests and those who will require further diagnostic workup.
- Considerations for treatment include the etiology of the subclinical hyperthyroidism, anticipated long-term natural history of the condition, potential benefits of correcting the thyroid dysfunction, and the risks and benefits of each treatment option.

Multiple-Choice Questions

1. Which of the following is the correct biochemical definition of subclinical hyperthyroidism?

   (a) Normal free T4, low TSH
   (b) Elevated free T4, low TSH
   (c) Low FT4, low TSH
   (d) Low FT4, high TSH

2. Which of the following is/are the next best step(s) if a patient was found to have initial biochemical evidence of subclinical hyperthyroidism?

   (a) Order radioactive iodine-123 thyroid uptake scan.
   (b) Review patient's prescription medications and over-the-counter supplements, in order to consider whether there may be potential culprit medications that may be causing the serum thyroid function abnormalities.

(c) Repeat serum TSH, FT4, and FT3 concentrations in 3–6 months to confirm the persistence of subclinical hyperthyroidism.
(d) Order thyroid ultrasound.
(e) Order thyroid antibodies [i.e., thyroid peroxidase antibodies (TPO), thyroid-stimulating immunoglobulin (TSI), and TSH receptor antibody (TRAb)].
(f) Both (b) and (c).

3. Which of the following is *not* a cause of low serum TSH concentrations and should *not* be considered as a differential diagnosis when evaluating a patient for subclinical hyperthyroidism?

(a) Use of glucocorticoids
(b) Pituitary dysfunction
(c) Serum heterophile antibodies
(d) Aging
(e) Pregnancy
(f) Non-thyroidal illness
(g) Amiodarone-induced thyroiditis

4. Which of the following should be considered when deciding if a patient with subclinical hyperthyroidism should be treated?

(a) Age
(b) Sex
(c) Bone loss (i.e., osteopenia, osteoporosis)
(d) Cardiovascular risk factors (i.e., atrial fibrillation)
(e) Presence of hyperthyroid symptoms
(f) Postmenopausal patients who are not on estrogens or bisphosphonates
(g) All of the above except (b)
(h) All of the above

Answers

1. (a)
2. (f)
3. (d)
4. (g)

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Chapter 8
A Case of Gestational Thyrotoxicosis

Terry F. Davies

Objectives
TSH levels may be suppressed in pregnancy, and it is important to determine the cause so that appropriate action can be initiated. This case aims:

1. To draw attention to the need for measurement and careful assessment of low TSH values in pregnancy.
2. To advise not to introduce antithyroid drugs in pregnancy unless one is sure they are needed.

Case Presentation

History This was a 27-year-old female teacher from the Upper West Side of New York City who was referred by a careful high-risk obstetrician from a group called Maternal-Fetal Medicine Associates. The patient had been found to have a very low TSH of 0.012 uU/mL and an increased FT4 of 2.23 ng/dL at a reliable commercial laboratory (see Table 8.1 for normal ranges). She was at 11 weeks with her first pregnancy and was reported to have normal fetal development on ultrasound.

The patient had a family history of Hashimoto's thyroiditis in a maternal grandmother and an aunt. Her history also included the current use of daily Lovenox injections because of factor 5 Leiden deficiency. She had no history of biotin intake which is well known to interfere with the TSH assay in many laboratories. And she had no history of taking thyroid hormone replacement or abusing such treatment which would have explained her low TSH.

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Table 8.1 Thyroid function studies

	Ref. range	11/9/2020
T3, total	Normal ref range: 71–180 ng/dL	298 (H)
T4, free	Normal ref range: 0.82–1.77 ng/dL	2.24 (H)
Thyroglobulin antibody	Normal ref range: 0.0–0.9 IU/mL	<1.0
Thyroid peroxidase (TPO) AB	Normal ref range: 0–34 IU/mL	<9
TSH	Normal ref range: 0.450–4.500 uIU/mL	<0.005 (L)
TSH receptor antibody (TBII)	Normal units: U/L	<0.3

Table 8.2 Pregnancy testing

	Ref. range	11/9/2020 11:00
hCG total, quant.	Units: mIU/mL	254,056

Presentation The patient was not in distress. At her initial visit, she was complaining of recurrent nausea but not sufficient to suggest hyperemesis gravidarum, and there was no weight loss and no dehydration. She had a normal clinical examination apart from a slightly enlarged soft thyroid. Her BMI was 22.0. She had no tremor, no tachycardia, no eye signs, and a normal BP.

Investigations My thyroid ultrasound at the visit showed a normal homogeneous thyroid with no evidence of nodules or heterogeneity suggestive of thyroiditis. Her repeat thyroid function testing confirmed the reported suppressed TSH with no thyroid autoantibodies detectable including TSH receptor antibodies (Table 8.1).

It was now unlikely that the patient had Graves' disease which was the initial thought on referral to endocrinology. The absence of TSH receptor antibodies would be very unusual. On review of her hCG levels, it became clear that the high levels were compatible with gestational thyrotoxicosis (Table 8.2). This result was further confirmed on dilution of the sample and re-assayed for hCG and was significantly higher than found in many women with a normal singleton pregnancy (Table 8.3). However, it was not as high as may be seen in multiple pregnancies and hydatidiform moles.

Outcome The decision not to treat was made, and the patient was followed up to see how she progressed since time confirms many diagnoses. By 3 months, at week 25 of pregnancy, she then had a normal TSH of 0.7uU/mL and normal FT4 0.95 ng/dL, and her pregnancy was progressing normally.

Differential Diagnosis The possibility of an active thyroid nodule was excluded very early by an immediate thyroid ultrasound examination at presentation. Graves' disease was excluded by the lack of TSH receptor antibodies since cases of antibody negative Graves' disease are very unusual although much talked about. Alternative diagnoses that were considered included either the "Hashitoxicosis" phase of autoimmune thyroiditis, which was unlikely in the absence of thyroid antibodies, or the acute thyrotoxic phase of subacute (DeQuervain's) thyroiditis, also unlikely without any thyroid tenderness although painless thyroiditis occurs and could not be instantly ruled out.

Table 8.3 The normal range of hCG (mIU/mL) in pregnancy

Female	(Non-pregnant)	0–5
	(Postmenopausal)	0–8
Female	(Pregnant)	
	Weeks of gestation	
	3	6–71
	4	10–750
	5	217–7138
	6	158–31,795
	7	3697–163,563
	8	32,065–149,571
	9	63,803–151,410
	10	46,509–186,977
	12	**27,832–210,612**
	14	13,950–62,530
	15	12,039–70,971
	16	9040–56,451
	17	8175–55,868
	18	8099–58,176

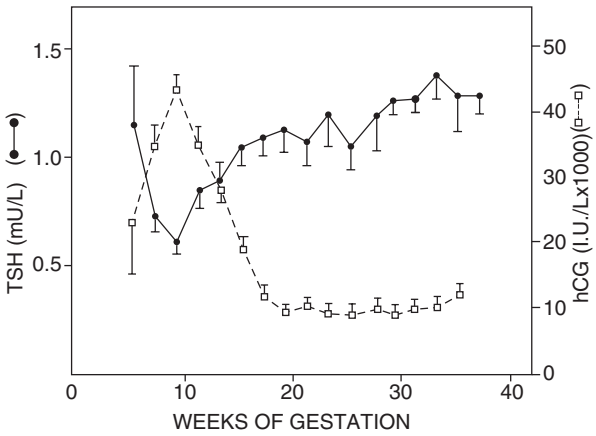

Fig. 8.1 The fall of TSH as hCG levels increase. (From Ref. [2])

Review of the Diagnosis

Hyperthyroidism in early pregnancy can quickly spin out of control and result in miscarriage [1]. It is, therefore, imperative that a clear diagnosis be made as soon as possible and severe cases of hyperthyroidism in pregnancy may require ICU admission. This was not the case with this patient who had a normal physical examination. The repeat measurement of her hCG level quickly suggested her diagnosis. The range for hCG in early pregnancy reaches a peak at 12 weeks, just when this patient presented, and correlates well with the suppression of TSH as emphasized by Glinoer [2] (Fig. 8.1). Serum levels of hCG in singleton pregnancies can vary

Table 8.4 Examples of hCG levels with low TSH concentrations

		TSH (mU/L)		hCG (U/L) (mean ± SEM)		
Trimester	*N*	≤0.20 N (%)	0.21–4.00 N (%)	in women with TSH ≤ 0.20	in women with TSH 0.21–4.00	*P*
I	338	62 (18%)	276 (82%)	52,400 ± 3900	34,900 ± 1200	<0.001
II	249	13 (5%)	236 (95%)	20,400 ± 5300	12,600 ± 1000	<0.001
III	102	2 (2%)	100 (98%)	ND	13,000 ± 1400	ND

From Glinoer [2]

considerably from 28,000 up to 210,000 mIU/mL in our laboratory and sometimes even higher (Tables 8.3 and 8.4). This patient's hCG was especially high and in keeping with the clinical suspicion for gestational thyrotoxicosis and supported by the lack of thyroid antibodies. If the patient was not pregnant, then this might well have been a case of silent subacute thyroiditis which would have been diagnosed by a radioactive iodine uptake of less than 1% although I would also have expected heterogenous changes on her thyroid ultrasound.

Lessons Learned

The commonest cause of a suppressed TSH in clinical practice is probably excessive intake of T4 medication directed by a physician. Outside this phenomenon, overt hyperthyroidism affects only 0.1–0.4% of pregnancies and is associated with poor maternal and fetal outcomes [3]. The problem for the clinician is that 10% or more of normal women show a low TSH in early pregnancy. This is usually secondary to the highly variable influence of hCG on the thyroid and is referred to as gestational thyrotoxicosis [1]. There are no data, yet, to suggest this phenomenon has adverse effects and such pregnancies progress normally as in the case discussed.

The thyrotropic action of hCG is explained by the structural homology between hCG and TSH molecules and between LH/CG and TSH receptors. Thus, hCG is able to bind to the TSH receptor of thyroid follicular cells [4] and exert its stimulatory effects by activating intracellular messengers, such as cAMP [5]. However, the thyroid-stimulating ability of hCG varies from person to person and appears to be secondary to the degree of glycosylation which not only lengthens its half-life but also enhances its "specificity cross-over" with the TSH receptor [6]. To date, two cases of a TSH receptor mutation have been reported that endow increased sensitivity to hCG, and these cases presented with hyperemesis gravidarum, the hallmark of which may be severe weight loss and dehydration except in such cases the hCG level may be normal for pregnancy [7].

Multiple-Choice Questions (There May Be More than One Correct Answer)

1. A suppressed TSH in a young female may be due to:

   (a) Biotin intake for "strong nails"
   (b) Excess "synthroid" tablets from her mother
   (c) Japanese food excess
   (d) Kosher salt use
   (e) A laboratory error

2. An enlarged thyroid in a pregnant woman indicates:

   (a) A normal thyroid expansion of pregnancy
   (b) Possible underlying Hashimoto's thyroiditis
   (c) The certain development of Graves' disease
   (d) A likely multiple pregnancy
   (e) Iodine deficiency in New York City

3. The TSH action of hCG is:

   (a) Secondary to the high TBG level in pregnancy
   (b) Related to the glycosylation pattern of T4
   (c) May vary intrinsically between patients
   (d) Indicative of a likely miscarriage
   (e) Can be assessed with a qualitative pregnancy test

4. Gestational thyrotoxicosis requires:

   (a) Immediate admission to the ICU for impending "storm"
   (b) Initiation of antithyroid drugs and possible corticosteroids
   (c) A clear diagnosis and reassurance to the parents
   (d) A sign that Graves' disease is likely to develop in the postpartum
   (e) An assessment of changes in serum hCG levels

5. Profuse and recurrent vomiting with weight loss in pregnancy and a suppressed TSH may be a sign of:

   (a) Hyperemesis gravidarum
   (b) Gestational thyrotoxicosis
   (c) An LH/CG mutation highly sensitive to hCG
   (d) Anorexia nervosa

Answers

1. (a), (b), (e)
2. (a), (b)
3. (b), (c)
4. (c), (e)
5. (a), (c)

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Part III
Thyroid Underactivity

Chapter 9
Introduction

Giuseppe Barbesino

The thyroid hormones are unique among the hormones in that their structure contains a micronutrient in short supply, iodine. The dependence on iodine, a scarce element in many regions of the world, exposes the thyroid gland to dietary iodine deficiency. In addition, the synthesis of thyroid hormone requires a number of complex enzymatic processes, including the concentration of iodine in the follicular cell; the organification of iodine into the side chain of tyrosine; the coupling of tyrosines to form T4; the incorporation of T4 in the primary structure of a large storage protein, thyroglobulin; and the secretion of stored thyroid hormone. This array of unique proteins such as thyroglobulin and thyroid peroxidase, and the TSH receptor, makes the thyroid particular susceptible to faulty immune tolerance, so that the thyroid is the most common target of organ-specific autoimmunity. As a consequence thyroid underactivity, or hypothyroidism, is one of the most common endocrine dysfunctions encountered in clinical practice. In addition, these complex processes expose the thyroid gland to surprisingly rare congenital defects affecting T4 production.

Causes of Thyroid Underactivity

In the past, severe iodine deficiency has represented a major cause of hypothyroidism worldwide, especially in the pediatric age. Nowadays severe iodine deficiency has become rare [1]. In moderately iodine-deficient regions, hypothyroidism is now more common than in iodine-sufficient regions. In both moderately

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iodine-deficient and iodine-sufficient regions, spontaneous hypothyroidism is almost always caused by thyroid autoimmunity, in the form of chronic lymphocytic, or Hashimoto's, thyroiditis (HT). In HT, autoimmune T and B cell lymphocytes reactive to thyroid antigens invade the gland and progressively exhaust it. This results in variable and variably progressive compromise of the gland's ability to synthesize thyroid hormone [2]. Iatrogenic thyroid underactivity is the second most common cause, resulting from total or partial thyroidectomy or from radioactive iodine treatment for a number of conditions, such as toxic multinodular goiter or Graves' disease. Interesting, but very rare cause of hypothyroidism includes inherited errors in the biosynthesis of thyroid hormone. Congenital hypothyroidism is mostly due to developmental or metabolic errors. Rarely, hypothyroidism may result from pituitary dysfunction, leading to insufficient TSH production.

Diagnosis

The diagnosis of hypothyroidism is based on the measurement of serum TSH. Since any minimal change in thyroid hormone results in logarithmic changes in TSH, and since there are no other significant physiologic determinants of the TSH level, a TSH measurement is considered the most sensitive test for hypothyroidism. A normal TSH level rules out hypothyroidism, with the rare exception of central hypothyroidism, in which the TSH may be normal or low. Central hypothyroidism is diagnosed by the finding of low thyroxine in a subject with low or normal TSH. The actual thyroid hormone level may be useful in assessing the severity of hypothyroidism. In subclinical hypothyroidism, the TSH is midly elevated, but thyroid hormones are in the normal range, while overt hypothyroidism is defined by abnormally low thyroid hormones. This distinction is somewhat artificial, as there is clearly a continuum of thyroid dysfunction, but it has been adopted in many published studies.

Clinical Manifestations

Symptoms of hypothyroidism depend on the severity of the dysfunction, but there is also individual variation in the response. Patients with subclinical hypothyroidism are typically asymptomatic, but several studies show a number of subtle cardiovascular, metabolic, and neurologic adverse changes, mostly in subjects younger than 65 and in those with TSH >10 mcIU/mL [3]. Whether subclinical hypothyroidism has significant untoward effects in the elderly remains unclear. With overt hypothyroidism more prominent symptoms are often observed, affecting virtually all organ systems (Table 9.1).

Table 9.1 A concise list of symptoms of hypothyroidism

Organ system	Manifestations
Cardiovascular	Bradycardia, heart failure, pericardial effusion
CNS	Depression, fatigue, cognitive dysfunction, myxedema coma
Hematopoietic	Macrocytic anemia, target cells
Metabolic	Hyperlipidemia, weight gain
Musculoskeletal	Arthralgias, myositis
Gastrointestinal	Constipation
Renal	Hyponatremia
Reproductive	Polymenorrhea, galactorrhea, erectile dysfunction, infertility
Skin and appendages	Alopecia, coarse hair, dry and discolored skin, myxedema

Treatment of Hypothyroidism

In the absence of symptoms, treatment of subclinical hypothyroidism is recommended only in the younger group of patients after confirmation of the diagnosis with a repeat test a few weeks after the first [3]. There is general agreement that overt hypothyroidism should always be treated [4]. While T3 is the only active thyroid hormone in all target tissues, the hormonal defect in hypothyroidism is lack of T4 production from the thyroid gland. Effective treatment is therefore achieved with the oral administration of T4 (levothyroxine), to be later deiodinated to T3 in peripheral tissues. This is indeed the most effective form of hormone replacement in medicine. Owing to its long half-life, levothyroxine achieves stable T4 levels and restores euthyroidism. Restoration of euthyroidism is verified by the achievement of normal serum TSH levels. There are remaining areas of uncertainty. In spite of biochemical euthyroidism, many patients continue to experience non-specific symptoms such as fatigue, weight gain, and subjective cognitive abnormalities. Thyroid hormone replacement with a mixture of T4 and T3 has been tried and generally proven ineffective in this regard, so that the practice is typically not recommended in most cases [5]. The bioavailability of oral levothyroxine is imperfect at best and a relatively common cause of inconsistent euthyroidism during treatment. Interaction with other drugs in the gastrointestinal tract is the most common cause [6]. Novel soft gel and liquid preparations of levothyroxine have recently been developed, but their role remains to be defined by well-designed studies [7].

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Chapter 10
Managing Hypothyroidism: Increasing Levothyroxine Requirements

Josephine H. Li

Objectives
To provide an overview of various causes of increasing levothyroxine requirements in patients with established hypothyroidism.

Case

A 53-year-old man reported that his dose of levothyroxine had been increasing over time. He was diagnosed with primary hypothyroidism approximately 7 years ago by his primary care physician on routine blood work. He was prescribed levothyroxine 88 mcg daily at the time of diagnosis, but the dose necessary to maintain euthyroidism had slowly increased to 200 mcg over the last year. He disclosed that he had always taken levothyroxine with his other medications in the morning and waited 30 minutes to eat. His past medical history was significant for metastatic renal cell carcinoma status post left nephrectomy, and he was being treated with an immune checkpoint inhibitor. Additionally, he had hypertension and a pulmonary embolism. His remaining medications included aspirin, apixaban, amlodipine, lisinopril, and oxycodone as needed for pain.

Recently, he noticed increased abdominal girth, whole body edema, and weight gain of 20 pounds. These features were notable on presentation. His weight was 220 pounds (110 kg). His thyroid function tests showed a markedly elevated TSH of 125 uIU/mL (reference range, 0.4–5.0) and low FT4 of 0.8 ng/mL (reference range, 0.9–1.8). The patient had hypoalbuminemia to 2.2 g/dL (reference range, 3.3–5.0), and significant proteinuria was detected on a 24-hour urine (25.2 g/24 h; reference

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Table 10.1 Thyroid function and urinary protein levels correlated with levothyroxine (LT4) dose

Weeks following initial presentation	TSH (uIU/mL), 0.4–5.0	FT4 (ng/mL), 0.9–1.8	24-hour protein (g/24 h), 0–0.165	LT4 dose	Intervention
0 weeks	125	0.8	25,207	200 mcg PO	Received several doses of 100 mcg IV in addition to PO
2 weeks	4.48	1.2		200 mcg PO	Increased to 250 mcg PO
10 weeks	41.9			250 mcg PO	Increased to 300 mcg PO
14 weeks	0.73	0.9		300 mcg PO	
17 weeks			20,764	300 mcg PO	
19 weeks	0.93	1.0		300 mcg PO	

range, <0.16). A diagnostic work-up by nephrology led to the diagnosis of nephrotic syndrome secondary to the patient's immunotherapy regimen.

The patient initially received several doses of IV levothyroxine in addition to his oral regimen with subsequent improvement in his thyroid function. He was also recommended to take levothyroxine on an empty stomach, separate from his other medications, and to wait 60 minutes before eating. Table 10.1 details his thyroid function, degree of proteinuria, and levothyroxine dose over time. Ultimately, he achieved normal thyroid function at a dose of 300 mg levothyroxine daily.

Review of How the Diagnosis Was Made

This patient presented with increasing levothyroxine requirements over time to maintain euthyroidism. He demonstrated clinical symptoms of hypothyroidism, confirmed by biochemical findings. Whereas his weight gain and generalized edema could have been attributed to hypothyroidism, the severity of his symptoms, particularly the presence of anasarca, raised the question of a co-existing illness contributing to hypothyroidism. Detection of profound proteinuria and hypoalbuminemia resulted in a diagnosis of nephrotic syndrome as the cause of increased levothyroxine therapy, the pathophysiology of which will be described in the subsequent section. Reduced intestinal absorption of levothyroxine due to gut edema and concurrent medication administration may have also been factors adding to his clinical presentation.

Lessons Learned

The inability to normalize serum TSH with oral levothyroxine is a frequently encountered clinical problem. Most individuals require a dose of 1.6–1.8 mcg/kg of oral levothyroxine daily, but some remain hypothyroid despite escalating doses. The most

common reason for ineffectiveness of thyroid hormone replacement is nonadherence to therapy ("pseudomalabsorption"). The first step in the clinical assessment is to ensure consistent daily levothyroxine ingestion, separate from food intake. Occasionally, pharmacy fill records may need to be obtained to ascertain compliance.

After exclusion of adherence issues, drug interactions should be assessed, as concomitant medications can impair absorption and affect metabolism of thyroid hormone. Multivitamin and dietary supplements may contain calcium or iron salts, which sequester levothyroxine by forming complexes that are poorly absorbed [1]. Since normal gastric acid secretion is necessary for full thyroid hormone absorption, dose adjustments are often needed when proton pump inhibitors and antacids are started [2]. Anti-epileptic drugs, such as carbamazepine, phenytoin, and phenobarbital, can increase the hepatic metabolism of thyroid hormone [3]. Drugs that decrease thyroid hormone synthesis (amiodarone, iodine, lithium) may result in a higher dose requirement in individuals who already have limited reserve. Medications that increase serum thyroxine-binding globulin (TBG), such as estrogen or tamoxifen, may result in a rise in TSH and signal the need for an increased dose [4]. A more extensive list and discussion can be found in the American Thyroid Association Guidelines for Treatment of Hypothyroidism [5].

Other conditions can precipitate worsening of known hypothyroidism in a previously well-controlled individual. In this case, the patient presented with progressive edema and was quickly identified to have nephrotic-range proteinuria and hypoalbuminemia. Early studies of nephrotic syndrome have demonstrated urinary losses of TBG and other proteins that bind thyroid hormone (albumin and transthyretin), resulting in low total T4 concentrations [6, 7]. Thanks to feedback adjustments effected by a normally functioning hypothalamic-pituitary-thyroid axis, most patients with proteinuria will remain euthyroid, but in patients with limited thyroid reserve, or dependent on oral levothyroxine, the urinary losses may trigger new-onset hypothyroidism or exacerbate preexisting hypothyroidism [8]. In pediatric studies, the daily urinary protein excretion appeared to correlate positively with the degree of urinary loss of TBG, FT4, and FT3 and associate negatively with corresponding serum levels [9].

More commonly, an undiagnosed disorder of the digestive tract is the culprit of an ineffective levothyroxine dose. Atrophic gastritis, which can result in achlorhydria, can impact levothyroxine requirements. Since levothyroxine absorption occurs primarily in the jejunum and ileum, a number of conditions (inflammatory bowel disease, celiac disease, intestinal surgery) can result in malabsorption [4]. Bowel edema from congestive heart failure, hepatic cirrhosis, or nephrotic syndrome can also contribute, the latter of which was likely relevant to this case study. Work-up of these etiologies may require additional consultative services or subspecialty input. If there is a high degree of suspicion of nonadherence, a levothyroxine absorption test can be considered to rule out compliance issues prior to initiating an extensive evaluation for a biological cause [10].

Correction of hypothyroidism revolves around the reason for inadequate dosing. If nonadherence is identified, clinicians should counsel patients on developing and maintaining good medication-taking behavior. Weekly oral administration of the full week's dose of levothyroxine or observed therapy can be considered in those for whom daily

ingestion is difficult [5]. Rearrangement of the patient's medication regimen can help resolve malabsorption related to drug interactions. In severe cases of malabsorption, alternative formulations of levothyroxine or parenteral delivery may be required. For those with concomitant illnesses, higher doses may simply be needed, and periodic titration is often necessary depending on fluctuations in disease activity.

In summary, there are many possible etiologies for the inadequate control of hypothyroidism with levothyroxine. As demonstrated by this case, the diagnostic work-up should incorporate a careful history and physical examination in order to identify the underlying cause and institute the proper treatment strategy.

Questions

1. A 70-year-old female status post a total thyroidectomy for multinodular goiter is seeking a new endocrinologist. Following surgery 5 years ago, she was on 100 mcg levothyroxine daily. Recently, she has increased to 150 mcg and was told that based on her most recent labs, she needs an even higher dose. She also has started a calcium and vitamin D supplement for osteoporosis. On examination, she complains of increased weight, facial puffiness, and bilateral pitting edema. Most recent labs reveal a TSH of 12.0 mU/L, free T4 of 0.8 ng/dL, and total T3 of 65 ng/dL. All the following are possible next steps except for:

   (a) Ascertaining the timing of the patient's calcium supplements
   (b) Adding liothyronine to the current regimen
   (c) Investigating the cause of the patient's pitting edema
   (d) Calling the patient's pharmacy to verify medication compliance

2. A 40-year-old man with hypothyroidism due to Hashimoto's thyroiditis presents for follow-up. His hypothyroidism has been under control for several years on 150 mcg levothyroxine daily. At his visit today, he reports weight gain and fatigue. Six months ago, he started a new job that requires frequent travel. He was taking levothyroxine on an empty stomach but had started taking it with breakfast due to his unpredictable schedule. His primary care physician also recently prescribed immediate-release omeprazole for heartburn in the morning. His TSH is 15.0 mU/L and free T4 is 0.7 ng/dL. What is the best initial approach to normalize thyroid function in his situation?

   (a) Tell the patient that he must rearrange his schedule to take levothyroxine in the same manner as previously.
   (b) Trial levothyroxine at bedtime.
   (c) Perform a levothyroxine absorption test.
   (d) Empirically increase his dose to 200 mcg daily.

3. Assume that each of these individuals follows proper instructions for levothyroxine ingestion. Each may still experience an increased levothyroxine requirement with the exception of:

   (a) A 55-year-old man who recently increased his phenytoin dose due to more frequent seizures
   (b) A 24-year-old female with type 1 diabetes and recent weight loss who tested positive for anti-tissue transglutaminase antibodies

(c) A 30-year-old man who is experiencing a flare of Crohn's disease
(d) A 65-year-old female taking biotin for hair loss

Answers

1. (b) Given the patient's age, combined therapy with T3 is discouraged. The other three answer choices investigate possible causes of the woman's persistent hypothyroidism, including medication nonadherence, drug interaction, and concomitant disease.
2. (b) The patient likely has impaired levothyroxine absorption due to the impact of food as well as proton pump inhibitor use. While levothyroxine is best absorbed on an empty stomach an hour before breakfast, this timing may be difficult for those with an erratic work schedule. Bedtime ingestion of levothyroxine would reduce the influence of food. Increasing the levothyroxine dose may also be effective in overcoming problems with absorption but might result in oversupplementation if his schedule changes again, so this would not be the initial step. A levothyroxine absorption test is also premature at this point.
3. (d) As described in this chapter, phenytoin can increase thyroid hormone metabolism and result in increased levothyroxine requirements. Positive anti-tissue transglutaminase antibodies indicate celiac disease, which can lead to decreased absorption of levothyroxine. Similarly, a flare of Crohn's disease can result in intestinal malabsorption. Biotin typically produces assay interference and causes spurious thyroid function results; however, it does not impact actual levothyroxine requirements.

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Chapter 11
Gastrointestinal Disease and Levothyroxine Absorption

Maria Gabriela Negron Marte and Francesco S. Celi

Objectives
Describing common and uncommon gastrointestinal conditions associated with levothyroxine malabsorption.

Case

A 31-year-old woman sought endocrinology consultation because of profound hypothyroidism. The patient was initially diagnosed with metastatic (T3 N1b M1, stage II) papillary thyroid cancer at age 17 and underwent total thyroidectomy, bilateral neck dissection, and three radioactive iodine treatments. The patient has been free of disease since the last radioactive iodine treatment at age 20. She notes that since the initial surgery, she has experienced significant weight gain, cold intolerance, and dry skin. She notes that her TSH has never been normal since the surgery despite her levothyroxine dose has been increased several times. She currently takes 450 mcg of levothyroxine early in the morning with water. She assures she is adherent to the regimen, and the refill history is consistent with the levothyroxine regimen.

Her past medical history is significant for anxiety and depression, and she was told she has gluten intolerance, but is not following any specific diet.

Her family history is significant for a sibling affected by type 1 diabetes and her mother who has history of Graves' disease.

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Physical exam is remarkable for obesity grade I, 97 kg (BMI 34 kg/m^2), BP 102/70 mmHg, HR 76 bpm with periorbital edema, dry skin, delayed relaxation phase of deep tendon reflexes, and diffuse, nonpitting edema.

Laboratory data are reported below:

TSH 128 mcIU/ml (n.v. 0.4–4.5), free T4 < 0.4 ng/dl (n.v. 0.7–1.5), total T3 29 ng/dl (n.v. 60–181), thyroglobulin 0.3 ng/ml, anti-thyroglobulin antibodies <1 IU/ml; 25 OH vitamin D 9.2 ng/ml (n.v. 30–100), gastrin 19 pg/ml (n.v. 0–115), vitamin B 12383 pg/ml (n.v. 213–816), anti-gliadin IgA 21 A.U. (20–30 moderate positive), anti-gliadin IgG 21 A.U. (20–30 moderate positive), anti-tissue transglutaminase IgA 3 U/ml (negative <4), anti-tissue transglutaminase IgG 7 U/ml (negative <5), anti-endomysial IgA negative.

The provisional diagnosis of intestinal malabsorption due to celiac disease was made, and the patient was instructed to follow gluten-free diet while reducing levothyroxine dose to 300 mcg/day and starting 25 OH vitamin D 50,000 IU/week. One month later, the patient reported significant improvement of her symptoms.

Review of how the Diagnosis Was Made

This patient presented with severe clinical and biochemical hypothyroidism notwithstanding supraphysiologic dose of levothyroxine (>4.5 mcg/kg). Once nonadherence to the regime is ruled out, one should consider gastrointestinal malabsorption or drug interference with levothyroxine absorption. The historical data of "gluten intolerance" and the family history of autoimmune disease (mother with Graves' disease and sibling with type 1 diabetes) point to an immune-mediated gastrointestinal malabsorption. The very low 25-OH vitamin D levels effectively confirm gastrointestinal malabsorption (refusing the possibility that the severe hypothyroidism is entirely due to nonadherence). Normal gastrin and vitamin B12 levels rule out the diagnosis of atrophic gastritis. Finally, although weakly positive, the serologic markers for celiac disease, coupled with the clinical response to dietary modification, confirm the diagnosis of celiac disease–/gluten intolerance-induced levothyroxine malabsorption.

Lessons Learned

Nonadherence to Replacement Therapy Poor adherence to therapy is probably the most common cause of inability of achieving the target TSH in patients affected by hypothyroidism. This is particularly challenging in patients devoid of residual endogenous thyroid hormone production whereby the entire pool of circulating hormones derives from levothyroxine. Clinical suggestions for nonadherence include unexpected changes in free T4 and TSH over a short period of time or elevated TSH and free T4.

This latter condition likely reflects the patient attempt of "catching up" before the blood sampling. Causes of nonadherence include underlying psychiatric conditions, secondary gain, or polypharmacy with mix-up of prescriptions. This situation can be difficult to confirm with certainty, and confronting the patient is seldom useful. In these events, direct observation of weekly administration of levothyroxine is a viable therapeutic option. The patient refill history strongly supported, although did not confirm, good adherence to the therapeutic regimen. Occasionally the measurement of free T4 rise following a pharmacologic dose of levothyroxine can be used as a diagnostic test to distinguish malabsorption of levothyroxine vs. nonadherence [1].

Factors Affecting Levothyroxine Absorption Levothyroxine is the sodium salt of thyroxine (T4), and its absorption is function of tablet crushing and dissolution in the acidic environment of the stomach. Subsequently, the active drug is absorbed (60–80%) in the proximal intestine. In ability of dissolving the tablets, reduction of gastric acidity, binding of levothyroxine with interference substances (drugs or food), and anatomical or functional impairment of intestinal absorption are all causes of impaired levothyroxine absorption leading to low and inconsistent delivery of thyroid hormone replacement therapy [2].

Food, Interference on Levothyroxine Absorption Food and in particular items containing high concentration of calcium (milk and derivate), inhibit the absorption of levothyroxine. Coffee also inhibits the gastrointestinal absorption of levothyroxine [3], hence the recommendation of taking the levothyroxine only with water, at empty stomach, 30–60′ before breakfast [4]. The use of levothyroxine tablets in patients receiving enteral feeding represents a particular challenge since even if the crushed tablets may be sufficiently dissolved, calcium-containing feeding solution can still be present in the gastrointestinal tract, and often patients are treated with anti-acids.

Drug Interference on Levothyroxine Absorption Drugs can affect levothyroxine intestinal absorption by increasing the gastric pH (H_2 blockers, proton pump inhibitors), physically binding levothyroxine (calcium carbonate, magnesium oxide, phosphate binders, and sucralfate), or binding bile acids (cholestyramine) reducing the enterohepatic reabsorption of thyroid hormone.

Post-Surgical Levothyroxine Malabsorption Surgical procedures in the foregut affecting gastric acid secretion and diverting the gastric content from the jejunum significantly decrease the absorption of levothyroxine. In particular, bariatric procedures, either sleeve gastrectomy or Roux-en-Y, are associated with increased relative requirement (as expressed in mcg/kg) of levothyroxine and variability in absorption [5]. Patients are often treated with proton pump inhibitors to ameliorate gastroesophageal reflux, and the extent of the intestinal resection associated with the Roux-en-Y procedure also plays a role in the degree of levothyroxine malabsorption.

Gastrointestinal Diseases Affecting Levothyroxine Absorption Similar to surgical procedures, gastrointestinal conditions affecting the upper portion of the intestinal tract can have dramatic effects on the absorption of levothyroxine resulting in increased requirements or difficulties in controlling hypothyroidism. Importantly, some gastrointestinal diseases affecting levothyroxine absorption are also associated *per se* with thyroid autoimmunity, and a high index of suspicion should be kept when replacement therapy requires unusual dose of levothyroxine (above 2 mcg/kg) or multiple adjustments.

Atrophic Gastritis Irrespective of the etiology, this condition is associated with decreased gastric acid output resulting in elevated gastric pH and impaired levothyroxine absorption. Atrophic gastritis can be the result of *H. pylori* infection, and in this case, it is a reversible condition or secondary to an autoimmune state resulting in the physical destruction of the parietal cells resulting in permanent loss of acid production. This latter condition "thyrogastric syndrome" [6] is associated with vitamin B12 deficiency due to lack of intrinsic factor, autoimmune thyroid disease, and vitiligo [7] and can be part of the spectrum of polyglandular autoimmune syndrome.

Celiac Disease This autoimmune condition due to exposure to gluten in individuals with genetic predisposition results in submucosal lymphocyte infiltration and loss of intestinal villi, particularly in the proximal ileum with malabsorption, often associated with diarrhea and weight loss. Similar to autoimmune gastritis, this condition is associated with thyroid autoimmunity and type 1 diabetes. The diagnosis is based on the combination of serological markers (autoantibodies anti-gliadin, anti-tissue transglutaminase, and anti-endomysial) and the findings on the duodenal biopsy. Institution of gluten-free diet results in resolution of the malabsorption [8].

Lactose Intolerance This non-autoimmune condition, more prevalent in non-Caucasian populations, is due to (relative) lactase deficiency resulting in inability of digesting lactose. This in turn can cause bacterial overgrowth with malabsorption. Lactose intolerance is not associated with autoimmune thyroid disease [9].

Diabetic Gastroparesis This late and severe complication of diabetes results in delayed and unpredictable stomach emptying; hence, even in a fasting state, some significant gastric residue can be present with resultant binding of levothyroxine to food and consequent reduced absorption of the drug. Moreover, patients may experience bacterial overgrowth with additional malabsorption and are often treated with antacids. Collectively, diabetic gastroparesis can represent a major challenge in the delivery of adequate dose of levothyroxine.

The following table illustrates the characteristics of gastrointestinal conditions affecting levothyroxine absorption (Table 11.1).

Table 11.1 Gastrointestinal conditions associated with reduced levothyroxine absorption

Condition	Etiology	Associated with autoimmune thyroid disease	Diagnosis	Specific characteristics
Surgical causes	Loss of gastric acid production, loss of proximal ileum	No	History	
Atrophic gastritis	Autoimmune, *H. pylori* infection	Yes (autoimmune form)	Anti-parietal antibodies, *H. pylori*	High gastrin levels, B12 deficiency (autoimmune form)
Celiac disease	Autoimmune	Yes	Autoantibodies, biopsy	Associated with generalized malabsorption, vitamin D deficiency
Lactose intolerance	Relative lactase deficiency	No	History, enzyme measurement, biopsy	More prevalent in non-Caucasians
Diabetic gastroparesis	Autonomic neuropathy	Yes	History, gastric emptying studies	

Questions

1. A 23-year-old woman is referred for evaluation of hypothyroidism with complaints of fatigue, "mental fog," hair loss, and constipation. She weighs 52 kg and has been taking levothyroxine 125 mcg/day. Physical exam is remarkable for vitiligo. Her TSH is markedly elevated at 35 mcIU/ml (n.v. 0.4–4.5), her Hb is 10 g/dl, and the MCV is 102 fl (n.v. 80–96). Which is the most likely cause of poor levothyroxine absorption?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

2. A 73-year-old woman is referred from a nursing home for evaluation of hypothyroidism. She was transferred 1 month ago from the hospital following a stroke with residual hemiparesis and dysphagia. The patient is receiving continuous enteral feeding. She weighs 75 kg and has been taking levothyroxine 125 mcg/day. Her TSH is 75 mcIU/ml (n.v. 0.4–4.5), and her free T4 0.7 ng/dl (n.v. 0.7–1.5). Which is the most likely cause of her hypothyroidism?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

3. A 21-year-old man with 3 years history of diabetes is referred for evaluation of hypothyroidism with complaints of fatigue, weight loss, and skin rash. He weighs 70 kg and has been taking levothyroxine 150 mcg/day. Physical exam is remarkable for itchy symmetrical papular rash on the elbows. His TSH is 25 mcIU/ml (n.v. 0.4–4.5), HbA1c is 7.1%, and 25 OH vitamin D is 12 ng/ml (n.v. 30–100). Which is the most likely cause of poor levothyroxine absorption?

   (a) Poor adherence
   (b) Atrophic gastritis
   (c) Celiac disease
   (d) Food interference
   (e) Gastroparesis

Answers

1. (b) This patient is most likely affected by autoimmune atrophic gastritis resulting in reduction of gastric acid production with consequent impairment of levothyroxine absorption. The patient is also affected by vitamin B12 deficiency caused by lack of intrinsic factor. The clinical clues of these conditions are represented by the neuropsychiatric symptoms and the macrocytic anemia.
2. (d) Enteral feeding represents a major challenge in the delivery of levothyroxine due to the difficulties in dissolution of the tablets and the interference with feeding, particularly if continuous.
3. (c) This patient has celiac disease resulting in malabsorption (weight loss and vitamin D deficiency) and impaired levothyroxine absorption. Malabsorption due to diabetic gastroparesis is extremely unlikely since the diabetes is of recent onset and it is well controlled. Additionally, the patient has dermatologic manifestations (dermatitis herpetiformis) of celiac disease.

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Chapter 12
Drug-Induced Central Hypothyroidism

Benjamin Gigliotti

Objectives

1. Diagnose central hypothyroidism from compatible symptoms, signs, and thyroid function tests, and describe principles of management.
2. Review the etiologies and pathophysiology of central hypothyroidism, with a focus on drug-induced central hypothyroidism.

Case

A 72-year-old man was referred for evaluation of a persistently low TSH despite reduction in levothyroxine dosage. He had a long history of hypothyroidism due to Hashimoto's thyroiditis and was clinically and biochemically euthyroid on 150 mcg daily levothyroxine (weight 88.4 kg, ~1.7 mcg/kg) for several years. Six months prior to referral, he was diagnosed with cutaneous T-cell lymphoma (CTCL) and started on oral bexarotene. After 1 month of therapy, he developed progressive fatigue, dry skin, cold intolerance, constipation, and both myalgias and muscle weakness. TSH was <0.01 with a normal FT4, so his levothyroxine was reduced to 137mcg. His symptoms worsened, and TSH remained <0.01 2 months later, so he was referred to endocrinology. Notable examination findings included mild bradycardia, isolated diastolic hypertension, slowed but appropriate responses to questioning, dry skin, and delayed relaxation of deep tendon reflexes. TSH was 0.01 with a FT4 of 0.7 and T3 of 41. Levothyroxine was increased to 175mcg daily, but symptoms persisted and FT4 remained low. Over the next 5 months, his levothyroxine was steadily increased to 300mcg daily despite careful adherence,

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Table 12.1 Thyroid function tests after initiation of bexarotene, titration of levothyroxine, and addition of liothyronine

Months after initiation of bexarotene	Levothyroxine-T4, mcg	Liothyronine, mcg	TSH (mIU/L), 0.4–5.0	FT4 (ng/mL), 0.9–1.7	T3 (ng/dL), 80–200
3 months prior	150		3.25	–	–
1 month	150		<0.01	–	–
3	137		<0.01	–	–
4 (referral)	137		0.01	0.7	41
6	175		<0.01	0.8	43
8	250		<0.01	0.8	54
11	300	5 BID	<0.01	0.9	63
13	400	10 BID	<0.01	1.3	99
15	400	10 BID	<0.01	1.4	114

All labs were drawn between 2 and 4 pm, prior to his second daily dose of liothyronine

administration >60 minutes before meals, and avoidance of interfering medications and supplements. Symptoms persisted, and his T3 remained low, so liothyronine was cautiously added. After titration to a final dose of 400mcg levothyroxine and 10mcg BID liothyronine, his symptoms improved which correlated with resolution of abnormal physical exam findings and normalization of FT4 and T3 levels (Table 12.1).

Review of How the Diagnosis Was Made

The presence of an unequivocally low serum FT4 level with a suppressed TSH (while already on levothyroxine therapy) and signs and symptoms of hypothyroidism in a bexarotene-treated patient was consistent with drug-induced central hypothyroidism. Failure for the abnormal symptoms and biochemistry to normalize despite levothyroxine titration was concerning for nonadherence or malabsorption, but persistence despite optimal administration suggested increased hormone metabolism, which responded to use of supraphysiologic levothyroxine and the addition of liothyronine.

Lessons Learned

Central hypothyroidism is a rare disease of deficient thyroid hormone production by an otherwise functional gland due to inadequate stimulation by pituitary TSH [1]. Under normal circumstances, hypothalamic TRH regulates TSH synthesis, glycosylation (which influences bioactivity), and release, which itself stimulates nearly every step in thyroid hormone production. Pituitary mass lesions are the most

common cause of central hypothyroidism and lead to suppression of TSH through compression or ischemia of pituitary thyrotrophs or interruption of hypothalamic stimuli. Other causes of central hypothyroidism include infiltrative disorders (e.g., deposition diseases, infections, central nervous system malignancies) of the hypothalamus or pituitary, traumatic brain injury, pituitary ischemia/apoplexy, disorders of development, or a medication adverse effect. The diagnosis requires measuring total or free T4 since TSH may be low, normal, or even slightly high since quantitative detection does not necessarily correlate with biological activity, especially when an interruption in TRH-mediated glycosylation is present. Central hypothyroidism is treated with exogenous levothyroxine. Thyroid hormone should be titrated to a goal mid-normal range free T4 value since TSH is unreliable; TSH levels usually drop to <0.01 after initiation of levothyroxine due to loss of what little TSH production was present from decreased negative feedback.

Drugs directly or indirectly affect thyroid function through a variety of mechanisms, including effects on thyroid hormone production, binding, activation, or metabolism; they can also interfere with thyroid hormone therapy and/or laboratory testing [2]. A small subset of drugs can negatively impact the hypothalamic-pituitary-thyroid axis, including glucocorticoids, dopamine, bromocriptine, somatostatin analogs, metformin, immune checkpoint inhibitors, and rexinoids. Other drugs, such as carbamazepine, oxcarbazepine, phenytoin, and salsalate, can spuriously mimic central hypothyroidism by inducing a low free T4, and to a lesser extent T3, through interference with thyroid hormone assays [3].

Glucocorticoids lower serum TSH levels at commonly used doses (e.g., ≥ 0.5 mg dexamethasone, ≥ 30 mg prednisone) through direct inhibition of TRH in the hypothalamus, which leads to reduced TSH production. Dopamine and bromocriptine (owing to their action as dopamine agonists) bind to pituitary D2 receptors and reduce TSH production. Somatostatin analogs bind to inhibitory pituitary somatostatin receptors which decrease adenylate cyclase signaling and ultimately cell polarization, which reduces TSH secretion. Metformin appears to reduce TSH in patients with hypothyroidism and type 2 diabetes although the exact mechanism is not known. Importantly, none of the aforementioned drugs has been shown to cause clinically significant central hypothyroidism at typical doses, although dopamine is admittedly difficult to study given concomitant nonthyroidal illness in critically ill patients. In contrast, immune checkpoint inhibitor therapy is an increasingly recognized cause of clinically significant hypopituitarism (in which central hypothyroidism may result) which results due to stimulation of pituitary autoimmunity and inflammatory hypophysitis.

Rexinoids are vitamin A derivatives that interact with the retinoid X nuclear hormone receptor (RXR). RXR functions as a heterodimer with other critical intranuclear receptors such as the thyroid hormone receptor, vitamin D receptor, and peroxisome proliferator-activated receptor. Bexarotene is the most clinically relevant rexinoid since topical and oral formulations are approved by the FDA treatment of cutaneous T-cell lymphoma. Clinically significant hypothyroidism is common and affects the majority of bexarotene-treated patients with cutaneous T-cell lymphoma [4]. Bexarotene rapidly and specifically suppresses TSH without

affecting other pituitary hormones, and the effect is observable in healthy controls as well as patients with cancer [3]. Mechanistic studies have demonstrated a direct suppression of the TSHβ subunit gene transcription which suggests the pituitary is the primary target, although a failure of hypothalamic TRH mRNA to rise in the presence of low T4 suggests the hypothalamus may be affected as well. Interestingly, bexarotene has also been shown to increase thyroid hormone metabolism, even in patients who are athyreotic, although the dominant mechanism (e.g., deiodination, sulfation, glucuronidation) remains unclear [5].

In the present case, the patient had clear evidence of central hypothyroidism due to bexarotene, which is an uncommon but well-characterized cause. His signs and symptoms of hypothyroidism, along with his low FT4, required very high doses of levothyroxine and the eventual addition of liothyronine to normalize. It is important to note that failure to respond to thyroid hormone replacement, especially in excess of weight-based doses (1.6 mcg/kg), should raise suspicion for nonadherence and/or malabsorption, even in patients who report optimal adherence and timing of therapy. This is a fairly common occurrence in clinical practice, and algorithms have been proposed to guide a thoughtful evaluation of the underlying cause(s): a thorough history and medication/supplement review, judicious use of levothyroxine absorption testing and/or workup for specific malabsorption syndromes, and optimization of timing, co-administered agents, and thyroxine formulation are clinically impactful [6]. In this patient's case, we did not definitely exclude malabsorption or nonadherence. However, his consistency in follow up, self-report of optimal administration, and stability in TFTs after achieving normal T4/T3 levels with titration in the presence of a drug known to increase thyroid hormone metabolism suggests hypermetabolism was the root cause.

Key Learning Points

1. Central hypothyroidism is rare, usually caused by pituitary mass lesions, and is diagnosed by signs and symptoms of hypothyroidism with a low free/total T4 level and an inappropriately low, normal, or slightly elevated TSH level.
2. Central hypothyroidism is treated with thyroid hormone replacement (levothyroxine in the vast majority of cases) and requires following free T4 rather than TSH levels for therapy titration; it is imperative that clinicians do not misinterpret the low TSH as a sign of overreplacement.
3. Bexarotene is a rare cause of central hypothyroidism and causes both inhibition of TSH release and increased thyroid hormone metabolism. High doses of thyroid hormone may be required to restore clinical and biochemical euthyroidism.
4. In patients who require higher than weight-based doses (1.6 mcg/kg) of thyroid hormone, nonadherence and/or malabsorption is the most common cause and should be strongly suspected and treated, unless a known cause of altered thyroid hormone metabolism is present.

Questions

1. A 84-year-old man is diagnosed with symptomatic overt hypothyroidism based on a TSH of 16 mIU/L, a free T4 of 0.7 ng/dL, and compatible symptoms. PMH is significant for mild cognitive impairment, performance anxiety (he is a pianist) HTN, HLD, diet-controlled DM2, GERD, iron deficiency, and obesity.

Medications include lisinopril, atorvastatin, omeprazole, ferrous sulfate, a daily multivitamin, and propranolol PRN. Levothyroxine is initiated and increased to 200mcg (82 kg, ~2.4 mcg/kg) over several months with ongoing symptoms and persistently elevated TSH. The most likely explanation for his persistently elevated TSH is:

(a) A drug-induced increase in levothyroxine clearance/metabolism
(b) Levothyroxine nonadherence and/or malabsorption
(c) Nephrotic syndrome
(d) TSH assay interference

2. A 48-year-old woman is referred for evaluation of a suppressed TSH <0.01 with palpitations, heat intolerance, and weight loss. A FT4 is 1.2 ng/dL and T3 is 150 ng/dL. PMH is significant for GERD. She takes 81 mg aspirin and 20 mg omeprazole. The most appropriate diagnosis is:

(a) Central hypothyroidism
(b) Subclinical hypothyroidism
(c) Subclinical hyperthyroidism
(d) Overt hyperthyroidism

3. All of the following are causes of drug-induced hypothyroidism, *except*:

(a) Lithium
(b) Amiodarone
(c) Anti-CTLA4 and anti-PD1/PDL1 immunotherapy
(d) Metoprolol

Answers

1. (b) Most patients who apparently fail to respond to levothyroxine therapy demonstrate therapy nonadherence and/or malabsorption. This patient has a risk factor for nonadherence (mild cognitive impairment) and is on several medications known to interfere with levothyroxine absorption (iron, MVI, omeprazole). Propranolol can affect thyroid hormone metabolism but only at very high doses; none of the other medications have a known effect on metabolism. Nephrotic syndrome is a rare cause of hypothyroidism due to urinary loss of TBG and thyroid hormone. TSH assay interference is unlikely if the elevated TSH continues to fit the clinical picture (e.g., hypothyroid symptoms persist), and a more likely explanation is present.
2. (c) A fully suppressed TSH with normal FT4/T3 is most consistent with subclinical hyperthyroidism; an elevation in FT4 and/or T3 would qualify as "overt" hyperthyroidism. Despite the confusing nomenclature, "subclinical" thyroid disease is purely a biochemical diagnosis, and presence or absence of symptoms is not included in the definition. TSH is almost never fully suppressed in central hypothyroidism unless measured after thyroid hormone initiation, and this patient has no risk factors for it.
3. (d) Lithium, amiodarone, and checkpoint inhibitor immunotherapy are all associated with drug-induced hypothyroidism. Metoprolol can cause bradycardia and fatigue, but does not have significant effects on thyroid function.

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Part IV
Thyroid Cancer

Chapter 13
Introduction

Kenneth D. Burman

It has been a privilege to edit the section on Thyroid Diseases, and we are honored to have excellent authors discussing three important thyroid cancers (see chaps. 14, 15 and 16). Thyroid cancer incidence has been increasing at a very rapid rate, probably due to increased detection of thyroid nodules by radiologic techniques, as well as a change in the underlying molecular mechanisms which cause or propagate this disease [1]. Therefore, it have become important to recognize the staging system for thyroid cancer and to decide which patients require more intensive therapy and monitoring [1].

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer and, in general, is treated with thyroidectomy (total or lobectomy) and sometimes with radioactive iodine [1]. Despite the fact that papillary thyroid cancer is usually very treatable and that most patients do well, the prognosis in older patients may be more guarded. Further, men seem to have a worse prognosis than woman, although the reasons for this are presently unclear. In their chapter Motazedi and Burman (see chap. 14) review various aspects of PTC. Risk factors, such as age, gender, and thyroid pathology, are discussed as well as hereditary disorders, such as Cowden's syndrome, which increase the likelihood of developing thyroid cancer, are reviewed. Appropriate management following thyroidectomy may include radioactive iodine scan and therapy and during monitoring includes physical exam, serum TSH and thyroglobulin levels, and neck ultrasound. In selected patients with aggressive disease, further radiologic studies including CT, PET, and bone scans and radioactive iodine scans/therapy may be indicated. Motazedi and Burman (see chap. 14) also note the use of FDA-approved oral chemotherapy to treat selected patients with oncogene targeted oral chemotherapy. Some patients may only require a thyroid lobectomy, whereas other may need a total thyroidectomy and additional treatment as noted.

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Radioactive iodine therapy has been used to treat PTC for about 80 years, but its use recently has been more limited to patients with more aggressive disease who are also radioactive iodine sensitive [1].

Patel and Bernet (see chap. 16) review the important clinical aspects of medullary thyroid cancer (MTC). Although less common than PTC, MTC can be aggressive, especially when detected later in its course [2]. Most cases of MTC occur sporadically, but a significant number are familial, related to a germline RET mutation. Familial disorders that are associated with MTC include multiple endocrine neoplasia type 2 (MEN2A and MEN2B) and familial MTC (see chap. 16).

It is important that all patients with MTC be assessed for the presence of a germline RET mutation. The finding of a specific relevant germline RET mutation in the initial patient mandates that all first-degree relatives be screened as well. The penetrance of a RET germline mutation is about 100%, and, therefore, a prophylactic thyroidectomy is usually recommended. The specific timing of the surgery depends on the clinical circumstance as well as the specific codon mutation identified [2].

All patients with a RET mutation should also be screened for a pheochromocytoma and hyperparathyroidism, especially prior to a thyroidectomy (or any surgery).

MTC patients are monitored by following serum TSH as well as serum calcitonin and CEA. Calcitonin doubling time is a reasonable assessment of progression of disease. Radiologic studies such as neck ultrasound, CT chest, MRI abdomen and adrenal glands, and bone scan are indicated in patients with residual evidence of disease after thyroidectomy. Oral chemotherapy is available for patients with aggressive or progressive disease. Several TKIs have been approved by the FDA, and specific targeted agents may also be available. It appears that early detection of MTC especially through RET testing of patients with familial MTC with early thyroidectomy decreases the risk of progression or return of disease.

Munir and Veytsman (see chap. 15) review salient aspects of anaplastic thyroid cancer (ATC). ATC is one of the most lethal tumors known, and it has a very poor prognosis [3]. It may occur de novo but also may occur in the setting of a previously known PTC. It is characterized by a rapidly growing neck mass and local symptoms such as sudden onset of hoarseness, neck discomfort, dysphagia, and/or dyspnea. Distant metastases may be noted at the time of diagnosis.

Treatment modalities may include thyroid/neck surgery or debunking, external beam radiation therapy, and/or chemotherapy [3]. Each case is evaluated individually with respect to which treatments may possibly be beneficial taking into account the potential adverse effects. The thyroid pathology typically shows spindle cells, giant cells, and/or squamoid cells with poorly differentiated thyroid cells. ATC typically does not stain (or stains poorly) for thyroglobulin, TTF1, or PAX8. However, ATC may stain for oncogenes, most notably bRAF. ATC that does not stain for bRAF may be a candidate for more standard chemotherapy, such as doxorubicin and paclitaxel. However, newer developments promulgated from M.D. Anderson Cancer Center indicate that early determination of bRAF status is critical [4]. If a bRAF mutation is present, treatment is instituted with combination of dabrafenib and trametinib as specific targeted agents. Monitoring includes clinical and

radiologic assessment. The rapid assessment and treatment of a bRAF mutation appears to be an important development in the treatment of patients with ATC.

In summary, there have been new, important developments in the management of PTC, MTC, and ATC mainly focusing on improved diagnostic and treatment modalities. The utility of performing either germline or somatic genetic analysis (depending on the tumor type) and the implementation of specific targeted chemotherapy appear to be an advance in thyroid cancer management.

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Chapter 14
Papillary Thyroid Cancer

Banafsheh Motazedi and Kenneth D. Burman

Objectives

1. To understand the presentation of papillary thyroid cancer (PTC)
2. To examine the high-risk features of PTC
3. To discuss the molecular genetics of PTC
4. To understand the surgical indications for PTC
5. To discuss the utility of radioactive iodine remnant ablation and treatment
6. To review the appropriate long-term follow-up for patients with PTC
7. To discuss therapeutic options with tyrosine kinase inhibitors (TKIs) for patients with radioactive iodine refractory metastatic PTC

Case Presentation

A 25-year-old male with history of asthma, depression, and hypertension was found to have a right palpable thyroid mass on physical exam. His thyroid ultrasound showed a right lower pole nodule measuring 4.7 × 2.4 × 2.7 cm which was described as solid and hypoechoic with irregular borders and a left upper pole nodule measuring 1.7 × 1.2 × 1.0 cm which was described as predominately solid and hypoechoic with microcalcifications. He subsequently underwent an ultrasound-guided

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fine-needle aspiration (FNA) of these nodules with findings of each nodule as being highly suspicious for papillary thyroid carcinoma (i.e., many enlarged follicular epithelial cells with increased nuclear to cytoplasmic ratio arranged in sheets with papillary structure along with pseudo-intranuclear inclusions, nuclear grooves, multinucleated giant cells, and psammoma bodies). The patient had no known family history of thyroid disorders or malignancy and no personal history of radiation exposure to head and neck. He also denied symptoms of mechanical obstruction, shortness of breath, dysphagia, or other symptoms of hyper- or hypothyroidism. CBC, CMP, thyroid peroxidase, and thyroglobulin antibodies were normal. Thyroid-stimulating hormone (TSH) was 3.2 mU/L (normal 0.8–4.2), and free thyroxine (FT4) was 1.2 ng/dL (normal 0.8–1.8), both within the normal limits.

A total thyroidectomy was recommended. Pathology from the total thyroidectomy demonstrated a 1.1 × 0.9 × 1.0 cm PTC on the left side and a right-sided 4.5 × 2.6 × 1.9 cm PTC with extrathyroidal extension, without angioinvasion, and with inked surgical margins and skeletal muscles negative for malignancy. In total 11 out of 28 lymph nodes were positive for metastatic disease (8 of 14 positive right level IV; 3 of 14 positive left level III). Patient was determined to have stage I PTC (T3aN1). His thyrogen-stimulated I-123 dosimetric-based pre-therapy scan showed two foci of radiotracer uptake in the thyroid bed without scan evidence of metastatic disease in the neck or distant metastases. He received 150 mCi radioactive iodine treatment under Thyrogen® stimulation. He was administered suppressive doses of levothyroxine to maintain a TSH of 0.1 mIU/L. His post-therapy whole body I-131 scan about 10 days after treatment showed two foci of radioiodine uptake in the thyroid bed which were unchanged from his pretherapy scan. His Thyrogen® stimulated thyroglobulin (Tg) was <2.0 ng/mL, and thyroglobulin antibody (Tg Ab) was <20 IU/mL.

One year after his initial surgery, his laboratory studies revealed TSH of 0.2 mU/L and FT4 1.7 ng/dL with unstimulated serum thyroglobulin level < 0.2 mU/L and absence of thyroglobulin antibodies. He had a neck ultrasound followed by Thyrogen® stimulated whole body scan (WBS) 1 year post-operatively, which showed no evidence of local recurrence or distant metastases. However, 2 years post-operatively his stimulated serum thyroglobulin level increased from <0.2 to 5.0 ng/ml with negative thyroglobulin antibodies.

Fundamentals of Well-Differentiated Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy and accounts for approximately 2.1% of all cancer diagnoses worldwide [1]. According to the American Cancer Society, the projected incidence of thyroid cancer for 2020 is 52,890 new cases (40,170 in women and 12,720 in men) with an estimated 2180 deaths from thyroid cancer (1140 women and 1040 men) [2]. Thyroid cancer death rates have increased at a rate of 0.6% per year from 2008 to 2017 [2]. Mortality rate especially for men over about age 60 is also increasing at a rapid rate.

Differentiated thyroid cancer (DTC) includes both papillary and follicular thyroid cancers, which account for more than 90% of all thyroid cancers, with PTC prevailing (about 80–90% of DTC) followed by follicular thyroid cancer. Over the past approximately 10–15 years, the incidence of PTC cases has been on the rise which is partly attributed to increased early detection of small papillary thyroid carcinomas possibly related to the frequent use of diagnostic head/neck or chest imaging (performed for other medical conditions), leading to incidentally found thyroid nodules which otherwise may not have been diagnosed or become symptomatic. However, the increasing frequency of thyroid cancer cases is not thought to be solely related to overdiagnosis or early detection. If detection alone was the predominant factor, then we would expect early treatment of potentially aggressive cases which should result in an eventual decline in thyroid cancer mortality rates. Yet, the mortality rate and recurrence risk of DTC are higher in men even when adjusted for stage at presentation than in women [3, 4]. This could be attributed to a more aggressive nature of DTC in males.

Most thyroid cancer risk factors are non-modifiable such as female gender and ethnicity. In fact, female gender confers three- to four-fold higher risk of thyroid cancer than men. Additionally, higher thyroid cancer incidence is observed in non-Hispanic whites than Hispanic and African American individuals [1]. Some authors have described modifiable risk factors such as obesity to be associated with increased risk of thyroid cancer [5]. However, the role of obesity in thyroid cancer incidence remains unclear.

Other risk factors associated with PTC include previous exposure to ionizing radiation (particularly at a young age), external neck radiation for treatment of other diseases, and rare hereditary conditions (i.e., Cowden's syndrome). It is worth mentioning that radiation-induced PTCs typically present with *RET* chromosomal rearrangements, whereas sporadic PTCs are more frequently associated with $BRAF^{V600E}$ or *RAS* mutations [6, 7].

Although mortality from thyroid cancer is low, with 10-year survival rates exceeding 90% in PTC patients, the recurrence rate may be greater than 30%, making risk stratification a priority [8]. Prognostic factors such as age ≥55 years, male gender, tumor size >4 cm, follicular histology or tall and columnar cell variants, multifocality, extra-capsular extension, number of lymph node metastases, and rising Tg levels are associated with increased risk of recurrence [8].

Treatment of DTC is individually tailored based on the 2017 revised American Joint Committee on Cancer (AJCC) eighth edition staging guidelines which assess mortality risk, as well as the 2015 American Thyroid Association (ATA) risk stratification guidelines which assess risk of recurrent or persistent disease. Staging is an extremely important tool in management of patients with malignancy. Currently, the TNM (tumor, node, and metastasis) staging system is used which was proposed by the AJCC and International Union Against Cancer Committee (IUCC). Patients <55 years of age are subdivided into stage I or II: stage I, tumor of any size with lymph node metastases and *absence* of distant metastases, and stage II, tumor of any size with lymph node metastases *and* distant metastases.

Patients 55 years and older are subdivided into stages I–IV. Stage I: Tumor is ≤4 cm and localized to the thyroid. Stage II: Tumor is of any size with lymph node metastases *or* extrathyroidal extension invading *only* strap muscles but *absent* distant metastases. Stage III: Tumor is of any size with lymph node metastases and gross extrathyroidal extension invading *beyond* strap muscles into subcutaneous soft tissues, larynx, trachea, esophagus, and/or recurrent laryngeal nerve but *absent* distant metastases. Stage IVa: Tumor is of any size with lymph node metastases and extrathyroidal invasion of prevertebral fascia or encasing carotid artery but *absen* distant metastases. Stage IVb: Tumor is of any size with lymph node metastases and extrathyroidal invasion of mediastinal vessels *and* distant metastases [9].

The 2015 ATA guidelines modified the risk stratification system for DTC to help guide prognostication, post-operative risk assessment, as well as disease management and follow-up. These guidelines have included various factors affecting risk of structural recurrence including extrathyroidal extension (ETE), lymph node involvement, tumor multifocality, and $BRAF^{V600E}$ mutation status, to help guide treatment and surgical intervention and ameliorate treatment-related morbidity.

The 2015 ATA risk stratification divides patients into low-, intermediate-, and high-risk categories. Low-risk patients have no metastases, all their macroscopic tumor has been resected, there is no tumor invasion of locoregional tissues/structures or vascular invasion, there are 0 to ≤5 pathological lymph nodes involved (measuring <0.2 cm in diameter), the tumor lacks aggressive histology, and if I-131 remnant ablation is performed, there is no uptake outside the thyroid bed on the first post-treatment radioactive iodine WBS. The characteristics for intermediate-risk patients include either microscopic tumor invasion into the perithyroidal soft tissues, vascular invasion, pathological lymph nodes >5 (measuring <3 cm in largest dimension), multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutation, aggressive histology (tall or columnar cell variants), and radioactive uptake in the neck on the first post-treatment WBS. High-risk patients have macroscopic tumor invasion into perithyroidal soft tissues, incomplete tumor resection, pathological lymph nodes ≥3 cm in greatest dimension, follicular thyroid cancer with vascular invasion (>4 foci), distant metastases, and elevated postoperative Tg levels suggestive of distant metastases [10].

Patients can also be reclassified based on their response to initial therapy following thyroidectomy and radioactive iodine ablation or treatment. This model provides a more individualized risk assessment strategy. Based on clinical outcomes using suppressed Tg, stimulated Tg, and imaging studies at any point during follow-up, patients are further divided into four response categories: excellent response, biochemical indeterminate response, structural incomplete response, and indeterminate response. This has been proven to be especially useful in intermediate- and high-risk patients since those who have an initial excellent treatment response have a very low likelihood of disease recurrence [11].

Molecular Genetics of Papillary Thyroid Cancer

Over recent years, advances have been made in identifying molecular markers from FNA samples that carry both diagnostic and prognostic values in the management of PTC. *BRAF* gene mutations occur in PTC, and in several other carcinomas such as melanoma and lung adenocarcinoma, although the exact *BRAF* mutations may vary. *BRAF* is a B-type Raf kinase, located on chromosome 7. It codes a cytoplasmic serine/threonine kinase and plays a role in regulating the mitogen-activated pathway kinase (MAPK), resulting in cell proliferation, inhibition of differentiation, and apoptosis [12]. The most common *BRAF* mutation in thyroid cancer is a point mutation resulting in change of valine to glutamic acid at codon 600, designated $BRAF^{V600E}$, and accounts for more than 90% of occurrences [12]. The incidence of *BRAF* gene mutations in patients with sporadic PTC ranges from about 40% to 70%. Tumors harboring $BRAF^{V600E}$ mutations are associated with higher rates of regional lymph node metastases, increased risk of recurrence, and persistent disease. *BRAF* mutations may insinuate a poorer prognosis in PTC and are associated with older age, tall cell variant, extrathyroidal extension, and advance disease stage at presentation (stage III and IV) [13]. Additionally, nearly 40% of patients with micropapillary carcinoma (<10 mm) have the $BRAF^{V600E}$ mutation, suggesting that it could be a useful tool for staging in the future [14]. Although *BRAF* mutation is possibly predictive of aggressive behavior of PTC and most studies recommend the use of *BRAF* mutation as a prognostic factor, other studies suggest *BRAF* mutation to be a rare clonal event, indicating its controversial use as a prognostic factor [15]. Given the lack of strong association between *BRAF* mutation and relapse risk, the revised 2015 ATA guidelines do not require application of *BRAF* status for initial risk stratification in DTC. Moreover, *BRAF* is not the only genetic variation found in PTC, as many as 70% of patients with non-familial PTC have some type of gene mutation (i.e., *TERT* promotor, *RET*, *RAS* genes, *NTRK1*, *PTEN, and PIK3CA*).

According to the Bethesda classification system, about 30% of thyroid nodules undergoing FNA biopsy are determined to be atypia of undetermined significance (AUS) (Bethesda category III) or follicular lesion of undetermined significance (FLUS) (Bethesda category IV) representing a diagnostic challenge. Commercial molecular genetic tests were developed to improve diagnostic accuracy of indeterminate thyroid nodules and to help minimize repeat FNAs and/or unnecessary diagnostic surgeries. There are presently several commercially available molecular genetic tests on the market that may be used in conjunction with FNA: *Afirma*® by Veracyte Inc., ThyroSeq® v2 by CBLPath Inc., and ThyGeNEXT® by Interpace Diagnostics Group Inc..

Afirma uses genomic sequencing classifier (GSC) to identify genomic profiles of indeterminate nodules which have been confirmed by surgical pathology as either benign or malignant. This system is designed to effectively recognize benign nodules and has a reported sensitivity of 83–100% and negative predictive value of 96%, making it a useful "rule-out test" [16, 17]. ThyGeNEXT utilizes next-generation sequencing (NGS) which tests for DNA mutation panel (e.g., *BRAF*, *RAS*, *TERT*,

TP53) and mRNA fusion transcripts and has demonstrated high specificity and positive predictive value, making it an effective "rule-in" test [16, 18, 19]. ThyroSeq v2 also uses NGS to evaluate specific point mutations, gene fusions, alterations, and expressions commonly found in thyroid cancer. It correctly identifies benign and malignant nodules by providing 94% sensitivity, 82% specificity, and 97% negative predictive value, providing both a valuable "rule-out" and "rule-in" test [20].

It is worth mentioning that the clinical utility of these tests is limited in nodules greater than 4 cm, due to high rate of false-negative results. Overall, molecular testing of AUS/FLUS nodules has advanced risk stratification of indeterminate nodules and has helped in distinguishing patients who would benefit from surgical resection versus those who could be managed conservatively. These tests have helped guide our decisions regarding PTC management, but their results should be interpreted with caution and on a case-by-case basis using clinical judgment and evaluation of malignancy risk.

Surgical Considerations in Papillary Thyroid Cancer

The revised 2015 ATA practice guidelines for the management and treatment of adult patients with DTC differ from the previously published 2009 ATA guidelines. Current guidelines are focused on patient preference and emphasize the importance of patient-centered decision-making. Initial surgical option for patients with a tumor size of >1 cm is near-total or total thyroidectomy, as was performed in our patient. Thyroid lobectomy should be reserved for patients with low-risk disease, micropapillary carcinoma, unifocality, absence of lymph node metastases, and no personal history of prior head and neck radiation or familial thyroid carcinoma. All patients with FNA-proven DTC should be staged pre-operatively and undergo a neck ultrasound with lymph node mapping to further evaluate the contralateral lobe and lymph nodes for the presence of disease [10]. Surgery should ideally be performed by an experienced surgeon performing a high volume number of thyroid surgeries to minimize post-operative complications such as hypoparathyroidism and/or vocal cord dysfunction. Performing prophylactic lymph node dissection at the time of thyroidectomy remains controversial, and surgical expertise is warranted. Postoperatively, serum Tg and Tg Ab should be monitored serially in all patients.

Utility of Radioactive Iodine Ablation

The 2015 ATA guidelines outline the initial dose of radioactive iodine 131 (^{131}I) after total thyroidectomy to be utilized primarily for one of three reasons: (1) remnant ablation (to destroy residual (presumptively) benign thyroid tissue), (2) adjuvant therapy (to decrease recurrence risk and mortality by destroying suspected but unproven metastatic disease), or (3) radioactive iodine therapy (for treatment of

persistent or recurrent disease in high-risk patients). ^{131}I treatment after total thyroidectomy is the mainstay of management for patients with intermediate- and high-risk disease (evidence of distant metastases, extrathyroidal extension, tumor size >4 cm). For low-risk patients (unifocal or multifocal papillary microcarcinoma <1 cm without high-risk features), the use of remnant ablation is not routinely recommended [10]. In intermediate-risk patients, postsurgical ^{131}I treatment has shown to improve overall survival in those with aggressive PTC histology, lymph node metastases, tumor >4 cm, or microscopic extrathyroidal invasion particularly in patients aged ≥ 45 years [10]. However, some studies have shown controversial results regarding the utility of postsurgical ^{131}I treatment on disease recurrence [21]. Additional studies are needed to determine the efficacy of ^{131}I treatment in intermediate-risk patients.

Radioactive iodine (RAI) administration requires either exogenous TSH stimulation via injection of recombinant human TSH (rhTSH) (Thyrogen®) or withdrawal of thyroid hormone to provoke endogenous rise in TSH. Studies have shown equal efficacy and safety using both methods [22]. Additionally, both methods were found to provide comparable benefit pertaining to progression-free survival and disease-related mortality in patients with metastatic DTC [22]. Conversely, RAI treatment using rhTSH may be more advantageous as it is associated with fewer clinical side effects of hypothyroidism and shorter stimulation of residual tumor as compared to TSH withdrawal method which requires 3–6 weeks of TSH withdrawal. rhTSH is approved by the Food and Drug Administration (FDA) for remnant ablation but not for use in metastatic DTC.

When using TSH stimulation or withdrawal, serum TSH >30 mIU/L is required and is associated with an increased RAI uptake in tumors, although this precise cutoff value has not been studied rigorously. However, regardless of preparation method for RAI remnant ablation or treatment, a low iodine diet (<50 ug iodine/day) should be consumed 7–10 days before and during ablation or treatment and maintained for 1–2 days after ^{131}I therapy [10]. Checking urine iodine level several days prior to the radioactive iodine scan is important, since excessive total body iodine measured via urinary iodine excretion often results in ablation failure, and this is particularly valuable in regions with high iodine consumption [23].

Indeed, there may be considerable iodine in many foods, such as dairy products, substances made using iodinated flour, seafood, kelp, and sea salt. Amiodarone contains about 37% inorganic iodine by weight and has a half-life of approximately 26–107 days when used chronically, intravenous (IV) radiocontrast agents also contain very high levels of iodine that persist for at least several weeks after administration, and both would preclude the use of RAI as long as the urine iodine concentration is elevated. Thus, it is imperative for clinicians to inquire about history of high-dose iodine exposure when determining the scheduling time of RAI imaging or therapy. Conversely, at times the dietary habits of a patient, as well as previous recent exposure to iodinated IV contrast, may not always be apparent; therefore we recommend routinely measuring a spot urine iodine several days before administering RAI. Although the exact cutoff value has not been determined rigorously, we recommend that a urine iodine value of less than about 150–200 μg/L be used before proceeding with RAI scans and treatment. It should be noted that levothyroxine

contains about 65% iodine which is maintained during radioactive iodine scan and treatment when rhTSH is utilized.

The 2015 ATA guidelines suggest using a low-dose (30–100 mCi) ^{131}I after total thyroidectomy for remnant ablation in selected low- and intermediate-risk patients who have low-risk disease. There has been uncertainty over the effective ^{131}I ablative dose in the past. Recent studies have demonstrated that remnant ablation with 30 mCi of RAI is as effective and associated with fewer adverse outcomes (e.g., sialadenitis and xerostomia) than using 100 mCi in low-risk patients [24].

The ATA guidelines also recommend using a dose of 75–150 mCi for adjuvant RAI treatment post-thyroidectomy in those with residual microscopic disease or aggressive tumor histology (e.g., tall cell, columnar cell carcinoma, insular).

As per the 2015 ATA guidelines, there are several approaches to RAI treatment of patients with loco-regional or metastatic disease: fixed high-dose empiric RAI administration using 100–200 mCi of ^{131}I, RAI therapy based on upper limit of blood and body dosimetry, and quantitative tumor or lesional dosimetry. However, the guidelines do not provide recommendations regarding superiority of one method of RAI treatment over another.

Dosimetric-based ^{131}I treatment of DTC was initially introduced in the 1960s. Since that time, it has been successfully used in treatment of DTC patients. Dosimetric approach utilizes radioactive iodine isotope 131 and is based on the notion of delivering the highest possible radiation dose which would not cause whole-body retention at 48 hours to result in permanent bone marrow suppression. This allows calculation of maximum tolerable activity or maximum safe dose, enabling doses as high as 630 mCi (200 Rad) to be safely administered. It is generally known that the first RAI treatment has the highest therapeutic effect as DTC is a slow-growing tumor, and therefore lower RAI doses may enable sufficient time for proliferation of the remaining residual thyroid cancer tissue. This is the reason that dosimetric-based ^{131}I treatment is preferred in patients with distant metastases (especially pulmonary metastases) and renal insufficiency and elderly (>70 years of age) [10].

Two to eight days after RAI remnant ablation or treatment, a post-therapy WBS (in conjunction with or without Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)) is recommended to establish RAI avidity of any structural disease and to determine staging. In high-risk DTC patients with elevated Tg levels (>10 ng/mL) and negative RAI imaging, ^{18}Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (^{18}FDG-PET/CT) scan is recommended as it confers higher sensitivity. The metastatic lesions/foci which show uptake or increase activity on ^{18}FDG-PET will not respond to RAI ablation and will likely need to be surgically removed or treated using targeted therapies such as Tyrosine Kinase Inhibitors.

In regard to our case, the patient has metastatic disease to the lymph nodes and therefore received dosimetry-based RAI therapy with 150 mCi of I-131.

Use of RAI in treatment of DTC is a common practice, but it has also been linked to increase risk of development of second primary malignancies in thyroid cancer survivors. The most common secondary malignancies include cancer of salivary glands, stomach, breast, leukemia, and lymphoma [25]. However, the risk for these cancers is relatively low in absolute terms and also remains controversial.

Hormone Suppressive Therapy and Long-Term Follow-Up

Typically, after initial therapy for PTC, patients are started on exogenous oral levothyroxine (LT_4) with a goal to suppress serum thyrotropin (TSH). Suppressing TSH with supraphysiologic doses of LT_4 has been shown to decrease the risk of recurrence and helps decrease the likelihood of major adverse events relating to progression of the cancer particularly in high-risk patients.

The 2015 ATA practice guidelines recommend a suppressed TSH <0.1 mU/L in high-risk patients and TSH of 0.1–0.5 mU/L in intermediate-risk patients. Furthermore, they suggest maintaining a TSH of 0.1–0.5 mU/L in low-risk patients with low detectable serum Tg levels and TSH goal of 0.5–2 mU/L in low-risk patients who have undergone lobectomy with undetectable serum Tg levels [10].

Clinicians should carefully evaluate the adverse effects of TSH suppression such as iatrogenic thyrotoxicosis, increased risk of cardiovascular adverse events particularly in elderly, and increased risk of osteoporosis in postmenopausal women. In one cross-sectional study, the rate of atrial fibrillation in PTC patients over the age 60 on TSH suppressive therapy was 17.5% [26]. In a longitudinal study of the Framingham cohort, the risk of developing atrial fibrillation was increased approximately three fold (in patients taking exogenous thyroid hormone or who had endogenous hyperthyroidism) if serum TSH was less than 0.1 mU/L as compared to a population that had normal serum TSH values [27]. Additionally, women >50 years of age with PTC on TSH suppressive therapy may have a significant decrease in their bone mineral density (BMD) 1-year post-thyroidectomy [28]. Thus, the risk of thyroid cancer recurrence should be balanced against the risks of atrial fibrillation and bone loss.

Current 2015 ATA guidelines endorse utilization of four response categories: excellent, biochemical incomplete, structural incomplete, and indeterminate to determine therapeutic response in patients who have undergone total thyroidectomy and RAI remnant ablation, adjuvant or therapeutic treatment based on imaging and Tg/Tg antibodies to help guide long-term disease surveillance and treatment strategies.

The 2015 ATA guidelines suggest that in the absence of contraindications, those patients with persistent disease (structural incomplete response) should maintain a TSH below 0.1 mU/L. Patients with biochemical incomplete response or those who initially presented with high-risk disease but have excellent or indeterminate therapeutic response should aim to keep their TSH between 0.1 and 0.5 mU/L for at least 5–10 years. Lastly, low-risk patients or those free of disease with excellent or indeterminate response to therapy can have TSH levels in the low normal range (0.5–2 mU/L) [10]. Two to three months after definitive treatment, thyroid function tests (TFTs) should be checked to determine the adequacy of TSH suppressive therapy. These general comments regarding suppressive therapy may vary in select patient groups (i.e., elderly, children and adolescents, pregnant women).

Follow-up at 6 months should ascertain disease status of the patient by performing a physical exam, neck ultrasound and baseline (and in some cases TSH-stimulated) Tg and Tg Ab measurement. Tg is only produced within the thyroid gland and is recognized as an excellent biomarker for the presence of residual or recurrent disease in patients

who do not have Tg antibodies. A diagnostic WBS is not necessary in all patients, especially those with negative neck ultrasounds and undetectable basal Tg with absence of Tg Ab. It should, however, generally be performed in high- and intermediate-risk patients, usually at 1-year post ^{131}I treatment. ATA recommends against performing TSH-stimulated Tg testing in low- and intermediate-risk patients with excellent response to therapy, but annual TFTs, Tg, and neck ultrasounds should be performed. In the subset of patients with detectable Tg, if this value increases, then imaging techniques for localization of disease should be pursued [10]. It is controversial whether performing serial rhTSH stimulated Tg levels that increase over time helps to detect progressive or recurrent disease. One study estimated the chance of a detectable stimulated serum Tg level after having an undetectable stimulated Tg to about 3% [29].

Serum Tg and Tg Abs for patients with DTC should ideally be measured using the same laboratory and the same standardized assays over time to minimize variability in measured values, although this is difficult using commercial laboratories. One of the major pitfalls in using serum Tg as a tumor marker is that Tg measured by methods such as immunometric assays (IMA) or radioimmunoassays (RIA) is subject to interference with Tg autoantibodies which are found in 20–25% of thyroid cancer patients [30]. These assays have thus proven to be unreliable, often resulting in falsely low serum Tg levels when IMA is used and either a falsely low or high Tg levels when RIA is utilized [30]. These variations in Tg levels pose a clinical challenge due to the uncertainty which is brought forth regarding the patient's disease status. In intermediate- or high-risk patients who have elevated Tg antibodies, the periodic use of chest CT or RAI scans is reasonable to identify possible recurrent or persistent disease.

Newer methods have become available which measure Tg via liquid chromatography-tandem mass spectrometry-based assay (LC/MS) that may minimize the autoantibody interference and therefore allow a more accurate quantification of Tg levels in patients with anti-Tg Ab [31]. However, LC/MS has been shown to have low sensitivity for detecting structural disease in those with anti-Tg Abs [30]. Additional clinical studies using this assay are required to assess its clinical utility.

The patient outlined in the case above has had an increase in his stimulated Tg level at 1 year. He will, therefore, need to remain on TSH suppression with TSH goal of 0.1–0.5 mU/L and have a physical exam, repeat TFTs, a neck ultrasound, perhaps TSH-stimulated Tg, and another WBS or chest CT the following year to screen him for local recurrence. Given these findings, the likelihood that he will have detectable neck recurrences requiring surgery or repeat ^{131}I therapy can be quite high. Therefore, it is imperative that this patient receives close surveillance moving forward.

Therapeutic Options in Patients with Iodine Refractory Metastatic Disease

Remission after ^{131}I treatment is achieved only in one third of patients with metastatic DTC [32]. Selected patients with metastatic disease may have ^{131}I refractory disease; other patients may have no ^{131}I avid lesions on repeat imaging or have

metastatic DTC that progresses despite repeat ^{131}I therapy, TSH suppressive therapy, local surgical resection, or focal treatment with external beam radiation. These patients may benefit from novel systemic therapeutic options depending on their age, performance status, extent of their metastatic disease, and prognosis. Systemic therapies for refractory DTC include tyrosine kinase inhibitors (TKIs) which inhibit kinase activity in the last step of the mitogen-activated protein kinase pathway. The FDA-approved TKIs for the treatment of DTC include lenvatinib and sorafenib. These agents have shown to delay disease progression in clinical trials [33–35]. Although these drugs have demonstrated efficacy in treatment of refractory metastatic DTC, they are not without side effects which could include hepatotoxicity, renal toxicity, gastrointestinal toxicity, increased levothyroxine dose requirement, dermatological, neurological, and cardiovascular adverse events to name a few. As a result, the importance of patient-centered decision-making should once again be emphasized as the value of these therapies on overall survival and quality of life remains unknown. Further, these agents should be used by healthcare providers experienced with their use and side effect profile. Patients taking lenvatinib can have cardiovascular events including new or worsening hypertension and QT/QTc prolongation requiring regular blood pressure monitoring as well as baseline and periodic electro- and echocardiograms. Moreover, serious thromboembolic and hemorrhagic events have been reported requiring routine CBC and, in cases of brain metastases, head imaging. Regular physical and neurological exams are needed for early diagnosis of palmar-plantar erythrodysesthesia and reversible posterior leukoencephalopathy syndrome which are unique side effects of lenvatinib [36]. Patients receiving sorafenib are also at risk of developing hypertension and QT prolongation in addition to cardiac infarction or ischemia and require routine monitoring of blood pressure and cardiac function similar to lenvatinib. Patients on sorafenib should also be closely observed for life-threatening bleeding and development of hand-foot skin reaction. Both agents can cause fatigue, bleeding, nausea/vomiting/diarrhea, as well as hepato- and renal toxicity requiring routine measurements of CBC, CMP, and urinalysis [37].

Somatic mutation analysis of the original thyroidectomy cancer sample or of a metastatic lesion could be performed to identify oncogenic activities (e.g., *BRAF*, *RET*, or *TRK*) that would enable targeted therapies. However, these tests are costly and may not be covered by insurance companies, therefore limiting their use. Various clinical trials are available and may be appropriate on a case-by-case basis for patients with RAI refractory metastatic DTC who have failed FDA-approved TKIs and are considered to have disease progression based on response evaluation criteria in solid tumors (RECIST).

There are other systemic therapies currently under investigation which provide a promising future in patients with progressive metastatic RAI refractory DTC.

Questions

1. A 51-year-old female was recently diagnosed with PTC. She was found to have a 2.5 cm focus of PTC in the left lobe of her thyroid with metastasis to her level VI lymph nodes, but no evidence of distant metastases.

   What stage is she?

(a) Stage I
(b) Stage II
(c) Stage III
(d) Stage IV

2. What is the goal TSH for the patient described in the case above?

(a) <0.1 mU/L
(b) 0.1–0.5 mU/L
(c) 0.5–2.0 mU/L

3. The presence of antithyroglobulin antibodies increases the accuracy for thyroglobulin antibodies. True or false?

(a) True
(b) False

4. Which of the following characteristics seen in a nodule on neck ultrasound is *not* suspicious for malignancy?

(a) Microcalcifications
(b) Irregular margins
(c) Spongiform appearance
(d) Central vascularity

5. What is the most common molecular marker found in PTC?

(a) *RET*
(b) *Ras* genes
(c) *NTRK1*
(d) *BRAF*

6. What is the most commonly used systemic therapy for patients with RAI refractory metastatic thyroid cancer?

(a) Tyrosine kinase inhibitors
(b) VEGFR inhibitors
(c) Clinical trials
(d) Chemotherapy

Answers to Questions

1. (a)
2. (b)
3. (b)
4. (c)
5. (d)
6. (a)

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Chapter 15
Anaplastic Thyroid Carcinoma

Ayesha Munir and Irina G. Veytsman

Objectives

1. To review the pathogenesis and epidemiology of anaplastic thyroid carcinoma.
2. To review assessment modalities and staging system for workup and evaluation.
3. To review treatment modalities for this rare cancer and recent advancements.

Case Presentation

A 71-year-old white female with history of atrial fibrillation taking amiodarone has developed an upper respiratory illness. Chest X-ray in 2019 demonstrated a 2.4 cm nodule in the left upper lobe of the lung. CT scan of the chest and neck demonstrated multiple lesions in the lung, thyroid mass, and cervical Lymphadenopathy. Representative nodules included a 2.0 × 1.6 cm nodule along the left major fissure; a 1.5 × 1.3 cm lingular nodule; a 1.6 × 1.4 cm left basilar nodule; a 1.2 × 0.9 cm lower lobe nodule; large, complex, heterogeneously enhancing mass predominantly involving the right lobe of the thyroid measuring approximately 4.7 × 4.2 × 5.1 cm with inferior extension into the superior mediastinum; and a 1.6 × 1.6 cm necrotic right level III lymph node of the neck.

Simultaneously, a neck ultrasound done revealed right neck lymphadenopathy. Largest node was 3.2 cm. An FNA (fine-needle aspiration) of the neck mass showed metastatic carcinoma with squamous features and keratin, while an FNA of the

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thyroid nodule showed papillary carcinoma. Lung nodule biopsy showed metastatic papillary carcinoma most likely from the thyroid. PET (FDG)/CT revealed right thyroid nodule 5 cm (SUV 15), multiple right cervical and mediastinal nodal metastases (SUV 7, 2.3 cm), and bilateral lung metastasis (maximum SUV 14.42 and size 1.4 cm). She was asymptomatic throughout the course of evaluation and underwent total thyroidectomy and bilateral neck lymph node dissection.

Thyroid pathology was consistent with thyroid carcinoma with mixed papillary and anaplastic (squamoid) carcinoma features. Background showed diffuse chronic lymphocytic thyroiditis. Anaplastic carcinoma component was reported to be invading into skeletal muscle with perineural invasion and extending to inked anterior margin. Three of four perithyroidal lymph nodes were positive for metastatic carcinoma.

The thyroid gland showed invasive carcinoma with two different morphologies, papillary and squamoid anaplastic component. Immunostains showed that both components were positive for AE1/AE3 and CAM5.2. The squamoid component was also positive for CK5/6 and P63 and negative for TTF-1 and thyroglobulin. The papillary component was positive for TTF-1 and thyroglobulin and negative for AE1/AE3 and CAM 5.2. Metastatic carcinoma in lymph node also showed both components. Although a collision tumor cannot be entirely excluded, anaplastic transformation of papillary carcinoma was favored; BRAF V600 mutation was also detected on the thyroid pathology specimen.

Patient was diagnosed with BRAF mutant positive aggressive anaplastic thyroid carcinoma metastatic to lung with positive margin and invasion into the skeletal muscle with perineural invasion.

Patient underwent concurrent chemo-radiation with carboplatin, Taxol weekly, and external radiation at a dose of approximately 60–72 Gy in 30–33 fractions using RapidArc to the neck due to positive margins. Repeat CT scan done June 2020 showed stable but persistent bilateral innumerable pulmonary nodules. Right supraclavicular mass/nodule was still persistent which corresponded to a hypermetabolic lesion on prior PET-CT (SUV 15.74). This was concerning for a residual tumor versus metastatic lymphadenopathy. Based on the repeat radiological imaging findings and clinical context, the patient was started on AntiBRAF therapy on June 22, 2020 – dabrafenib 150 mg BID and trametinib 2 mg daily. Due to nausea, loss of appetite, and febrile neutropenia requiring hospitalization, her dose of dabrafenib was decreased to 75mgBID and trametinib to 1 mg daily on July 2, 2020, and eventually discontinued toward end of July 2020 due to persistent fatigue and fever up to 104 F.

Patient was then followed by an interval PET/CT scan in August 2020 that showed numerous metabolically active bilateral pulmonary metastases. When compared to the prior PET/CT dated February 25, 2020, the nodules had decreased in size but continued to demonstrate significant hypermetabolic activity (max SUV 11). Patient was then started on vemurafenib 960 mg BID in August 2020. Patient, unfortunately, developed side effects to the regular dose for which it had to be held for a while (severe fatigue, anorexia development, and worsening of rash on face and body). It was then restarted at a reduced dose of 480 mg BID. Patient is

currently maintained on this dose of vemurafenib (last clinic visit December 2, 2020) with stable CT neck and chest findings at the time of this chapter writing (January 11, 2021).

Introduction

In the last three decades, there has been a marked rise in the incidence of thyroid cancers [1, 2]. The rising incidence rates are thought to be mostly due to differentiated thyroid cancer, e.g., papillary thyroid cancer. The incidence rate for anaplastic thyroid cancer has remained relatively stable [3]. The majority of the thyroid cancers (95%) arise from follicular epithelial cells, while medullary thyroid cancers arise from thyroid C-cells. Anaplastic thyroid cancer (ATC) is an undifferentiated cancer arising from thyroid follicular cells [4].

Among the thyroid cancer types, ATC is the most aggressive variant while being the rarest [5]. It has an invasive nature, and due to high proliferative index, the mortality related to ATC is estimated to be approximately 69.4% at 6 months and 80.7% at 12 months [6].

It is generally resistant to conventional chemotherapy and radioactive iodine treatment.

Methods

We used search engines (i.e., EMBASE and Medline) using the keywords as mentioned above. Based on two independent reviewers' abstract selection, we chose 187 articles of which 83 full text articles were retrieved for the review of this chapter.

Pathogenesis

Poorly differentiated thyroid carcinoma (PDTC) has been associated with necrosis and high mitotic index which is consistent with its aggressive nature of the disease. The Turin criteria distinguishes PDTC from other thyroid cancer subtypes including ATC (Table 15.1) [7]. The Turin-PDTC criteria is based on the following: (i) solid/trabecular/insular pattern of growth, (ii) absence of conventional nuclear features of papillary carcinoma, and (iii) at least one of the following features: convoluted nuclei, mitotic activity $\geq$3/10 high-power microscopic fields (HPF), and tumor necrosis [8]. PDTC and ATC also have variations in their mutational landscape that is very important for treatment approach (Table 15.1) [7].

ATC accounts for less than 1% of thyroid cancers and is predominately found in elderly patients with a mean age at diagnosis of 71 years [9]. ATC also appears to

Table 15.1 Characteristics of PDTC vs ATC

Disease characteristics	Poorly differentiated thyroid carcinoma	Anaplastic thyroid carcinoma
Proportion among all thyroid cancers	0.5–7%	<1%
Mean age of diagnosis	60 years	71 years
Immunostains	Positive: CK7, CK18, CK19, TTF-1, thyroglobulin, Ki-67, cyclin D1, IMP3 Negative: Calcitonin, chromogranin, CEA, synaptophysin	Positives: CK7, CK18, CK19, CK10/13, Ki-67, p53, vimentin, cyclin D1, EMA Negative: Calcitonin, chromogranin, TTF-1, RET/PTC oncoprotein, synaptophysin, thyroglobulin
Histology	Follicular cell origin A solid/trabecular /insular pattern of growth Presence of at least one of the following: convoluted nuclei, mitotic activity (>3 × 10HPF) or necrosis	Follicular cell origin Three patterns 1. Spindle cell resembling sarcoma 2.Large giant pleomorphic cells resembling osteoclasts 3.Squamoid pattern
Signaling pathways	MAPK, P13k-Akt, P13k-Akt/mTOR/inactivation, WNT-beta-catenin, TSHR, p53	NOTCH, NFkB, MAPK, P13k-Akt, P13k-Akt/mTOR/inactivation, WNT-beta-catenin, TSHR, p53, IDH-1
Gene alterations	BRAF, RAS, TP53, CTNNB1, PIK3CA, PTEN, AKT1, TERT, TSHR, ALK, STRN	BRAF, RAS, TP53, CTNNB1, PIK3CA, PTEN, AKT1, TERT, TSHR, ALK, mTOR, NF1, NF2, MLH1, MLH3, MSH5, MSH6 ERBB2, RET-PTC, IDH1, RTK, USH2A

have a female preponderance. On gross examination, ATCs are typically large, necrotic tumors that exhibit widespread hemorrhagic changes [10]. The morphology consists of the unique combination of spindle, giant, and squamoid cells [10]. Squamous cell carcinoma can be misdiagnosed, and CK5/6 and CK63 can be used to distinguish it from thyroid anaplastic cancer; it is usually also negative for PAX8. ATC shows high mitotic rates and atypical mitoses. On immunohistochemical analysis, the majority of ATCs are negative for TTF1 and thyroglobulin [10].

Staging and Evaluation

ATC is diagnosed by FNA or pathological tissue examination. If a thyroid FNA is suspicious for diagnosis, one should consider obtaining a core or open biopsy. Morphological examination along with IHC (immunohistochemistry) is needed in order to diagnosis ATC. Molecular testing should include analysis for oncogenes to include BRAF, NTRK, ALK, RET, BCR-ABL, PDL-1, and tumor mutation burden.

Preoperative evaluation for ATC includes CBC; CMP; TSH; neck ultrasound; CT with contrast of the neck, head, chest, abdomen, and pelvis; and PET (FDG)-CT. Vocal cord assessment is also recommended. Due to the rapid doubling time of this tumor, preoperative evaluation should be completed quickly, and the patient should be referred to a center with multidisciplinary approach for this cancer. MD Anderson came up with a FAST (Facilitating Anaplastic Thyroid Cancer Specialized Treatment) algorithm to decrease the time from referral to disposition for these patients. The FAST team is dedicated to confirming the diagnosis of this cancer promptly and coming up with a treatment plan within 7 days, which provided a rapid access to care, mutation testing, and personalized treatment.

As per their study, historical data revealed a mean referral to disposition time for patients with ATC of 8.7 days. After the implementation of FAST, the mean referral to disposition time was reduced to 0.5 days [11]. It's imperative that all major institutions come up with such algorithm to speed up the diagnostic and treatment plan for this highly aggressive carcinoma.

Staging of ATC has been established through AJCC (American Joint Committee on Cancer) Cancer Staging Manual eight edition.

NCCN (National Comprehensive Cancer Network) guidelines provide a comprehensive treatment approach for ATC based on its stages.

Treatment and Recent Therapeutic Advances

Although rare, anaplastic thyroid cancer is the most lethal of all the thyroid cancers. The median survival for this type of cancer is estimated to be 3–10 months [12]. There frequently is rapid tumor growth, invading vital neurovascular and tracheal structures within the confined neck space. Unfortunately, despite the treatment options available, the prognosis remains poor. However, there have been recent advances in treatment.

Surgery

Many patients present with extensive disease at initial diagnosis with inoperable disease; in selected cases these patients may be offered palliative surgery. It is important to evaluate and treat these patients extremely expeditiously. If delayed or in advanced disease, palliative surgery for airway protection may be the best option [13].

As noted, MD Anderson Cancer Center has developed a protocol to evaluate these patients expeditiously based on rapid determination of BRAF mutations.

There however might be few cases where surgery might impact the outcomes. A retrospective study from Memorial Sloan Kettering cancer center [14] showed that median survival for these patients was 8 months. The group of patients without

surgery only survived 2 months. Absence of residual disease post-surgery was associated with the best outcome; age < 60 years, lack of nodal neck involvement, absence of extra-thyroidal extension, and multimodality treatment modalities were associated with better outcomes.

Chemotherapy

Systemic therapy as a single agent modality can be used for unresectable or metastatic disease. Single agent doxorubicin is the only agent approved by FDA for ATC [15]. Hyper-fractionated EBRT (external beam radiation therapy) combined with radio-sensitizing doses of doxorubicin may increase the response rate by 80% with a median survival of 1 year [16]. Paclitaxel targets tubulin and has been used for treatment of ATC. Onoda et al. [17] demonstrated that the median overall survival was 6.7 months, and 6 months survival rate was 54% for patients treated with weekly paclitaxel. None of the patients reached complete remission, and progressive disease was seen in 19% of the studied patients. A retrospective analysis showed that combination of external radiation therapy and concomitant docetaxel is effective in ATC. After a median follow-up of 21.5 months, five of the analyzed patients were alive [18].

A Japanese study published in 1995 showed a combined chemo modality treatment for ATC. The regimen included cisplatin, doxorubicin, etoposide, and peplomycin with support of granulocyte colony-stimulating factor (GCSF) [19]. This was a pilot study with 17 study subjects involved with a median age of 66 years. The combination chemotherapy was given to them once every 3 weeks. The overall poor outcome of the study (none of the patients survived beyond 11 months) along with severe toxicity made it a non-attractive approach. This can also be generalized to the current treatment guidelines.

External Radiation

External radiation therapy is another treatment modality that has been considered in the management of ATC. Kwon et al. performed a meta-analysis with [20] 17 retrospective studies including 1147 patients. Post-operative radiation therapy significantly decreased mortality in patients with resected ATC compared with those with surgery alone. However other studies also demonstrated that significant radiotoxicity and the small benefit gained from radiotherapy alone render this an unsuitable single-agent treatment modality for the treatment of ATC [21].

Combination chemo-radiation therapy (CRT), preferably following neck surgery, is another treatment modality that has been evaluated for ATC treatment. This multimodality therapy was associated with longer survival [22]. In the Memorial Sloan-Kettering study, the absence of clinical extrathyroidal extension, use of

multimodality therapy, and gross total resection were predictors of improved outcome. Patients treated with multimodality therapy were three times less likely to die from ATC [23]; chemo-sensitizing radiation therapy prolonged survival.

Tyrosine Kinase Inhibitors

Sorafenib was the first oral multi-kinase inhibitor that targets Raf kinase (Raf-1, wild-type B-Raf, and BRAF V600E) mutations. It also targets receptor tyrosine kinases associated with angiogenesis such as vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, platelet-derived growth factor receptor (PDGFR)-β, and receptor tyrosine kinases associated with tumor progression (Flt-3, c-kit). Initially it was approved for treatment of radioiodine-resistant metastatic papillary thyroid carcinoma. Use of sorafenib was investigated in ATC patients in a phase 2 study [24]. Sorafenib at 400 mg twice a day achieved partial response in two patients and disease stabilization in five patients. Median progression-free and overall survival was 1.9 months and 3.9 months, respectively. The 6-month and 1-year survival rates were 30% and 20%, respectively. The most common side effects were anemia and hyponatremia.

Pazopanib is another oral tyrosine kinase inhibitor that inhibits VEGFR. Pazopanib showed good activity in progressive metastatic differentiated thyroid cancer (DTC), but in a phase 2 trial of advanced ATC, pazopanib monotherapy demonstrated minimal clinical benefit [25].

Lenvatinib is an oral inhibitor of platelet-derived growth factor receptor α, RET, and KIT; VEGFR 1, 2, and 3; and fibroblast growth factor receptors 1 through 4. A phase II study of 54 Japanese patients with advanced thyroid cancer receiving lenvatinib showed that patients tolerated lenvatinib treatment well because the side effects were manageable. Lenvatinib treatment showed promising antitumor effects for patients across all thyroid cancer subtypes tested in this trial, which also included ATC [26].

Recent Advances

In May 2018, the FDA approved the combination of dabrafenib plus trametinib for the treatment of ATC in patients who had BRAF mutation. Dabrafenib is an inhibitor of mutated forms of BRAF kinases (e.g., V600E, V600K, and V600). Dabrafenib also inhibits wild-type BRAF and CRAF kinases. A phase II study of both drugs showed that the overall response rate was 69% among 16 patients who enrolled in this study. All patients had unsuccessful prior therapy including surgery and/or radiation therapy or other systemic modalities of therapy [27]. A complete response was observed in 4% of patients and partial response in 57% for an overall response rate of 61%. All patients had a BRAF mutation. The response of 6 months duration lasted in 64% of the responders.

Table 15.2 Multikinase inhibitors and other mutations identified in ATC and their commercially available drugs

BRAF	VEGFR	RET	PDL1	MEK1/ MEK2	ALK
Dabrafenib	Apatinib	Vandetinib	Pembrolizumab	Trametinib	
Vemurafenib	Pazopanib	Sorafenib			
	Lenvatinib	Lenvatinib (also inhibits PDGFR, KIT, fibroblast growth factor receptors 1 through 4)			
	Sorafenib (also inhibits PDGFR,c-Kit,Flt-3)				
	Axitinib				

The dose used in these studies was dabrafenib 150 mg PO twice daily and trametinib 2 mg once daily. These studies are important as they showed that an oral combination regimen of two drugs can impact the course of disease for ATC. Although the change was modest, it nonetheless is considered important given the otherwise lethality of this disease. Left ventricular ejection fraction needs to be assessed before and monitored during therapy as a major side effect of dabrafenib is cardiomyopathy and congestive heart failure. Other major side effects include uveitis, hyperpyrexia, severe hyperglycemia, and serious skin toxicity. Trametinib is a reversible mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 inhibitor. BRAF V600E autonomously and constitutively activates BRAF pathway, which in turn induces activation of MEK1 and MEK2. The major side effects of trametinib are colitis and gastrointestinal perforation, deep vein thrombosis, retinal vein thrombosis, and left ventricular dysfunction with cardiomyopathy [13]. Most patients also have skin issue (e.g., acne) while taking trametinib.

Vemurafenib is an inhibitor of the BRAF serine threonine kinase. It has been successful in treating melanoma patients with a BRAF mutation. Melanoma patients with this mutation treated with vemurafenib had a 63% reduction in mortality [28]. A patient was treated with vemurafenib, following failure of standard chemotherapy, and went into remission after 38 days [29]. Table 15.2 summarizes all the potential targetable mutations studied for ATC and the drugs developed for them.

Single-Agent Pembrolizumab in Anaplastic Thyroid Carcinoma

A case study demonstrated a rapid and dramatic response to pembrolizumab used as a single first-line agent, in a 75-year-old patient with poor performance status [30].

A phase 2 trial of pembrolizumab, 200 mg intravenously (IV) every 3 weeks, combined with chemoradiotherapy (docetaxel/doxorubicin, 20 mg/m2 each IV weekly plus volumetric modulated arc therapy), was initiated as frontline therapy (with or without surgery) in ATC to assess efficacy and toxicity. Although initially

tolerated and effective in locoregional disease control, disappointing survival outcomes were observed compared with historical controls. As effective treatments for ATC are still limited, it is imperative to explore new therapies for this untreatable disease [31].

Non-conventional Therapies

A study done on seven patients with inoperable ATC showed that embolization of the superior and/or inferior thyroid arteries resulted in palliation in breathing, swallowing, and pain control in selected patients. Five patients felt improvement in their general condition [32].

Another case report demonstrated the use of 125I seed implantation combined with apatinib. The 125-I seed implantation and vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor apatinib were combined to treat a 49-year-old woman with anaplastic thyroid cancer. The tumor shrank successfully. After a follow-up of 13 months since the initial diagnosis of anaplastic thyroid cancer, the patient survived with a stable disease pathology [33].

Some preliminary data suggest that ALK inhibitors might play a role in papillary thyroid cancer who have ALK gene fusions. However, they are rarely reported in ATC [34].

Regardless of surgical intervention, all patients should be offered clinical trials given the dismal prognosis of this disease.

Conclusion

Anaplastic thyroid carcinoma (ATC) is an aggressive disease with very limited therapeutic options. There is an urgent need for new and efficacious drugs. Unfortunately, there are only a few ongoing clinical trials for this disease. The rarity of the disease, poor performance status of the patients at the time of diagnosis, and high lethality make it difficult to recruit patients for clinical trials. Nonetheless, it is imperative to explore new therapies for this untreatable disease.

Multiple-Choice Questions

1. A 77-year-old male with rapidly progressive neck mass with associated local discomfort and dysphagia. On exam, a bulky mass extended from the thyroid gland appreciated, as well as bilateral lympho adenopathy, left more the right. Biopsy of the mass reveals anaplastic thyroid cancer. PET/CT demonstrated some pulmonary nodules consistent with metastatic disease.

   Patient underwent tracheostomy for airway protection and PEG tube placement.

   A. Perform next-generation sequencing on tissue to identify different targetable mutations
   B. Proceed with surgery

C. Proceed with surgery follow-up by chemotherapy and radiation
D. Discuss hospice with patient considering poor prognosis and outcome

Correct answer is A.

2. A 77-year-old-male with rapidly progressive neck mass with associated local discomfort and dysphagia. On exam, a bulky mass extended from the thyroid gland appreciated, as well as bilateral lympho adenopathy, left more the right. Biopsy of the mass reveal anaplastic thyroid cancer. PET/CT demonstrated some pulmonary nodules consistent with metastatic disease.

   Patient underwent tracheostomy for airway protection and PEG tube placement. Next-generation sequencing on tissue was ordered.

   Results came back positive for BRAF V600E mutation.

   A. Start on anti-BRAF therapy dabrafenib and trametinib
   B. Start on chemotherapy and radiation
   C. Start on chemotherapy alone
   D. Discuss hospice with patient considering poor prognosis and outcome

   Correct answer is A.

3. A 47-year-old-male presents with increasing neck mass, US of the neck demonstrated 5 × 4 cm thyroid mass, no lymph nodes were found. Biopsy of the mass demonstrated anaplastic thyroid cancer.

   PET/CT scan was done and demonstrated no disease outside of the thyroid area.

   Your next step is

   A. Surgery
   B. Surgery follow-up by chemotherapy and radiation
   C. Chemotherapy and radiation
   D. Hospice referral due to poor prognosis
   E. Dabrafenib and trametinib treatment

   Correct answer is B.

4. A 65 year-old-female presented with rapidly progressing neck mass, US of the neck demonstrated large thyroid mass, and bilateral lymph nodes. PET/CT demonstrated no disease outside of the neck area. Patient underwent surgery, her pathology came back demonstrating positive margins.

   Patient completed chemotherapy with carboplatin and paclitaxel weekly with concurrent chemotherapy and radiation. In 3 months, her CT scan of the neck demonstrated progression of disease. Next-generation sequencing was performed and demonstrated no BRAF mutation, ALK, NTRK, or any other targetable mutations; her PDL1 was 90%.

   A. Start patient on the chemotherapy
   B. Start patient on vemurafenib
   C. Start patient on pembrolizumab
   D. Refer patient to hospice due to poor prognosis

   Correct answer is C.

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Chapter 16
Medullary Thyroid Carcinoma

Payal Paresh Patel Shooliz and Victor Bernet

Case Presentation

A 64-year-old non-smoking male with medullary thyroid carcinoma (MTC) is referred for increasing calcitonin levels. The clinical course of his MTC began when he presented with a palpable thyroid nodule. He underwent fine-needle aspiration (FNA) of the nodule which yielded cells consistent with MTC that prompted him to undergo total thyroidectomy and central neck lymph node dissection. The surgical pathology demonstrated medullary thyroid carcinoma in two foci. The largest tumor focus was 4.5 cm in the right thyroid lobe and a 0.6 cm focus in the isthmus. Extrathyroidal extension along with lymphovascular and perineural invasion was noted. All four harvested thyroidal lymph nodes were positive for MTC. Of note, electrolytes, parathyroid level, 24-hour urine catecholamine, and metanephrines were within the appropriate reference ranges. RET proto-oncogene sequencing was negative for any mutations.

After surgery, he was monitored with serial calcitonin and carcinoembryonic antigen (CEA) levels for several years (see Table 16.1). Eleven months after initial total thyroidectomy, because of rising calcitonin levels, the patient completed a 2-[fluorine-18]fluro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) scan which demonstrated a 1 cm FDG avid right supraclavicular lymph node and a 0.7 cm FDG avid right neck level 4 lymph node. FDG-PET demonstrated multiple low attenuation lesions thought to be cysts scattered throughout the liver with no corresponding FDG uptake with the largest being 4.5 cm. Given the FDG-PET imaging findings, FNA of the

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Table 16.1 The changes in tumor marker levels over time in this patient

Time in months from thyroidectomy	Calcitonin (ref, ≤ 1.4 pg/mL)	CEA (ref ≤ 3.0 ng/mL)	Calcitonin doubling time in months [1]	Important notes
0	332	9.3	–	Pre-thyroidectomy
2	30	1.9	–	Post-thyroidectomy
11	40	1.9	–	Pre-right neck dissection
14	46	2.4	–	Post-right neck dissection
21	108	1.9	11	
28	481	4.5	6.5	

right level 4 lymph node was performed and demonstrated MTC. At that time, the patient's serum calcitonin level was 40 pg/mL (reference range, ≤10 pg/mL). He subsequently underwent right lateral and central neck lymph node dissection. Pathology demonstrated MTC in 5 out of the 39 right-sided lymph nodes that were dissected, with the largest demonstrating extra-nodal extension. About 28 months after initial thyroidectomy and 16 months after the repeat neck dissection, he was referred for evaluation of a newly found significantly increased calcitonin level of 481 pg/mL (<=1.4 pg/mL) and CEA level of 4.5 ng/mL (<=3.0 ng/mL).

The patient subsequently underwent extensive imaging to locate possible distant metastatic disease as a cause for the elevated calcitonin and CEA levels. A neck ultrasound revealed four lymph nodes with the largest measuring 1.5 cm. Both magnetic resonance imaging (MRI) of the abdomen and Gallum-68 DOTATATE (^{68}Ga-DOTATATE) PET imaging were performed. ^{68}Ga-DOTATATE PET imaging demonstrated an increased uptake along the right paratracheal area consistent with a lymph node. In the liver there was heterogeneous tracer activity without discrete tracer activity in the areas of the previously noted liver cysts. There was indeterminate uptake in a lumbarvertebral body. Right cervical lymph node FNA demonstrated MTC. Patient underwent endoscopic ultrasound with biopsy of a liver lesion which resulted in the diagnosis of distant metastatic MTC. He was started on tyrosine kinase inhibitor therapy with vandetanib 300 mg daily and now continues to undergo serial surveillance testing.

Overview of Medullary Thyroid Carcinoma

Medullary thyroid carcinoma is a neuroendocrine cancer originating from the parafollicular C-cells of the thyroid [2, 3]. These parafollicular C-cells secrete multiple different endocrine signaling proteins such as calcitonin, CEA, chromogranin A, and somatostatin [3]. Medullary thyroid carcinoma is classified as a thyroid cancer because of its anatomical location; however, it is a neuroendocrine tumor as the parafollicular C-cells originate embryologically from neural crest cells [3].

Medullary thyroid carcinoma is exceedingly rare with an occurrence of 1–2% of all thyroid cancer cases [3]. Despite its rarity, the diagnosis and treatment of MTC are important as it accounts for 14% of thyroid cancer-related deaths [4]. Medullary thyroid carcinoma is sporadic in 75% of cases or familial in 25% of cases and associated with a germline mutation [3, 5–8]. Mutations in the RET proto-oncogene, which is a tyrosine kinase receptor pathway that directs cell proliferation, are present in about half of the sporadic cases and nearly all of the hereditary cases of MTC [3, 5, 7].

Hereditary MTC is associated with at least three well-described genetic syndromes associated with a germline RET mutation: multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial medullary thyroid carcinomas (FMTC). Due to this genetic association, all patients should be tested for a germline RET mutation upon diagnosis with MTC [8, 9]. It need be noted that not all germline mutations are detected with standard testing. Testing may only screen exons 10, 11, 13, 14, 15, and 16, but mutations have been reported in exons 5, 8, and 12. In cases where initial genetic testing is negative, whole RET gene sequencing can be obtained in an attempt to identify less common mutations. Those with a germline RET mutation should be screened for a pheochromocytoma and hyperparathyroidism in order to determine if the syndrome is present in the patient. MEN2A is associated with pheochromocytoma and primary hyperparathyroidism. MEN2B is associated with pheochromocytoma, marfanoid body habitus, and mucosal ganglioneuromas. Those with FMTC have an MTC associated with the germline RET mutation but without other characteristics of an MEN2 syndrome. Of the different syndromes associated with MTC, those with MEN2B have a more aggressive form of medullary thyroid carcinoma [3, 8, 10].

In both sporadic and hereditary cases, the presence of a RET proto-oncogene mutation is associated with a more aggressive disease [6, 9, 11, 12]. There are also other mutations in signaling pathways that promote tumor growth and cell proliferation in MTC such as HRAS, KRAS, and NRAS [3, 5, 6, 11]. The RAS genes encode the GTPase signaling pathways that drive cell proliferation and apoptosis [6]. Mutations in the RAS genes are associated with malignancies other than MTC including follicular thyroid cancer as well as pancreatic, large intestine, and urogenital cancers [6]. For MTC, RET mutations and RAS mutations have not been found simultaneously in the same tumor to date [11]. The presence of RAS mutations in MTC has been shown to be associated with a better prognosis [11]. Poor prognostic factors in MTC, aside from the presence of a RET mutation, include older age at the time of diagnosis, male sex, lymph node metastasis present on diagnosis, presence of tumor invasion into surrounding tissue, and the presence of distant metastatic disease [3, 6, 11, 13].

Metastatic Medullary Thyroid Carcinoma

Regional metastatic disease to the cervical lymph nodes is observed in about 50% of patients upon diagnosis with MTC, while distant metastatic disease can be found in 20% of cases [9]. The 10-year survival in patients with distant metastatic MTC is

about 40% as compared to 96% in those with disease confined to the thyroid [14]. In our patient, locally metastatic disease was found on initial presentation. It is important to be aware that patients with a palpable nodule that is positive for MTC have a 70% chance of having local metastatic MTC and 10% have distance metastatic disease [3, 8].

The primary treatment for MTC is surgical with total thyroidectomy with or without lymph node dissection, which is in turn a decision guided by neck imaging, initial calcitonin levels, and intraoperative findings [3, 15]. There is no role for hormonal suppression of the thyroid-stimulating hormone as with differentiated thyroid cancers. Since MTC is not iodine avid, there is also no role for radioactive iodine therapy [8, 16]. All patients, prior to thyroidectomy for MTC, must have pheochromocytoma ruled out. Prior to thyroidectomy, imaging of the neck with ultrasound is required along with baseline calcitonin and CEA levels. The parafollicular C-cells secrete calcitonin and CEA which serve as tumor markers for MTC. These tumor markers not only are critical for post-thyroidectomy surveillance but also guide the decision on how far to extend imaging that is recommended prior to proceeding with initial surgical resection [2]. Of note, prior to total thyroidectomy, men generally have a higher baseline calcitonin level because of their increased C-cell mass compared to women [3]. Patients with a baseline calcitonin level less than 500 pg/dL may proceed with thyroid surgery without additional imaging beyond the neck as they are unlikely to have distant metastatic disease [3, 15]. Those with a calcitonin level greater than 500 pg/dL prior to total thyroidectomy should undergo more extensive imaging to evaluate for evidence of distant metastases [3, 15, 17, 18].

Medullary thyroid carcinoma generally metastasizes to the liver, bones, lungs, and cervical lymph nodes [2, 3, 9]. Various imaging modalities have proven to be more sensitive for evaluating for metastatic disease in each of the different regions. In general, patients should be evaluated with computerized tomography (CT) of the neck and chest for mediastinal lymphadenopathy and pulmonary metastatic disease, bone scintigraphy and whole-body magnetic resonance imaging (MRI) for bone metastatic disease, and MRI of the abdomen or triple phase CT for liver metastases. MRI of the brain should be pursued if neurologic symptoms are present but is not recommended for initial screening. If all appropriate imaging is inconclusive, further imaging with FDG-PET or ^{68}Ga-DOTATATE PET scan should be pursued [3, 17].

How the Diagnosis Was Made

Role of Calcitonin and CEA Monitoring Post-Total Thyroidectomy

Metastatic medullary thyroid carcinoma can occur in patients after total thyroidectomy. Calcitonin and CEA are signaling proteins that are secreted by the parafollicular C-cells which serve as important tumor markers for MTC. While these tumor

markers are used for post-surgical surveillance monitoring, their doubling time also determines prognosis.

After total thyroidectomy, monitoring calcitonin and CEA levels are important in surveillance of patients as 3% of patients with biochemical cure experience a recurrence of MTC [3, 18, 19]. After total thyroidectomy with complete resection of disease, calcitonin levels should be undetectable in 3 months, which is the time needed to reach nadir level [3, 17]. After successful thyroidectomy, if there is an undetectable calcitonin level, it is consistent with a biochemical cure. These patients should be initially monitored every 3 months with CEA and calcitonin levels, physical exam, and neck US, with intervals subsequently extending to every 6 and then every 12 months if there were to be no recurrence of disease [3]. If calcitonin levels are detectable 3 months post-thyroidectomy, then residual disease is likely. If post-total thyroidectomy calcitonin levels are less than 150 pg/mL, then recurrence or residual disease is typically confined to the neck [3, 15, 17, 20]. In this instance, patients are monitored with neck ultrasound, physical exam, and tumor markers every 3 months initially and then every 6 months as long as there is no recurrence of disease. If post-total thyroidectomy calcitonin levels are ever greater than 150 pg/mL, then extensive imaging for distant metastatic disease should be pursued [3, 17].

CEA and calcitonin levels help assess tumor aggressiveness and the rate of growth and should be monitored simultaneously. While calcitonin is a late marker of differentiation in cell development, CEA is an early marker for cell development. If the medullary thyroid carcinoma is particularly aggressive, it may lose the ability to make calcitonin causing a decrease in calcitonin and an increase in CEA levels. Therefore, society guidelines recommend obtaining both markers while monitoring patients after thyroidectomy [3, 17]. An important caveat to remember is that CEA levels can be increased with smoking and non-thyroidal malignancies [3]. If a patient has a low-grade MTC with an increased CEA and decreased calcitonin levels, this warrants further evaluation for non-thyroidal malignancies such as a colonoscopy for gastrointestinal malignancies.

Calcitonin and CEA doubling times hold prognostic implications for patient outcomes. The doubling time is calculated by obtaining at least four calcitonin and CEA levels over a minimum of a 2-year span that have been performed on the same assay [3]. According to one study, patients with a calcitonin doubling time of less than 6 months exhibit a 5-year survival of 25% and 10-year survival of 8%. All those with a doubling time of greater than 24 months were alive at 10 years [21]. If the doubling time for CEA and calcitonin is discordant and only one of them reflects a less than 6-month doubling time, then the prognosis can be expected to be poor [3].

In our patient, the doubling time was 13 months. He underwent a right neck dissection in light of concerning imaging findings and consistently elevated calcitonin levels. Once his calcitonin levels became greater than 150 pg/dL, a concern arose for distant metastatic disease; therefore further evaluation was performed with integrated imaging modalities.

Evaluation for Metastatic Disease and Comparison of Imaging Modalities

Evaluation by imaging for distant metastatic medullary thyroid carcinoma has been particularly challenging as no single imaging modality is superior for assessing the whole body's various organ systems [2]. In other malignancies, FDG-PET is sensitive given their high metabolic activity and increased glucose consumption [2, 20, 22]. Medullary thyroid carcinoma, like most neuroendocrine malignancies, is less metabolically active and more indolent in nature; therefore, the sensitivity of FDG-PET is decreased when searching for distant metastatic disease leading to false negatives, as in the case of our patient [2, 23]. There are multiple different imaging modalities with varying levels of sensitivity in detecting metastatic MTC, and it is important to be familiar with their respective strengths and weaknesses.

For the evaluation of distant metastatic medullary thyroid carcinoma, recommended imaging consists of neck US and neck and chest CT for mediastinal disease. MRI of the liver and both MRI and bone scintigraphy(BS) of the bones are performed in the initial evaluation for metastatic MTC [3, 17]. If initial imaging with these modalities is inconclusive or negative, then there is a role for ^{68}Ga-DOTATATE imaging to evaluate for metastatic disease [17]. FDG-PET can also be used, but varying levels of sensitivity have been reported for this imaging modality [2, 3, 20].

One study evaluated 55 patients with elevated calcitonin levels with different imaging modalities to determine the most sensitive test for the detection of metastatic MTC. All patients underwent US of the neck and liver, CT of the neck, CT of chest and abdomen, MRI of the liver and whole body, bone scintigraphy, and finally FDG-PET. In this study, 82% of patients were found to have metastatic disease, all of whom had elevated calcitonin levels [20]. Neck recurrence was detected in 56% of all patients undergoing US, 42% with CT, and 32% with FDG-PET. Mediastinum lymph node recurrence was detected in 31% undergoing CT and 20% with FDG-PET. Lung metastatic disease was detected in 35% with CT and 15% with FDG-PET. Liver metastatic disease was detected in 41% undergoing US, 41% with CT, 49% with MRI, and 27% with FDG-PET. Bone metastatic disease was found in 40% with MRI, 40% with bone scintigraphy, and 35% with FDG-PET [3, 20]. Overall, FDG-PET identified metastatic disease in 58% of patients; however, these patients tended to have a heavier tumor burden, and their disease was more aggressive [2, 3, 10, 20]. The combination of BS + MRI for bone disease is the current standard because through combination of both imaging modalities, 94% of the metastatic bone lesions were detected [20].

This study did not take into account ^{68}GA-DOTATATE PET imaging which has varying levels of sensitivity in the literature [2, 22, 23]. ^{68}GA-DOTATATE scan uses a radiolabeled somatostatin analogue (Gallum-68) to target somatostatin receptors which in turn lead to detection on imaging. Somatostatin receptors are generally found in neuroendocrine tumors. Because medullary thyroid carcinoma is a neuroendocrine tumor, it can also be used as supplementary imaging [2, 17]. In one study,

in a comparison of 30 patients who underwent conventional imaging for metastatic MTC and ^{68}GA-DOTATATE PET, conventional imaging was superior in the detection of metastatic disease in all areas except the bones. ^{68}GA-DOTATATE PET scan proved to be more sensitive than BS; therefore, it proposed to be used in conjunction with whole-body MRI for the evaluation of metastatic bone disease [2]. While^{68}GA-DOTATATE PET scan does have a role in the evaluation for metastatic MTC, it does not have the sensitivity to be used as the single imaging modality in comparison to FDG-PET as is the case with other malignancies [5, 17, 22].

Consensus guidelines currently recommend imaging with US of the neck, CT of the neck and chest, MRI of the abdomen and bones, and BS. If not identified on the those images, there is a recommendation to further evaluate with ^{68}GA-DOTATATE scan or FDG-PET [2]. In our patient's case, the MRI of the abdomen was initially thought to reveal liver cysts. The ^{68}GA-DOTATATE scan did demonstrate some increased diffuse liver uptake; however, this uptake did not correlate specifically to the cysts.

For our patient, despite the use of several imaging modalities in conjunction, localization of metastatic MTC foci could not be achieved. The primary endocrinologist did pursue more invasive testing to include biopsy of the liver lesions through endoscopic ultrasound resulting in the diagnosis of metastatic MTC. Based on the literature, an elevated calcitonin level is associated with a high likelihood of metastatic disease. If there is concern for a high pretest probability of metastatic MTC in combination with low sensitivity of imaging modality, then invasive testing should be considered.

Approach to Systemic Treatment

At present, there are no means by which to achieve a cure in patients with metastatic MTC. It was not until 2011 when vandetanib became the first FDA-approved systemic therapy for medullary thyroid carcinoma. Patients were previously treated with cytotoxic chemotherapy and radiation with limited success [5, 16]. With the shift in oncology toward targeted therapy, first-line treatment for metastatic MTC is with tyrosine kinase inhibitors such as vandetanib or cabozantinib or the RET kinase inhibitor selpercatinib [5, 17, 24, 25].

As discussed previously, RET mutations and RAS gene mutations are important cell proliferation pathways that are commonly found in MTC [5]. In MTC, tumor growth is also impacted by the vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) pathways which promote angiogenesis and cell proliferation, respectively [5, 16, 26].The VEGFR, RET, EGFR, and other signaling pathways such as RAS and MET serve as targets in treatment for MTC. Vandetanib and cabozantinib are both tyrosine kinase inhibitors; however, vandetanib targets the RET kinase signaling, while cabozantinib targets the MET, VEGF, and RET signaling pathways [4, 5, 7, 26, 27]. Both vandetanib and cabozantinib are approved in the treatment for metastatic MTC and have demonstrated an

improvement in progression-free survival (PFS) [4, 5, 17, 24]. Adverse side effects for cabozantinib include fistula formulation, hypertension, diarrhea, and clotting abnormalities. The adverse effects of vandetanib include QTc prolongation, diarrhea rash, and hypertension as well as arrhythmias and electrolyte disturbances. Currently, an improvement in overall survival has not been associated with cabozantinib nor vandetanib therapy [4, 5, 7]. Use of other tyrosine kinase inhibitors such as sunitinib, imatinib, and sorafenib has been reported if vandetanib or cabozantinib has not been tolerated. These later agents are considered second-line therapy [7, 17]. More recently, the RET kinase selective inhibitors, selpercatinib and pralsetinib, have been approved for the treatment of medullary thyroid cancer with either germline or somatic RET mutations [25, 28]. In published trials to date, patients with RET mutation-positive MTC treated with selpercatinib have demonstrated a response in 70% of patients even if treated with vandetanib or cabozantinib beforehand [25]. Pralsetinib has shown to improve progression-free survival in patients with RET mutation-positive MTC tumors, whether they be treatment-naïve or previously treated with cabozantinib and/or vandetanib [29, 30]. Testing of metastatic tissue for their mutational profile should be considered as available systemic agents allow for the potential of targeted therapy such as when a RET mutation is present.

Local treatment for metastatic disease can be used in conjunction with the tyrosine kinase inhibitors. For metastatic disease to the liver, treatment options include surgical resection and radioembolization. Nervous system metastases can be treated with whole brain radiation, surgical resection, or radiosurgery. Metastatic disease to the bone can be treated with radiation or anti-resorptive bone therapy such as zoledronic acid and denosumab for palliation [3, 7]. Some patients who experience flushing and diarrhea benefit from somatostatin analogues and anti-diarrheal agents [17, 31]. Despite being incurable, systemic targeted therapy has proved promising for treatment of metastatic MTC.

Lessons Learned

Medullary thyroid carcinoma can be a challenging disease to manage, requiring both an understanding of the role of tumor markers and various imaging modalities. MTC can vary significantly in its spectrum of disease by either being very aggressive or indolent in nature. To understand the clinical course of MTC in a particular patient, the provider must understand the role of calcitonin and CEA levels. An important detail to remember is that patients with a calcitonin level of greater than 500 pg/mL on initial diagnosis prior to thyroidectomy as well as patients with a calcitonin level greater than 150 pg/mL after thyroidectomy warrant extensive imaging evaluation for metastatic disease. Of note, in the evaluation for metastatic MTC, no single imaging modality is superior for the entire body. The combination of MRI whole body, bone scintigraphy, CT chest and neck, and MRI of the abdomen is the initial recommended imaging for distant disease. ^{68}GA-DOTATATEPET and FDG-PET are recommended in cases where the initial imaging is negative in

order to discover foci of distant metastatic disease. It is vital to understand the shortcomings of imaging in the detection of metastatic MTC, especially in a patient with extremely elevated calcitonin levels. In these cases, the pretest probability of distant disease is extremely elevated, and if the testing is negative, then the likelihood of a false negative is extremely elevated, and more invasive testing should be pursued. Lastly regarding the tumor markers, a calcitonin and CEA doubling time of greater than 2 years is associated with improved survival compared to those with a doubling time less than 6 months. Though systemic therapy with tyrosine kinase inhibitors has not improved overall survival in patients with metastatic MTC, they have been associated with improved progression-free survival. MTC may be uncommon; however, its management requires significant knowledge of the literature from understanding the tumor markers and doubling times to the most appropriate imaging modalities and systemic treatments.

Question

1. A 50-year-old male with a history of MTC status post-total thyroidectomy and lymph node dissection is being followed regularly by his endocrinologist. His calcitonin and CEA levels are listed below. Which of the following is true regarding this patient?

Time (in months from thyroidectomy)	Calcitonin (<=1.4 pg/mL)	Calcitonin doubling time in months [1]	CEA (<=3.0 ng/mL)	CEA doubling time in months [1]
2	10	–	1.9	–
11	15	–	2.0	121
14	16	–	2.5	36
27	19	28	2.5	59

(a) Calcitonin and CEA doubling times are >2 years, indicating a good prognosis for a survival of greater than 10 years.
(b) Calcitonin and CEA doubling times are <6 months, indicating an indeterminate prognosis.
(c) Calcitonin and CEA doubling times are >2 years, indicating an indeterminate prognosis.
(d) Calcitonin and CEA doubling times are <6 months, indicating a poor prognosis for his 10-year survival.

Answer: A. This patient's calcitonin and CEA doubling time is greater than 2 years; those with a calcitonin and CEA of greater than 2 years demonstrate a good 10-year survival. The doubling time must be collected over four discrete data points in a greater than 2-year span on the same assay. The American Thyroid Association has a calculator on their website for determining doubling time levels. For detailed information refer to the **Role in Calcitonin and CEA Monitoring Post Total Thyroidectomy** section.

2. Which of the following is the next best step in a patient 2 years post-total thyroidectomy with a calcitonin level of 200 pg/mL (<=1.4 pg/mL) and a CEA level of 4.5 ng/mL (<=3.0 ng/mL)?

   (a) Evaluate with ultrasound of the neck, CT chest, and MRI of the liver.
   (b) Evaluate with FDG-PET.
   (c) CT scan of chest, abdomen, and pelvis.
   (d) Evaluate with ultrasound of the neck, CT chest, MRI of the liver, MRI whole body, and bone scintigraphy.

   Answer: D. From consensus guidelines, US of the neck, CT chest, MRI of the liver, MRI whole body, and bone scintigraphy scans are the initial imaging modalities of choice. Each organ system has a specific imaging modality which is superior for metastatic MTC. For detailed information refer to the **Evaluation for Metastatic Disease and Comparison of Imaging Modalities** section.

3. What is the role of ^{68}GA-DOTATATE scan in the evaluation of metastatic MTC?

   (a) Initial evaluation for metastatic disease
   (b) Evaluation for metastatic disease with negative/inconclusive initial testing
   (c) Surveillance of those with metastatic MTC
   (d) Surveillance of those cured from MTC post-thyroidectomy

   Answer: B. ^{68}GA-DOTATATE scans are used if initial evaluation for metastatic disease is negative or inconclusive given the varying levels of sensitivity through studies. For detailed information refer to the **Evaluation for Metastatic Disease and Comparison of Imaging Modalities** section.

4. In a patient with metastatic medullary thyroid carcinoma, which of the following is the first-line treatment?

   (a) Tyrosine kinase inhibitors or direct RET inhibitors
   (b) Chemotherapy
   (c) Radioactive iodine therapy
   (d) Radiation therapy

   Answer: A. Tyrosine kinase inhibitors are first-line therapy in metastatic thyroid cancer. The direct RET inhibitor has recently proven efficacious in the treatment of MTC; for detailed information refer to the **Approach to Systemic Treatment** section.

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Part V
Adrenal Disorders

Chapter 17
Introduction

Alice C. Levine

Over 150 years ago, Brown-Sequard demonstrated that the adrenal glands are essential for life. In the late nineteenth and twentieth centuries, the hormones secreted by the adrenal cortex and medulla were isolated, purified, and synthesized for therapeutic use. In addition, their receptors, stimulators, inhibitors, co-activators, co-repressors, intracellular signaling cascades, and downstream effectors have been delineated. In the twenty-first century, the molecular genetics underlying many adrenal disorders have been uncovered.

Although physiologic levels of adrenal hormones are necessary for the proper functioning of all tissues and organs and critical for the stress response, pharmacologic levels of these hormones have devastating effects on multiple organ systems. Clinical studies over the past 20 years have revealed that many cases of so-called "idiopathic" hypertension are due to underlying adrenal hypersecretory syndromes. A number of retrospective studies over the past decade indicate that any degree of hypercortisolism is deleterious to bone, metabolic, and cardiovascular health. Advances in radiologic imaging, particularly the introduction of the CT scan in the early 1970s, led to the epidemic of "adrenal incidentalomas"—incidentally discovered adrenal masses, an entity that is particularly prevalent in older individuals. Detailed hormonal testing of patients with adrenal incidentalomas has revealed that many are associated with mild hypercortisolism. At the other end of the spectrum, Cushing's syndrome due to ectopic ACTH produces severe and potentially life-threatening hypercortisolism. The cortisol excess must be expeditiously addressed, even in patients with metastatic cancer, as reduction in cortisol levels improves morbidity and mortality and allows the patient to receive cancer treatments. Excessive catecholamine secretion from pheochromocytomas, even if only episodic, can result in sudden death. Pheochromocytomas are considered "ticking time bombs" that

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require careful preoperative and perioperative management in order to insure a safe outcome.

In this section, three cases of adrenal hormonal hypersecretion are presented. The case of an adrenal incidentaloma describes the necessary workup to rule out malignancy and adrenal hypersecretion. This case also focuses on the controversies surrounding the diagnosis of mild hypercortisolism as well as the current medical and surgical therapies. The cases of Cushing's syndrome due to ectopic ACTH underscore the difficulties in localization of the source of the ACTH and the challenges in the treatment of severe, life-threatening hypercortisolism. Finally, the case of pheochromocytoma illustrates the biochemical and radiologic tools available to identify adrenal medullary tumors, the molecular classification of these tumors, as well as the best available approaches for their management.

Chapter 18
Adrenal Incidentalomas and Autonomous Cortisol Secretion

Effie Tsomos and Alice C. Levine

Case Description

A 68-year-old woman was referred to an endocrinologist by her primary care physician after a 2.5 cm adrenal mass was incidentally noted on an abdominal CT urogram of the abdomen performed for the work-up of persistent hematuria. It measured 3 Hounsfield units before contrast was given, consistent with an adrenal adenoma.

The patient's past medical history was significant for hypertension treated with a single agent (labetalol 100 mg daily), hyperlipidemia, and osteopenia. Upon further questioning the patient noted that she had gained 25 pounds in the previous 18 months. She had undergone menopause at 50 years of age.

On physical exam the patient was well appearing. She was obese with a BMI of 32 (height 5′6″, weight 198 lb). Her blood pressure was 158/88 mmHg and her pulse was 70 beats/min. She did not exhibit the typical stigmata of Cushing's on exam. Specifically, there was no scalp hair loss, hirsutism, acne, increased dorsocervical fat, hyperpigmented striae, bruising, lower extremity edema, proximal muscle weakness, or wasting. Cardiovascular exam revealed a regular heart rate and rhythm, with no extra heart sounds. Lung exam was clear to auscultation with no wheezes. Abdomen was obese and soft.

Biochemical work-up revealed a fasting glucose of 102 mg/dl, creatinine of 0.7 mg/21 dl, BUN of 16 mg/dl, AST of 19 U/L, and ALT of 15 U/L. The patient's

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late afternoon serum cortisol level was 6.5 mcg/dl, ACTH was <10 pg/ml, and DHEA-S was 31 mcg/dl (normal 35–430 mcg/dl). Midnight salivary free cortisol concentrations were 1.4 nmol/l and 1.6 nmol/l (normal <0.3–4.3 nmol/l). Serum cortisol concentration after a 1 mg dexamethasone suppression test was 6.1 mcg/dl with a therapeutic dexamethasone level. 24-h urine free cortisol levels were 55 mcg/24 h and 32 mcg/24 h (normal <50 mcg/24 h).

Serum aldosterone was 7.0 ng/dl (normal 0.0–30 ng/dL), and plasma renin activity was 1.6 units ng/mL/hr (normal 0.167–5.380 ng/mL/hr). Serum catecholamine and 24-h urine catecholamine levels were normal. Based on the partial serum cortisol suppression after 1 mg dexamethasone and mild elevation in urinary-free cortisol in the setting of a suppressed plasma ACTH and serum DHEAS concentration, the diagnosis of autonomous cortisol secretion (ACS) was made. Treatment options were discussed with the patient including surgical removal of the adenoma or conservative management. The patient opted for conservative management with serial imaging and biochemical evaluation.

What Is the Prevalence of Incidentally Identified Adrenal Nodules?

Increasingly, patients are found to have adrenal incidentalomas (AI), defined as unsuspected adrenal adenomas on imaging performed for other purposes. With the advent of CT imaging, there has been a striking increase in the detection of AI, with a prevalence similar to that reported in autopsy studies. An older literature review that included autopsy data from 13 studies with a total of 71,206 patients reported an overall prevalence of 1.0–8.7% [1]. A subsequent study demonstrated that AI are found in about 5% of the population with increased incidence with advancing age [2]. The highest rates of incidence are between the fifth and seventh decades of life [3]. A recent meta-analysis that included 32 studies encompassing over 4000 patients with AI showed a mean age of 60.2 years and a female predominance (61.5%) [4].

Is the Nodule Malignant?

The discovery of an adrenal mass can raise concern for malignancy, specifically adrenocortical cancer (ACC) or metastatic disease. Adrenal metastases are ordinarily easily identifiable as they tend to occur late in the course of metastatic cancer [5].

ACC is a rare and aggressive cancer with an unfavorable prognosis. The Surveillance, Epidemiology, and End Results (SEER) database provides an estimation of incidence of about 0.72 per million cases per year in the United States [6]. ACC is usually diagnosed between the fifth and seventh decades of life. Radical resection by open adrenalectomy is the only potential curative treatment [7]. After initial resection, however, locoregional recurrence often occurs. Unfortunately, the

incidental discovery of ACC on imaging does not improve survival. A cohort study of 4275 patients with incidentally found ACC did not shift toward lower stage or smaller tumor size in a 22-year period with a median survival of 24 months [8].

The most common hormones produced by an adrenocortical carcinoma are cortisol and adrenal androgens. Oftentimes, signs of hormone excess are minimal as steroid hormone synthesis in ACC is inefficient with a pattern of disorganized steroidogenesis resulting in a disproportionate rise in steroid hormone precursors relative to cortisol. Blood and urine levels of precursor adrenal cortical hormones may be useful in distinguishing benign vs. malignant adrenal cortical tumors [9, 10].

Size and imaging characteristics can be used to help distinguish benign from malignant lesions. ACCs are typically large tumors, usually greater than 6 cm in diameter [11]. Due to the presence of internal hemorrhage, necrosis, and calcifications, ACC usually has a heterogeneous appearance on imaging. Benign lesions are typically lipid rich, which results in a hypodense lesion on CT with low Hounsfield units, typically less than 10. In contrast, ACC lesions tend to be lipid poor and thus have high Hounsfield units, often greater than 25 [12]. Additionally, on delayed contrast-enhanced CT, adenomas show rapid washout (greater than 60% at 10 min), while ACCs show delayed washout (less than 60% at 10 min) [13]. The patient's nodule in this case has benign characteristics: it is small (2.5 cm) with benign imaging characteristics consistent with a lipid-rich, benign adenoma (density on CT pre-contrast 3 HU).

Is the Nodule Secreting Any Hormones?

The majority of adrenal masses are nonfunctional adrenocortical adenomas. However, recent studies indicate that more than 30% of all AI display at least subtle hypersecretion, primarily of cortisol [14]. Work-up for hormonal hypersecretion should include a careful history and physical exam focusing on possible signs of hypercortisolism, elevated catecholamines, primary aldosteronism, and hyperandrogenism. Biochemical testing should focus on evaluation for pheochromocytoma, hypercortisolism, and primary aldosteronism. Hormonal work-up should be performed regardless of imaging phenotype or lesion size.

Pheochromocytomas are generally large tumors with characteristic radiologic features demonstrating a lack of intracellular fat and a capillary-rich framework [15]. However, because pheochromocytomas may be small and silent, work-up for a pheochromocytoma should be carried out in all patients presenting with AI, even in the absence of hypertension. Plasma free metanephrines have high sensitivity and are simpler to perform than 24-h urine testing and thus are an excellent initial test for the identification of a pheochromocytoma [16]. Confirmatory testing in the form of a 24-h urine fractionated metanephrines and normetanephrines may be performed if the initial screening test is positive. Estimates of the frequency of pheochromocytoma in patients with adrenal incidentalomas are variable. Retrospective analyses report a prevalence of 1.5–23% [11]. Most studies demonstrate that approximately 5% of adrenal incidentalomas are clinically silent pheochromocytomas [17].

Work-up for primary aldosteronism should only be performed in patients with hypertension [18]. Plasma aldosterone concentration and plasma renin activity are recommended for screening. A ratio of plasma aldosterone to plasma renin activity >20 mg/mL/hr is highly suggestive of primary hyperaldosteronism with the caveat that aldosterone levels must be elevated and plasma renin activity suppressed. Such patients should undergo confirmatory testing. Serum potassium cannot be used for screening as the majority of patients with primary aldosteronism are normokalemic [17]. Approximately 1% of incidentalomas secrete aldosterone [19].

Pure virilizing tumors of the adrenal cortex are rare. Work-up for hyperandrogenism in AI should be carried out in patients with signs and symptoms of virilization and should include adrenal precursor hormones as well as testosterone levels.

The most common secretory syndrome in adrenal adenomas is hypercortisolism [20]. ACS is reported to be present in up to 30% of all adrenal incidentalomas [21]. In patients with signs and symptoms of overt Cushing's in the presence of an adrenal adenoma, the Endocrine Society recommends using two out of three screening tests: 24-hour urine free cortisol excretion (UFC), late-night salivary cortisol, or 9 AM cortisol concentrations after an overnight low-dose dexamethasone suppression test (LDDST). A serum cortisol concentration of >1.8 μg/dL (50 nmol/L) after LDDST is recommended by the American Association of Clinical Endocrinologists as the cutoff of cortisol suppression used to diagnose overt Cushing's syndrome.

There is no gold standard for the diagnosis of milder hypercortisolism due to adrenal adenomas. Oftentimes in ACS, the 24-hour UFC and midnight salivary cortisol levels are not elevated. A variety of studies and guidelines supports the use of the LDDST as having the highest sensitivity for screening for ACS. Results of the LDDST should be interpreted as a continuous rather than categorical variable. A post-dexamethasone cortisol level ≤1.8 μg/dL (≤50 nmol/L) is considered normal and rules out cortisol excess. Levels between 1.9 and 5.0 μg/dL (50–140 nmol/L) indicate "possible ACS," and cortisol levels above 5.0 μg/dL (140 nmol/L) are suggested to confirm ACS [14, 22]. While it is counterintuitive to set the cutoff higher for subclinical compared to overt disease, considering that the probability of hypercortisolism is lower in patients without symptoms, a post-dexamethasone serum cortisol of >1.8 mcg/dl would result in more false-positive than true-positive results [21].

Other diagnostic tests are used to assess for hypercortisolism such as measurement of 24-h urinary free cortisol (UFC) and midnight salivary free cortisol as less helpful when diagnosing ACS. 24-h UFC concentrations are frequently normal in such patients with a sensitivity of 32–76% and thus cannot reliably detect a slight cortisol excess [23]. Likewise, although circadian cortisol secretion is reportedly altered in ACS, most studies have not found differences in midnight salivary free cortisol concentrations in patients with ACS [24].

In the clinical scenario described above, our patient did not have signs and symptoms of overt hypercortisolism, and her 24-hour UFC was only marginally elevated. However, her serum cortisol level was 6.1 mcg/dl with a therapeutic dexamethasone level after an LDDST. Therefore, her clinical presentation and biochemical evaluation are consistent with ACS due to an adrenal adenoma.

What Are the Clinical Sequelae of ACS?

Patients with ACS do not develop classic signs and symptoms of overt Cushing's syndrome like hyperpigmented striae, easy bruising, and muscle weakness. However, they often develop features of the metabolic syndrome including hypertension, diabetes, central obesity and also manifest osteoporosis.

Accumulating data indicate that exposure to even low levels of excess cortisol can result in long-term metabolic and cardiovascular effects which may not be completely reversible. ACS due to adrenal incidentalomas has been shown in multiple, large retrospective studies to be associated with an increased prevalence of hypertension and type 2 diabetes mellitus (T2DM) and cardiovascular risk [14, 22, 25, 26]. Cardiovascular event prevalence is higher in patients with ACS, regardless of age and the presence of T2DM [27]. Studies demonstrate increased mortality due to cardiovascular disease in patients with even mild cortisol excess due to adrenal adenomas [14]. In fact, in a recent systematic review of over 4000 patients with non-functioning adrenal incidentalomas or adrenal adenomas resulting in ACS, cardiovascular mortality represented 43.2% of all deaths with an incidence of 5% in those with ACS [4].

Clinically overt hormone excess is unlikely to develop over time in those with ACS. In the abovementioned systematic review and meta-analysis from 2019, only 6 out of 2745 patients with a non-functioning adrenal tumor or ACS at baseline developed overt Cushing's syndrome over a mean follow-up of 49.6 months. Although unlikely to worsen, the same review showed that ACS resolution is *also* unlikely to occur. In 17 studies involving 840 patients, ACS resolved in only 18 patients during a mean follow-up of 49.8 months [4].

ACS also has a detrimental effect on bone resulting in a higher risk of vertebral fracture. Cortisol exerts direct and indirect effects on bone, enhancing its resorption and inhibiting its formation. One cannot fully analyze the effect of hypercortisolism on bone with a DEXA scan as ACS impairs bone microarchitecture rather than bone density. Therefore, most studies that have looked at the effects of cortisol on bone look at the incidence of vertebral fractures or changes in the spinal deformity index which integrates both the number and severity of fractures using the sum of vertebral deformity grades along the spine. A longitudinal study investigating the incidence of vertebral fractures and spinal deformity index changes in patients with ACS showed an increase in new vertebral fractures with an incidence of 48% over 2 years of follow-up. The same study observed a worsening of spinal deformity index despite a stable BMD in patients with ACS [27].

There is no literature to suggest malignant transformation of adrenal tumors resulting in ACS. In 26 studies involving 2854 patients, none of the adrenal tumors determined to be benign non-functioning tumors or ACS transformed into an adrenocortical carcinoma during a mean follow-up of 49.3 months [4].

In our case, the patient has hypertension and osteopenia, two conditions that would not be considered out of the ordinary for her age. However, as we have now learned, her hypercortisolism has increased her risk of vertebral fracture and cardiovascular disease.

Does Treatment Improve ACS?

Once ACS is diagnosed, treatment options should be considered. The selection of an appropriate surgical candidate can be challenging as the comorbidities caused by cortisol excess are otherwise prevalent in the general population and may be difficult to distinguish from those induced by hypercortisolism. European guidelines from 2016 regarding the management of patients with adrenal incidentalomas suggest adrenalectomy in patients with higher degrees of biochemical hypercortisolism with a DST >5 μg/dL (140 nmol/L) and the presence of cortisol-related comorbidities like hypertension, diabetes, obesity, or low bone mass [28]. Patients with ACS undergoing adrenalectomy experience improvement in such comorbidities.

There are no large, controlled clinical studies of medical treatment of subclinical hypercortisolism. Additionally, no randomized controlled trials have yet been conducted to compare adrenalectomy to intensive medical therapy affecting clinically relevant outcomes like major cardiovascular events and mortality [28]. A small pilot study using the glucocorticoid receptor blocker mifepristone for patients with ACS demonstrated significant reductions in fasting glucose measurements and insulin resistance as measured by HOMA-IR in six of eight study patients in whom these measurements were available [29].

How Should This Nodule Be Monitored?

Surgical resection is recommended for a functional unilateral adenoma with clinically significant hormone excess or an adenoma with imaging characteristics concerning for ACC. With benign appearing, non-functioning adenomas, the American Association of Clinical Endocrinologists recommends repeated imaging for up to 5 years [30]. Studies reporting on long-term follow-up observation of adrenal incidentalomas, however, suggest that the majority of benign, non-secretory masses remain as such without changes in hormone secretion or significant growth [4].

There is no absolute size for the recommendation of surgery in non-functioning adenomas, but tumors >4 cm in diameter should be considered for surgical removal particularly if there are worrisome features on imaging [31]. Patients with such adrenal lesions who have not undergone surgery are recommended to have repeat CT or MRI imaging in 6 to 12 months. Surgical management is recommended if there is a 20% increase in size and at least a 5 mm increase in diameter over this time [32].

The adenoma mentioned in the patient case did not meet criteria for surgical removal based on size and imaging characteristics. We discussed the lack of clear evidence regarding the superiority of medical therapy or adrenalectomy over a conservative approach of observation. Medical options were discussed with the patient, but she opted to defer this approach and treat comorbidities.

Summary

Incidentally discovered adrenal nodules are a common dilemma with the increased use of CT imaging for other indications. The highest rates of incidence are between the fifth and seventh decades of life with a female predominance. While most incidentalomas are benign, nonfunctioning adrenal adenomas, recent studies indicate that more than 30% of all incidentalomas display some degree of autonomous cortisol secretion. ACS does not present with classic signs or symptoms of Cushing's syndrome, and biochemical evaluation for the disease remains a topic of debate. Thus, there is no gold standard for the diagnosis of ACS.

ACS is associated with obesity and derangements in metabolic parameters including impaired glucose tolerance, hypertension, dyslipidemia, and an increased risk of fractures and cardiovascular disease. To date, there is little data to support surgical intervention for the treatment of ACS, and large, controlled trials investigating the effects of medical therapies for this condition have not yet been reported.

Multiple-Choice Questions

1. A 72-year-old female presents for endocrine evaluation after the incidental discovery of a 2.5 cm lipid-rich adrenal adenoma on CT abdomen performed for abdominal pain. She has osteoporosis, hypertension, and hyperlipidemia. On physical exam, her BP is 147/84, and BMI 31 kg/m^2. She has no clinical features consistent with Cushing's. Her labwork shows ACTH 8 pg/mL (<50), morning cortisol 16 ug/dL (<22), and plasma metanephrines within normal range. Subsequent testing showed a 24-hour UFC of 48 ug/24 h (<50) and a cortisol of 6 ug/dL after a LDDST with a therapeutic dexamethasone level.

   What is the best next step in management?

   (a) Refer the patient for surgery.
   (b) Medical management.
   (c) Observation.
   (d) Medical management and observation are acceptable options based on the patient's preference.

2. The highest rate of incidence for adrenal adenomas is seen in the following age range:

   (a) 30–50 years of age
   (b) 50–70 years of age
   (c) 70–90 years of age

3. What is the best way to assess bone quality in patients with ACS?

   (a) DEXA
   (b) CT scan
   (c) Spinal deformity index
   (d) Quantitative ultrasound

Answers

1. (d)
2. (b)
3. (c)

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Chapter 19
Pheochromocytoma

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A 66-year-old female with history of diabetes and hypertension presented with left upper quadrant abdominal pain and lower back pain. Review of systems revealed a significant weight loss of 22 kg over the past 2 years and episodes of fatigue, headaches, and anxiety. She had several emergency department (ED) visits for palpitations, dyspnea, diaphoresis, and alternating hypertensive emergency and orthostatic hypotension. Her only medications were lisinopril and metformin. Her blood pressure at this visit was 105/55. On physical exam, she did not have thyromegaly or thyroid nodules, but was tachycardic at 100 beats per minute with a regular rhythm and with mild left upper abdominal tenderness without a palpable mass.

Biochemical testing showed elevated plasma and urine normetanephrines and metanephrines, along with elevated levels of urinary dopamine (Table 19.1). Renin, aldosterone, and 1 mg overnight dexamethasone suppression testing were normal. Her serum calcium was elevated to 11.4 mg/dL (8.5–10.5) with an intact PTH of 154 pg/mL (10–65), concerning for primary hyperparathyroidism, with a slightly

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Table 19.1 Pre- and post-operative lab values for the case patient

	Normal range	Preoperative values	Post-operative values
Plasma normetanephrines (pg/mL)	0–145	2418	98.7
Urine normetanephrines (ug/24 h)	82–500	8610	
Plasma metanephrines (pg/mL)	0–62	245	16.3
Urine metanephrines (ug/24 h)	45–290	2076	
Plasma normetanephrine to metanephrine ratio		10:1	
Urine normetanephrine to metanephrine ratio		4:1	
Urinary dopamine (ug/24 h)	0–510	1701	

low 25-hydroxy vitamin D level at 25.1 ng/mL (30–100). Ultrasound of the thyroid demonstrated a 0.3 cm right lower pole thyroid nodule, but there was no evidence of a parathyroid adenoma. CT scan of the abdomen and pelvis revealed a heterogeneously enhancing mass measuring 6.3 × 4.8 cm in the left adrenal gland, which measured 87 Hounsfield units on the portal phase.

Given the concern for pheochromocytoma based on the elevated plasma and urine metanephrines and the adrenal mass, she was placed on selective alpha (α)-adrenergic blockade with terazosin 1 mg daily, subsequently followed by beta (β) adrenergic blockade with metoprolol tartrate 12.5 mg twice daily. She was instructed to liberalize salt intake and maintain adequate hydration. Her symptoms of headaches, diaphoresis, palpitations, and anxiety improved on this regimen. She underwent an uncomplicated left laparoscopic adrenalectomy a few weeks later. Pathology confirmed an 8 cm pheochromocytoma with a PASS score of 10 that suggested a higher potential for malignant behavior.

Post-operatively, her blood pressure was well controlled on lisinopril, and her tachycardia resolved. She also gained back ~4 kg of the weight she had lost. Fasting glucose decreased from 166 mg/dL to 93 mg/dL and her calcium normalized to 9.7 mg/dL. Plasma metanephrines and normetanephrines also normalized post-operatively (Table 19.1). Lastly, given the pheochromocytoma and hyperparathyroidism, she was referred for genetic testing, which was negative for MEN 2A.

How Could the Location of the Patient's Pheochromocytoma Be Predicted by the Biochemical Profile?

Pheochromocytomas (Pheo) and paragangliomas (PGL) are rare neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla and the sympathetic ganglia, respectively. Paragangliomas that secrete catecholamines are also termed

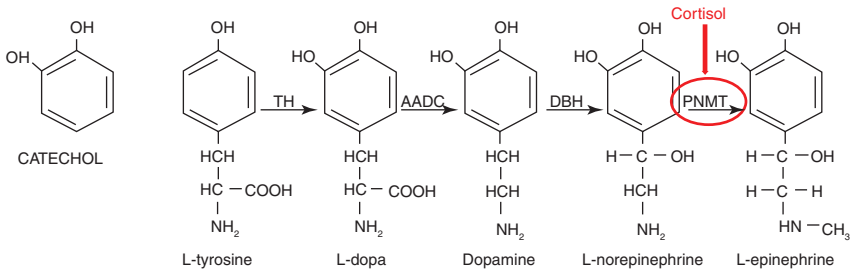

Fig. 19.1 Biosynthetic pathways for catecholamines. Cortisol stimulates PNMT that catalyzes the conversion of norepinephrine to epinephrine in the adrenal. TH tyrosine hydroxylase, AADC aromatic amino acid decarboxylase, DBH dopamine β-hydroxylase

extra-adrenal pheochromocytomas. It is important to recognize (1) not all paragangliomas (extra-adrenal pheochromocytomas) are secretory and (2) the distinction of paraganglioma, whether secretory or non-secretory, has important clinical implications, particularly when the potential for metastatic and familial disease is being assessed.

Catecholamines are synthesized from tyrosine that is converted by tyrosine hydroxylase into dopa as the rate-limiting step of the synthetic cascade. Norepinephrine is the predominant catecholamine synthesized and secreted by the cells of the paraganglia and adrenergic neurons. Epinephrine is synthesized from norepinephrine by the enzyme phenylethanolamine N-methyltransferase (PNMT), which is largely restricted to the chromaffin cells of the adrenal medulla. PNMT is induced by cortisol produced in the neighboring adrenal cortex. Therefore, epinephrine secretion is largely exclusive to intra-adrenal pheochromocytomas, and the epinephrine secretion in this patient was consistent with an adrenal medullary tumor (Fig. 19.1).

Why Was This Patient Evaluated for Pheochromocytoma? What Is the Danger of Missing the Diagnosis? Who Should Be Screened for the Presence of a Pheochromocytoma?

Pheochromocytoma has been described by the moniker “the great mimicker” because the symptoms are nonspecific and intermittent, occurring in paroxysms. This patient’s presentation was no exception. During her first presentation to the ED, she endorsed intermittent palpitations, shortness of breath, and diaphoresis concerning for acute coronary syndrome. Workup was found to be negative and she was later discharged. Several months later she returned to the ED for dizziness and fatigue that was attributed to her to orthostatic hypotension. Both of her presentations consisted of non-specific, common chief complaints, and diagnoses of pheochromocytoma could be easily overlooked if a thorough workup was not conducted. Patients with pheochromocytomas may report sudden onset of chest pain, palpitations, shortness of breath, throbbing headache, diaphoresis with pallor, and nausea.

Episodes may be unprovoked or precipitated by medications, stress, anxiety, positional change, or Valsalva. A lethal paroxysm or pheochromocytoma hypertensive crisis is the most feared complication of catecholamine excess. Although the exact mechanism of hypertensive crisis remains unclear, two mechanisms are proposed to occur simultaneously. The first is failure of proper autoregulation, or ability of organs to maintain a stable blood flow irrespective of alterations in perfusion pressure, in the vascular beds. This lack of autoregulation causes an abrupt increase in BP and systemic vascular resistance, leading to endothelial injury and mechanical stress [1]. The second mechanism that is believed to contribute to hypertensive crisis involves activation of the renin-angiotensin system that promotes a continuous cycle of worsening vasoconstriction and ischemia [1].

Further complicating the identification of patients with pheochromocytoma is the rarity of the disease. The estimated prevalence of pheochromocytomas is 2.13 per 100,000 persons, and incidence rate is 0.18–0.46 per 100,000 person-years [2, 3]. Despite the rarity of these tumors, identification and treatment of pheochromocytoma are crucial to prevent the morbidity and potential mortality from a crisis. Therefore, all patients with symptoms compatible with pheochromocytoma should be screened, even in the absence of sustained hypertension. The sustained effects of catecholamine excess include orthostatic hypotension, resistant hypertension, and the sequelae of untreated hypertension, such as retinopathy, congestive heart failure with hypertrophic or dilated cardiomyopathy, and hyperglycemia or diabetes. Patients with resistant hypertension, unexplained cardiomyopathy, or diabetes should be screened as well [4, 5]. The clinically silent pheochromocytoma is an entity more recently appreciated with the increased incidental detection of adrenal masses and, in fact, represents approximately half of all pheochromocytomas diagnosed [6]. Of note, the prevalence of pheochromocytoma is higher, from 4.2% to 6.5% in patients with a known adrenal mass, regardless of the presence of symptoms [6–8]. Screening for pheochromocytoma should be performed in all patients with incidentalomas >1 cm discovered on adrenal imaging due to the risk of silent pheochromocytoma [9].

How Are Patients with Suspected Pheochromocytoma Diagnosed?

Plasma free or urinary fractionated metanephrines are the recommended initial approach to screen for pheochromocytoma [6]. Catecholamines are stored within vesicles in the chromaffin cells; however, there is continual leakage into the cell cytoplasm where norepinephrine, epinephrine, and dopamine are metabolized by catechol-O-methyltransferase into their plasma metabolites, normetanephrine, metanephrine, and methoxytyramine, respectively. Normetanephrine and metanephrine undergo further sulfate conjugation prior to excretion in the urine. These processes account for the majority of measured metabolites in the blood and the

urine. Because catecholamine secretion tends not to be continuous and even venipuncture can quickly raise blood catecholamine levels, measurement of metabolites is a more sensitive and specific marker of catecholamine excess [10, 11]. Our approach is to measure plasma metanephrines first given the ease of collection and high sensitivity, such that a negative value excludes pheochromocytoma. In 80% of patients with pheochromocytoma, plasma metanephrines are elevated fourfold over the upper limit of normal, and if present, localization of the tumor is the next diagnostic step [12]. Measurement of plasma free metanephrines is 96–100% sensitive and 89–98% specific for disease detection [4, 11]. Renal dysfunction does not influence plasma metanephrines measurement [13]; however, false-positive results may occur with use of tricyclic anti-depressants, monoamine oxidase inhibitors, buspirone, phenoxybenzamine, or sympathomimetics such as pseudoephedrine and weight-loss medications. False positives may also occur due to recent abrupt clonidine or benzodiazepine discontinuation, alcohol excess or withdrawal, untreated obstructive sleep apnea, or if samples are drawn in the seated rather than supine position [4]. When patients are seated in an upright position, activation of the sympathetic nervous system is triggered, thus leading to increased production of norepinephrine and its metabolites. Use of gas chromatography with mass spectrometry or liquid chromatography-tandem mass spectrometry has increased the diagnostic accuracy of plasma metanephrines [14]. Urinary fractionated metanephrines are less sensitive (86–97%) and slightly less specific (86–95%) than plasma metanephrines and require 24-h urine collection. Renal dysfunction and diets rich in biogenic amines may alter interpretation of urine metanephrines [4].

What Are the Relative Contributions of Epinephrine Versus Norepinephrine Excess in this Patient's Signs and Symptoms?

The classic triad associated with pheochromocytomas includes headache, sweating, and palpitations, although only a minority of patients present with this triad. However, hypertension is present in over 90% of patients with pheochromocytoma due to excess catecholamine release, with approximately half of these cases presenting with sustained hypertension, 45% with paroxysmal hypertension, and the remaining 5–15% with normotension [15–17]. Catecholamines, principally norepinephrine and epinephrine, are stored in vesicles and typically are released in the setting of stressful stimuli. Pheochromocytomas may mirror this secretion with sudden unpredictable release or slow, steady release.

Norepinephrine and epinephrine increase heart rate, blood pressure, myocardial contractility, and cardiac conduction by their actions at adrenergic receptors. There are five subtypes of adrenergic receptors, α_1, α_2, β_1, β_2, and β_3, each with differential tissue expression, response to norepinephrine vs. epinephrine, and actions (Table 19.2). Alpha-1 receptors are located on vascular smooth muscle in addition to apocrine glands and cause contraction of smooth muscle with a resultant increase

Table 19.2 Adrenergic receptors and their action

Type	Location of receptors	Action
α_1	Vascular smooth muscle contraction, intestinal and bladder sphincter muscle contraction, apocrine glands	Increased contraction of muscle, increased peripheral resistance, sweating
α_2	Post-synaptic CNS neurons, nerve endings, vascular smooth muscle, islet cells, adipose tissue	Autoreceptor-mediated feedback inhibition: decreased release of NE leading to arterial vasodilation and coronary vasoconstriction Decreases insulin release, decreases lipolysis
β_1	**Cardiac muscle, JG cells—kidney, posterior pituitary, adipose tissue**	**Cardiac stimulation (increase heart rate and contractility), increase renin release, ADH release, fatty acid mobilization from adipose tissue causing lipolysis**
β_2	**Smooth muscle (bronchioles), skeletal muscle, liver, adipose tissue**	**Bronchodilation, smooth muscle vasodilatation/ decreased peripheral resistance, glycogenolysis, lipolysis**
β_3	Adipose tissue	Lipolysis, thermogenesis, promotes development of brown preadipocytes into fully mature brown adipose tissue

in peripheral resistance. Stimulation of α_1 receptors on apocrine glands causes sweating, mostly localized to the palms. Activation of α_2 receptors that are expressed in presynaptic neurons exerts a negative feedback effect on norepinephrine secretion, while activation of α_2 receptors on vascular smooth muscle causes vasoconstriction. In addition, α_2 receptors are expressed on islet cells, and stimulation decreases insulin release leading to hyperglycemia. β_1 receptors are expressed in the cardiac muscle, juxtaglomerular cells in the kidney, posterior pituitary, and adipose tissue. Triggering of the β_1 receptor leads to cardiac stimulation, increased renin and ADH release, and increased lipolysis. Beta-2 receptor activation has a myriad of effects, but is not involved in vasoconstriction and hypertension due to pheochromocytomas. Stimulation of β_2 receptors leads to smooth muscle dilation (bronchodilation) and ultimately decreased peripheral resistance and glycogenolysis and, to some degree, increases lipolysis. Lastly, β_3 receptors are expressed in the adipose tissue, and stimulation of this receptor has the most potent effect on enhancement of lipolysis and thermogenesis (Table 19.2) [18].

Both norepinephrine and epinephrine stimulate α_1 and α_2 adrenergic receptors with the overall effect of vasoconstriction and increased peripheral vascular resistance. However, epinephrine notably has a more potent stimulatory effect than norepinephrine at the β_2 adrenoreceptors, leading to vasodilatation. Patient symptoms, likewise, may reflect the relative secretion of norepinephrine vs. epinephrine by the tumors. Tumors that predominately secrete norepinephrine or particularly with a continuous pattern of secretion are often associated with sustained hypertension [19, 20]. Predominantly epinephrine-secreting tumors, on the other hand, often present with paroxysmal hypertension and episodes of orthostatic hypotension due to epinephrine effects at the β_2 adrenergic receptors. It is important to note,

however, that patients with early disease may not have hypertension at all. Our patient had markedly elevated plasma levels of both norepinephrine and epinephrine metabolites. Her high levels of both catecholamines explain her intermittent, dramatic symptoms of diaphoresis, anxiety, and palpitations. Her elevated norepinephrine levels explain her hypertension, while her elevated levels of epinephrine acting at the β_2 receptor may underlie her intermittent, symptomatic orthostatic hypotension.

Other metabolic effects of norepinephrine and epinephrine include hyperglycemia, hyperlipidemia, and thermogenesis. In this patient, stimulation of the β_3 receptors, likely from excess norepinephrine, potentially explains her 22 kg weight loss [18]. Additionally, stimulation of α_2 adrenergic receptors by both catecholamines likely played a role in increasing this patient's blood glucose, albeit via different mechanisms; norepinephrine increases insulin resistance, whereas epinephrine impairs the secretion of insulin [21]. These effects of elevated catecholamines on hyperglycemia, hyperlipidemia, and thermogenesis causing weight loss are partially reversible after surgical removal. Impressively, within just 1 week postoperatively, she had a 4 kg weight gain and improvement of her fasting glucose from diabetic to pre-diabetic levels.

Once Confirmed Biochemically, What Is the Best Tumor Localization Study?

Imaging should only be pursued in cases with biochemical evidence of catecholamine excess or for surveillance in patients with hereditary syndromes predisposing them to the development of pheochromocytoma. About 85% of these tumors arise from the adrenal glands and 95% are localized within the abdomen [5]. Computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is the preferred initial imaging techniques in localizing pheochromocytoma, with subsequent imaging of the neck and chest if a tumor is not located. There is no consensus regarding the choice of imaging modality [22]. MRI may be useful in indeterminate cases, as pheochromocytomas tend to have high signal uptake on T2-weighted images. This modality is especially useful in the evaluation of adrenal incidentalomas in which there is concern for silent a pheochromocytoma. 123 I-labeled meta-iodobenenzylguanide (MIBG) scintigraphy provides functional information about pheochromocytoma because MIBG is taken up into the secretory granules of chromaffin cells via the norepinephrine transporter [23]. MIBG lacks the sensitivity of CT and MRI and should only be used when CT and MRI are negative, in cases where metastatic disease is suspected or for surveillance in patients with hereditary diseases [24]. Positron-emitted tomography can also be used to detect pheochromocytoma but should be reserved for detection of metastatic disease when MIBG is negative [22, 24]. More recently, ^{68}Ga-DOTATATE PET/CT has demonstrated superiority in localization of metastatic Pheo/PGL when compared to

other functional imaging modalities (including ^{18}F-FDG PET/CT) [25]. Our case patient had biochemically confirmed disease with a large adrenal tumor identified on CT; therefore, there was no indication to pursue further imaging prior to surgical resection.

How Should the Patient Be Managed Preoperatively?

A multidisciplinary approach that includes the patient as well as endocrinologists, anesthesiologists, and surgeons that are expert in this area has been regarded as essential to ensure good outcomes. There is an argument that with close intraoperative monitoring by an anesthesiologist familiar with the nuances of pheochromocytoma management, preoperative medical treatment is unnecessary, particularly in patients who do not have hypertension [26]. However, due to lack of sufficient evidence, most centers institute a preoperative treatment plan preceding surgery aimed at blood pressure control and volume expansion [5, 27]. Alpha-blockers lower blood pressure by blocking the overstimulation of α-adrenergic receptors by the high levels of circulating catecholamines and are the conventional agents of choice in preoperative blood pressure management [28]. However, there is little data on dose, duration of therapy or BP goals [29]. Several α-blockers are available for use. Phenoxybenzamine is a nonselective, irreversible α-antagonist, and, because of its long duration of action and irreversibility, it is the preferred initial choice, particularly in patients who have sustained hypertension. Perioperative hypertension control seems to be slightly superior with phenoxybenzamine, especially in patients with high catecholamine release [30]. However, practical issues, including expense, availability, and side effects (e.g., nasal congestion, severe fatigue, and orthostatic hypotension), limit its use [27]. Instead, the selective α_1-adrenergic antagonists such as doxazosin, prazosin, or terazosin can be used in patients as an alternative to phenoxybenzamine [31]. Adequate blood pressure control with α-blockers is recommended for at least 10–14 days prior to surgery. If α-blockers are not initiated prior to surgery, there is a danger of severe cardiovascular events occurring intraoperatively. It is also essential to achieve blood pressure control with α-adrenergic blockage, as was done with this patient, prior to the initiation of a β-blocker to prevent unopposed α-adrenergic stimulation. The use of β-blockers in the absence of α-receptor blockers is not recommended due to unopposed stimulation of α-adrenergic receptors leading to hypertensive crisis.

It is important to note that the combined α- and β- blocker, labetalol, has more potent antagonistic activity at the β_1 and β_2 receptors than at the α-receptors (β:α of 5:1) and therefore can result in paradoxical hypertension or hypertensive crisis. If patients develop tachycardia on (the preferred) α-receptor blockade, β_1 selective drugs, such as atenolol, metoprolol, or bisoprolol, may be added to avoid antagonism of β_2 receptor-mediated vasodilator action [32]. There is mixed data on the use of CCB as additive vs. monotherapy. Calcium channel blockers (CCB) may be used as additions to existing α-blockade when blood pressure control is inadequate or used alone for blood pressure control [30, 31]. Recent data demonstrates that monotherapy with CCB may have

similar outcomes to α-blockade [28, 33], but as per the Endocrine Society guidelines, monotherapy with CCB should only be considered in patients with normal or mildly elevated preoperative blood pressures or those who have severe orthostatic hypotension on α-adrenergic blocker [6]. Additionally, in patients with cardiomyopathy, or markedly elevated catecholamine levels, the catecholamine synthesis agent methylparatyrosine (metyrosine) can be added for a short duration prior to surgery to stabilize blood pressure in conjunction with an α-blocker [20]. Agents acting on the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), may improve blood pressure control in patients with elevated renin due to β-adrenergic-stimulated release, although renin elevation is not present in all patients with pheochromocytoma [34]. Following initiation of antihypertensive therapy and BP improvement, a liberalized salt diet (5000 mg per day) should be instituted for volume expansion (2.5 L per day), although little data exists for this practice [5].

This patient was successfully treated preoperatively with the α_1-selective blocker terazosin for 10 days before the initiation of a β-adrenergic blockade with metoprolol tartrate 12.5 mg twice daily. She soon after underwent an uncomplicated left adrenalectomy.

What Is the Expected Intraoperative Course? What Precautions Are Required?

Laparoscopic minimally invasive unilateral adrenalectomy is the procedure of choice for most pheochromocytomas [22]. However, open resection is preferred for pheochromocytomas larger than 6 cm or invasive pheochromocytomas to ensure complete tumor resection and prevent rupture or local recurrence [6]. Intraoperatively, medications and tumor manipulation can cause high amounts of catecholamine release and lead to significant hemodynamic complications such as hypertensive crisis, stroke, myocardial infarction, or multi-organ failure [5]. Induction of anesthesia (especially with succinylcholine), selective β-blockers (such as labetalol), corticosteroids, or tyramine-containing drugs (TCA, metoclopramide, or monoamine oxidase inhibition) can also precipitate hypertensive crisis and therefore must be avoided. These complications can even occur in patients who had asymptomatic or biochemically silent pheochromocytomas at the time of diagnosis. Catecholamine excess is associated with significant mortality in the perioperative setting with rates as high as 30% [28]. However, surgical outcomes have improved drastically with the use of specific surgical techniques and medical management with intravenous infusion of a short-acting CCB such as clevidipine and nicardipine, or vasodilating drugs such as nitroprusside are the preferred intraoperative anti-hypertensive agents. These treatments and techniques have lowered the surgical mortality rate to 0–3.0% [28]. In patients who may not have adequate preoperative α-adrenergic blockage, the intravenous α-adrenergic antagonist phentolamine may be used [29]. Anesthetic agents known to stimulate catecholamine secretion such as fentanyl, morphine, ketamine, halothane, and desflurane must be avoided, whereas propofol, barbiturates,

synthetic opioids, etomidate, and the other anesthetic gases are safe [27]. Intravenous volume expansion is often begun preoperatively provided cardiac and renal function will tolerate, and patients are encouraged to eat a high salt diet with adequate hydration prior to surgery. Lastly, intravenous insulin may also be required for catecholamine-induced hyperglycemia. Immediately post-operative, approximately 50% of patients have sustained hypertension [35], whereas others experience hypotension, usually a multifactorial response to sudden catecholamine depletion, hypovolemia, and persistence of α-adrenergic blocking drugs. Intravascular volume replacement followed by pressor support is the cornerstone of management. Initial post-operative rebound hypoglycemia is also possible, and therefore glucose levels should be closely monitored for 24–48 hours [6].

What Post-operative Monitoring Is Required for the Patient?

Complete tumor resection should be assessed 2–6 weeks post-operatively with collection of plasma or urine metanephrines [22, 27]. Normal values do not exclude the possibility of remaining microscopic disease; therefore, biochemical screening must be performed annually, as planned for our case patient, although no further imaging is required unless the biochemistry shows evidence of recurrence. Residual essential hypertension should be managed following the eighth report of the Joint National Committee (JNC 8) hypertension guidelines [36]. Persistent metanephrine elevations may signal residual tumor, multifocal disease, or metastatic disease and must be followed by CT, MRI, or functional imaging. Hypertension and symptoms of catecholamine excess should be managed as they were preoperatively, primarily with α-adrenergic blockade; however, the selective α-blocking agents are typically employed in these cases to minimize the side effects of expected long-term use. In patients with refractory disease, such as those with residual or metastatic disease, metyrosine, a tyrosine hydroxylase inhibitor, can be used [27]. The side effects of metyrosine can be disabling, including extrapyramidal symptoms, depression, galactorrhea, and sedation, particularly with long-term use. Therefore, metyrosine therapy should be reserved for inoperable, persistent disease with intractable symptoms despite α-adrenergic blockade. Finally, genetic testing should be discussed at the initial post-operative visit in any patient with a family history of pheochromocytoma, a paraganglioma, age younger than 45 years, a malignant tumor, bilateral or multicentric disease, or clinical presentation consistent with one of the known hereditary syndromes [37, 38].

Should This Patient Be Tested for Genetic Syndromes/What Is This Patient's Risk of Genetic Syndromes?

Pheochromocytomas occur equally in both men and women at any age, but is most commonly found in those age 40–50 years old. About 10–17% of all pheochromocytomas are malignant, with the most common sites of metastases reported as liver, lung, bones, and lymph nodes [39, 40]. Of all those diagnosed with pheochromocytomas, 30–40% are hereditary, and another 40–50% are found to have somatic mutations in 1 of approximately 20 pheochromocytoma susceptibility genes [6, 30, 41]. Several autosomal dominant heritable syndromes, including neurofibromatosis type 1 (NF-1), von Hippel-Lindau (VHL), MEN 2a and 2b, and paraganglioma syndromes types 1–5, carry an increased incidence of pheochromocytoma. About 5% of NF-1 patients may develop unilateral or bilateral PCC, and up to 12% of those are metastatic. Patients with VHL mutations have slightly higher rates of pheochromocytomas, occurring in 10–20% of patients, but lower malignant potential (5%) as compared to patients carrying the NF-1 mutation [39]. The highest rate of pheochromocytomas occurs in MEN2 patients at approximately 50%. Patients with MEN2 have a 50% chance of bilateral disease but only a 5% risk of malignancy [40]. Interestingly, patients with PCC associated with MEN-2 mutations typically have tumors with an epinephrine predominant secretory pattern [39]. It is also important to note that patients with increased risk of bilateral pheochromocytomas and a low risk of malignancy (such as VHL and MEN2) might be considered for adrenal cortico-sparing surgery to avoid complete removal of both adrenals.

Hereditary paraganglioma syndromes are associated with autosomal dominant mutations that are found in the succinate dehydrogenase (SDH) complex II. Mutations can occur in any subunit of genes (SDHA, SDHB, SDHC, SDHD) or cofactors; however, loss-of-function mutations in subunit SDHB is most commonly linked to pheochromocytomas [40]. Those with SDHB mutations have a mean age of 32 at time of initial diagnosis and have the highest risk of metastasis at 23% [40, 42]. Patients with any of these diagnoses should be screened annually for pheochromocytoma [4, 5]. Further, pheochromocytoma may be the initial manifestation of any of these syndromes, so identification of index cases is essential for screening relations.

This patient's personal history of pheochromocytoma warranted a genetic referral for testing given the high probability of finding a mutation. Geneticists analyzed 77 genes from our case patient and, surprisingly, no known pathogenic variants were found.

Can We Predict the Malignant Potential for This Patient?

Malignancy in pheochromocytomas is defined as the presence of metastasis into nonchromaffin tissue. The prevalence varies between 10 and 22% [39]. However, it is difficult to predict which tumors will become metastatic. Unlike most tumors, histologic features and vascular or capsular invasion alone are not helpful in predicting aggressive and malignant behavior of the tumor. Therefore, identifying biomarkers of malignant potential has proven helpful. There are two histopathologic scoring systems that have been used to help guide clinicians.

The first is identified as "Pheochromocytoma of Adrenal Gland Scaled Score" (PASS) that was derived from a retrospective analysis of 100 adrenal PCC that determined both the histopathologic features and the clinical behavior of the tumors over 10-year time period. Up to 20 points are assigned to certain histologic features, i.e., large nesting patterns, high cellularity, presence of necrosis, vascular or capsular invasion, and high number of mitoses or atypical mitoses. This study found that if the PASS score is less than four, tumors were more likely to be clinically benign, whereas tumors with a PASS score of four and above carry a higher risk of malignancy. Unfortunately, the PASS score has several limitations. Firstly, it was not developed for paragangliomas. Secondly, the PASS score has an extremely high inter-observer and intra-observer variability that makes it unreliable. Despite this, given the lack of a validated scoring system, the PASS score can be used with caution as a supplement to guide clinical surveillance.

The second scoring system is the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP). As the name implies, this grading system is used for both pheochromocytomas and paragangliomas. GAPP uses histopathologic features and also includes biochemical secretory markers and the Ki67 proliferation index. The GAPP score uses a maximum of 10 points, with tumors scored as 0–2 (well differentiated), 3–6 (moderately differentiated), and 7–10 (poorly differentiated). However, this scale has not been validated, and furthermore, it was later found that about 4% of tumors with a low GAPP score did metastasize [39, 42, 43].

Both the PASS and GAPP scores do not factor in patient genotypes. Immunohistochemistry of a succinate dehydrogenase complex subunit B (SDHB) loss-of-function germline mutation has proven as one of the only reliable predictors of malignancy. Tumors with loss-of-function SDHB mutations carry an increased risk of developing metastatic disease (40%) [6]. Furthermore, tumors that are larger than 4–5 cm or those that secrete the dopamine metabolite, methoxytyramine, have an increased risk of malignancy. For our patient, her PASS score was 10, and her tumor was large enough to put her at risk of future recurrence and metastases, though she lacked any of the 77 mutations that would predispose her to malignant potential.

Lessons Learned

Pheochromocytomas are rare, potentially fatal tumors that may be clinically silent or present with hypertensive emergencies, sustained arrhythmias, or sudden death. The manifestations of pheochromocytoma result from catecholamine

excess and may be variable based on the predominant catecholamine released and the adrenergic receptors affected. Our case patient experienced both hypertension and episodes of orthostatic hypotension, which were consistent with the markedly elevated norepinephrine and epinephrine levels, respectively. Her tumor was identified immediately on presentation, and her blood pressure was controlled with α-blockade, followed by heart rate control with β-blockade. This case highlights the need for a high index of suspicion for this sometimes elusive tumor, particularly in patients who experience paroxysms of symptoms, in young patients with hypertension, or in patients with a suspicious family history. Her presentation was initially concerning for MEN 2A given the pheochromocytoma and hyperparathyroidism, but the patient tested negative for any heritable syndromes. However, it is important to remember that many patients with pheochromocytoma harbor a germline mutation that merits genetic workup and possibly increased surveillance.

Test Your Knowledge

1. Which of the following is the proposed mechanism of hypertensive crisis?

   (a) Failure of proper autoregulation or ability of organs to maintain a stable blood flow irrespective of alterations in perfusion pressure, in the vascular beds, leading to endothelial injury and mechanical stress.
   (b) Excess catecholamines cause activation of the renin-angiotensin system that promotes a continuous cycle of worsening vasoconstriction and ischemia
   (c) Unopposed beta-stimulation leading to an abrupt increase in blood pressure and systemic vascular resistance.
   (d) Both A and B
   (e) All of the above

   Answer: D

2. Stimulation of which of the following receptors on apocrine glands causes sweating, mostly localized to the palms?

   (a) α_1
   (b) α_2
   (c) β_1
   (d) β_2
   (e) β_3

   Answer: A

3. Which receptor is not involved in vasoconstriction and hypertension due to pheochromocytomas? Stimulation of these receptors leads to smooth muscle dilation (bronchodilation) and ultimately decreased peripheral resistance and glycogenolysis and, to some degree, increases lipolysis?

   (a) α_1
   (b) α_2

(c) β_1
(d) β_2
(e) β_3

Answer: D

4. Which combined α- and β- blocker has more potent antagonistic activity at the β_1 and β_2 receptors than at the α-receptors (β:α of 5:1) and therefore can result in paradoxical hypertension or hypertensive crisis?

(a) Atenolol
(b) Metoprolol
(c) Bisoprolol
(d) Labetalol
(e) Carvedilol

Answer: D

5. The genetic predisposition which has the highest rate of pheochromocytoma is _____, while _____has the highest rate of malignancy.
(a) NF-1 mutation, MEN2
(b) MEN2, NF-1 mutation
(c) MEN2, VHL
(d) VHL, MEN2
(e) VHL, NF-1 mutation

Answer: B

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Chapter 20
Ectopic ACTH Syndrome

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Case #1: The Presentation and Diagnosis of Ectopic ACTH Syndrome

A 77-year-old female with rheumatoid arthritis on etanercept, worsening depression on venlafaxine, and treated hypothyroidism presented with easy bruising and muscle weakness for seven months. She denied any steroid use. Her blood pressure (BP) was 124/76 mmHg and BMI 21 kg/m^2, but she appeared mildly Cushingoid with round facies and had increased dorsocervical and supraclavicular fat. She had osteopenia of the spine and hip on bone densitometry, but no history of falls or fractures.

Laboratory evaluation showed the following: ACTH 75 pg/mL (<50), cortisol 35.2 μg/dL (<22), 24-hour urine free cortisol (UFC) 362 ug / 24 h (<50), salivary cortisol 0.428 μg/dL (<0.15), DHEA-S 165.7 μg/dL (<142.8), LH 0.1 mIU/mL, FSH 2.7 mIU/mL, potassium 4.1 mEq/L (3.5–5.2), and hemoglobin A1C 6.1% (<5.6%). All other hormonal testing was normal.

MRI of the pituitary showed a 4 × 2 × 3 mm hypoenhancing defect of the anterior pituitary. CT of the chest and abdomen showed a 1.1 cm left adrenal nodule and a 1 cm non-specific right middle lobe lung nodule. Inferior petrosal sinus sampling (IPSS) with CRH did not show a central ACTH step-up. ^{68}Ga-DOTATATE PET/CT (somatostatin receptor imaging) showed mildly increased tracer uptake in the right middle lobe measuring 1 cm with SUV max 3.7 and a 0.6 cm left apical subpleural nodule with SUV max 1.9.

The patient underwent a right middle lung lobectomy, and pathology was positive for typical carcinoid. Post-operatively, she needed hydrocortisone replacement

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therapy for nine months. ACTH was 19.7 pg/mL, cortisol 9.5 μg/dL, DHEA-S 31.3 μg/dL, LH 61.8 mIU/mL, and FSH 112.4 mIU/mL. Her Cushingoid features and myopathy resolved slowly over ten months.

How Do You Establish the Diagnosis of ACTH-Dependent CS?

The evaluation for CS, regardless of the origin, begins with a thorough history-taking and physical examination. In regard to the patient's history, it is important to exclude exogenous glucocorticoid exposure including scalp, intraarticular, and epidural injections of glucocorticoids. The long-acting steroid triamcinolone acetate is often given epidurally and can create CS symptoms albeit with suppressed cortisol, DHEA-S, and ACTH values. It is also imperative to inquire about any malignancies or conditions causing pseudo-CS like alcoholism, depression, obesity, or pregnancy. Though patients with CS possess signs of metabolic dysfunction, like hypertension, central adiposity, and impaired glucose tolerance, these findings can be common in the general population. Per the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2012, the prevalence of metabolic syndrome in US adults 18 years or older was 34.2% [1]. In contrast, the incidence of endogenous CS from any cause is much lower, cited to be 0.7–4.9 per million population per year [2–4]. Thus, it is the catabolic features that are the most discriminatory for CS, like violaceous striae >1 cm wide, ecchymoses, proximal muscle weakness, and decreased bone mass and quality leading to fractures especially at a younger age [5].

Once CS is suspected clinically and confirmed biochemically with 24-hour UFC measurements, overnight 1 mg dexamethasone suppression test, and/or late-night salivary cortisol levels, determination of ACTH independence or dependence can be easily ascertained by a serum ACTH level. However, once ACTH dependence is established based on a high or inappropriately normal ACTH level in the face of hypercortisolism, it can be challenging to determine whether the ACTH source is eutopic (deriving from a pituitary tumor) or ectopic (caused by a non-pituitary ACTH-producing tumor).

In this case of a slim, elderly female with only pre-diabetes, the typical features of CS were subtle. Elderly patients in particular may not exhibit the classic clinical stigmata. The scientific literature is sparse on CS in elderly patients, but a retrospective study of 45 cases of CS due to eutopic ACTH in patients >60 years old showed that lower BMI and muscle wasting were the most significant signs of CS [6]. Elderly patients appear to present more frequently with these catabolic features, regardless of thyroxine, testosterone, IGF-1 levels, or the etiology of their CS. In addition, there are case studies in which elderly patients have only psychiatric manifestations as their presenting symptom [7–9]. It is postulated that this might be due to differing responses to chronic hypercortisolemia, such as alterations in the glucocorticoid receptor sensitivity or intracellular signaling [10].

CS also presents primarily with catabolic features of hypercortisolism when the source is ectopic ACTH. Patients with EAS generally have a more rapid onset of

symptomatology (average seven months) and very elevated UFC level (above five times the upper limit of normal). The general features of the history and physical exam that are typically more distinguishing for EAS are male gender, older age, history of a neuroendocrine tumor, rapid onset of typically <18 months, prominent catabolic signs like weight loss, extremely high levels of cortisol and ACTH, profound hypokalemia, and severe hypertension. It is especially the rapid onset and catabolic signs that have the greatest positive likelihood ratios at 15 and 20, respectively, of predicting ectopic ACTH as the cause of CS [11].

How Can the Source of ACTH Secretion Be Determined from the Biochemical Profile?

The determination of ACTH independence or dependence should be assessed by measurement of the plasma ACTH level. In the presence of hypercortisolism, plasma ACTH should be suppressed unless there is pituitary or ectopic ACTH production. Other interesting findings in our case's biochemical profile that supported ACTH dependence was the high DHEA-S level. DHEA-S decreases with age typically [12], and thus the high levels in this case were unusual and suggested continuous ACTH stimulation of the adrenal cortex.

Localizing the source of the excess ACTH secretion can be challenging. Both eutopic and ectopic ACTH can present with high levels of ACTH and cortisol, and there is overlap in the degree of suppression by exogenous glucocorticoids. The severity of the ACTH and 24-hour UFC elevations can help distinguish between eutopic and ectopic ACTH secretion. In a ten-year retrospective study of 21 ectopic CS patients in India, ACTH levels higher than 200 pg/mL were observed in a majority of these patients when compared to eutopic CS [13]. In another retrospective study of 110 patients with EAS, a 24-hour UFC above five times the upper limit of normal was seen in 69.9% of patients [14], similar to our case. In addition, the presence of hypokalemia is common in EAS. Hypokalemia was observed in 70–86% of patients with EAS in these studies.

Dynamic biochemical testing with the high-dose dexamethasone suppression test (HDDST) and CRH stimulation test can also be performed to assist in the source localization of ACTH secretion. Typically, pituitary ACTH-secretory tumors still retain CRH and cortisol receptors needed for positive and negative feedback, respectively. Therefore, in theory, pituitary ACTH-producing tumors should be further stimulated to make ACTH with CRH administration and should suppress after high-dose dexamethasone. In contrast, ectopic ACTH-producing tumors do not express receptors needed for positive or negative feedback and therefore will not increase ACTH after CRH, or suppress cortisol after high-dose dexamethasone. But in practice, the HDDST does not reliably distinguish eutopic from ectopic ACTH-dependent CS, with sensitivity and specificity ranging from ~60% to 100% [15–17]. Some benign carcinoid tumors are regulated in the same way as eutopic ACTH-producing tumors [18]. The CRH stimulation test is often used together with the

HDDST, as CRH should stimulate eutopic ACTH-producing tumors to increase ACTH and cortisol. Alone, the CRH stimulation test has a sensitivity and specificity of 80–90% to detect eutopic ACTH-secreting tumors [19, 20]. In combination, the HDDST and CRH stimulation tests are more sensitive – in a recent study of 35 patients, the combined test had a sensitivity of 94% and specificity of 100% in identifying eutopic ACTH-producing tumors [21].

Given that the above dynamic tests have less diagnostic accuracy for EAS, the diagnosis largely depends on sophisticated imaging and IPSS. In our case, dynamic biochemical testing was not needed given that the history, physical examination, initial biochemical evaluation, and imaging strongly suggested EAS.

What Is the Role of Imaging in the Diagnosis of Ectopic ACTH Syndrome?

Since dynamic biochemical testing cannot reliably distinguish eutopic from ectopic ACTH syndrome (particularly from very small, benign carcinoid tumors), imaging becomes a helpful modality to validate source localization.

Pituitary MRI is useful to determine whether there is a lesion present to suggest a eutopic ACTH-secreting tumor. However, pituitary incidentalomas have been estimated to be present in 1.5–38% of the population, with an increasing proportion being recognized in the elderly [22, 23]. In a retrospective study of 130 CS patients, a pituitary lesion was found in 23% of patients with EAS. When stratifying by size, it was determined that the size cutoff of above 6 mm for the pituitary tumor had a 40% sensitivity and 96% specificity to diagnose a eutopic ACTH-secreting tumor [24].

The basis for IPSS is that if the ACTH production is from the pituitary gland, the ACTH levels in the inferior petrosal sinuses will be higher than that in the periphery, i.e., inferior vena cava (IVC). In addition, in pituitary causes of ACTH overproduction, CRH administration will further stimulate central secretion of ACTH, as pituitary tumors retain CRH receptors for positive feedback. A central-to-peripheral plasma ACTH gradient of >2 before CRH administration or >3 after CRH administration is diagnostic of an eutopic/pituitary source of ACTH secretion. When performed at experienced centers, sensitivity and specificity were 95–100% for localization of the source of excess ACTH [25].

The demonstration of a pituitary tumor in our case initially suggested a possible pituitary source of ACTH although the tumor seen was smaller than the 6 mm cutoff suggested by previous reports. IPSS was carried out and did not show a central step-up in ACTH before or after CRH administration, virtually ruling out a pituitary ACTH-secreting tumor. In addition, there were other clinical and biochemical features of this case that were highly suggestive of EAS including the advanced age of patient, the relatively acute onset of signs and symptoms, and the very high 24-hour UFC values.

Even once the source of ACTH overproduction is confirmed to be ectopic as was the case in this patient, the precise localization of the tumor can be challenging.

^{68}Ga-DOTATATE PET/CT (somatostatin receptor imaging) has emerged as a sensitive test for the detection of ectopic ACTH-producing tumors. In the majority of ectopic ACTH cases, the neuroendocrine tumors arise from the lung (40–50%), with bronchial carcinoid tumors comprising 5–40% and small cell lung cancers comprising 3–50% [26, 27]. However, these ranges vary depending on the population studied. Other less common sources include islet cell tumors of the pancreas, thymic carcinoid tumors, pheochromocytomas, and thyroid medullary carcinomas. In spite of newer localization techniques, the source of ectopic ACTH often remains unidentified (6–18%) [28]. False negatives on somatostatin receptor imaging may be due to cortisol's suppressive effect on the somatostatin receptor expression in neuroendocrine tumors [29–31]. Thus, in cases of ACTH-dependent CS with negative IPSS and failure of localization of the ectopic source on initial imaging, re-evaluation should be done after medical treatment of the hypercortisolism. Fortunately in this patient, the lung source was demonstrated on initial somatostatin receptor imaging even in the presence of severe hypercortisolism, and her CS resolved with successful surgical removal of a typical lung carcinoid.

What Is the Postoperative Management After Removal of the Primary Tumor?

The guidelines for monitoring and replacement of glucocorticoids after surgical removal of the primary tumor can be extrapolated from those about CS in general [32]. After successful removal of primary tumor, glucocorticoid replacement therapy will be required, as the HPA axis can be suppressed for up to two years. Of note, patients will not require mineralocorticoid replacement therapy as aldosterone secretion is not suppressed due to ectopic ACTH because it is primarily regulated by the renin-angiotensin system.

Hydrocortisone is the preferred agent given its physiology and short half-life, as it allows for recovery of the hypothalamic-pituitary-adrenal (HPA) axis. Immediately postoperatively, stress doses are likely needed with a quick taper to maintenance doses. Axis recovery should be assessed at least every three months with a morning cortisol or ACTH stimulation test.

Case #2: The Acute Presentation of Severe Hypercortisolism from Ectopic ACTH Syndrome and the Need for Urgent Medical and Surgical Management

A 72-year-old male with a history of melanoma that was resected 15 years prior, and prostate cancer treated with radiotherapy ten years prior, presented to the hospital with weakness and confusion for one week.

Initial laboratory evaluation was notable for glucose 454 mg/dL (65–99) and potassium 1.7 mEq/L (3.5–5.2). His BP was 164/97. He appeared Cushingoid, with a round, flushed face, mild proptosis, supraclavicular and dorsocervical fat pads, hyperpigmentation, and scattered ecchymoses of the extremities. He was stabilized medically with antidiabetic and antihypertensive medications and discharged with potassium chloride 20 mEq daily, spironolactone 100 mg twice daily, repaglinide 2 mg with meals, amlodipine 10 mg daily, and hydralazine 50 mg twice daily.

Five weeks later, he returned to the hospital with worsening weakness, weight loss of 20 lbs., and somnolence. His laboratory evaluation disclosed: potassium 2.6 mEq/L (3.5–5.2), ACTH 443 pg/mL (<50), and 24-hour UFC 9447 mcg/dL (<50). EAS was suggested based on the patient's age, sex, rapidity and severity of symptoms, the very high ACTH and UFC values, and the failure of HDDST to suppress cortisol, with serum cortisol 259 mcg/dL and ACTH 546.7 pg/mL after 8 mg dexamethasone.

MRI of the brain showed an unremarkable pituitary gland, and MRI of the abdomen and pelvis showed bilateral adrenal masses (right 3.3 × 2.7 cm and left 3.8 × 2.8 cm) with benign radiographic features. CT of the chest was unremarkable, but PET/CT of the entire body showed a 1.2 cm hypermetabolic soft tissue mass plastered along the right pericardium along the inferomedial right middle lobe, with a probable new inflammatory focus in the right upper lobe measuring up to 2.2 cm in its largest diameter.

Due to his rapid deterioration over the preceding five weeks, and biochemical evaluation and imaging suggestive of ectopic ACTH causing acute, severe hypercortisolism, he underwent urgent laparoscopic bilateral adrenalectomy.

One month after surgical adrenalectomy, he was much improved medically with a normal mental status exam and normal glucose and potassium values on glucocorticoid and mineralocorticoid replacement therapies. He then underwent an octreotide scan that revealed a somatostatin-avid 1.8 cm right upper lobe nodule corresponding to the FDG avid nodule on the initial PET/CT, compatible with a neuroendocrine tumor. Right upper and middle lobe wedge resections were performed with pathology demonstrating a typical carcinoid tumor that was 1.2 cm along with the uninvolved lung with multiple tumorlets and multifoci of bronchiolar subepithelial neuroendocrine cell hyperplasia. He was maintained on glucocorticoid and mineralocorticoid replacement and continued to do well without recurrence.

What Are the Clinical Features That Necessitate Urgent Surgical Management in Patients with Ectopic ACTH Syndrome?

Severe hypercortisolism from CS should be considered an "endocrine emergency" given that certain sequelae can be fatal if not addressed. Based on expert opinion, severe hypercortisolism is defined as a 24-hour UFC above five times the upper

limit of normal, or a serum cortisol above 41 μg/dL and the presence of life-threatening complications [28, 33]. If left untreated, the morbidity and mortality in severe hypercortisolism are high, as it leads to hypertension, heart failure, hypokalemia, thromboembolism, gastrointestinal hemorrhage, hyperglycemia, infection, and altered mental status.

Once severe hypercortisolism is identified, the patient should be admitted to the intensive care unit. The aims of emergency medical management are to control the acute hypercortisolism with medical therapy and prevent life-threatening complications due to infection, diabetes, hypertension, and hypokalemia. If the primary tumor cannot be identified or is deemed unresectable, the patient should undergo urgent bilateral adrenalectomy. Bilateral adrenalectomy provides immediate control of the negative downstream effects of acute hypercortisolism and was reported to be relatively safe in a retrospective review of 53 patients in Munich, with 3.6% of patients having an adverse outcome and a 5.7% surgical mortality rate (compared to 2.1% and 2.4% in Cushing's disease, respectively) [33]. In another retrospective study of 48 patients with EAS all of whom underwent bilateral adrenalectomy at the Mayo Clinic, the survival rate at five years for patients with a known primary tumor was 52%, and 35% for those with an unknown primary tumor, but the contributors to death are multifactorial [34].

Our case presented with new onset hypertension, hyperglycemia, and hypokalemia, controlled preoperatively with supportive medical therapy. But given his clinical deterioration with altered mental status and persistent hypokalemia, urgent bilateral adrenalectomy was indicated.

What Medications Are Available to Manage Severe Hypercortisolism Preoperatively?

The choice of medical management depends on the severity of the hypercortisolism, symptoms of the patient, and whether the disease is resectable or metastatic. In severe hypercortisolism requiring immediate management, medical therapy needs to be efficacious in reducing cortisol levels and mitigating complications as a bridge to surgery. Immediate-acting steroidogenesis inhibitors include etomidate, metyrapone, ketoconazole, mifepristone, and potentially osilodrostat (Fig. 20.1).

For acute lowering of cortisol within 12–72 hours, etomidate can be administered close to the operative period. Etomidate inhibits both 20,22-desmolase and 11β-hydroxylase in the cortisol synthesis pathway. Typically used as an anesthetic agent for induction or sedation, in acute hypercortisolism it is used at subhypnotic doses. It is also useful in patients who cannot tolerate oral medication, as it is given intravenously at a continuous rate. However, because of the risks of hypopnea and apnea, patients must be monitored closely in the intensive care unit [35].

Metyrapone also inhibits 11β-hydroxylase and can cause a significant decrease in serum cortisol levels within hours [36] and UFC within weeks [37, 38]. Due to its

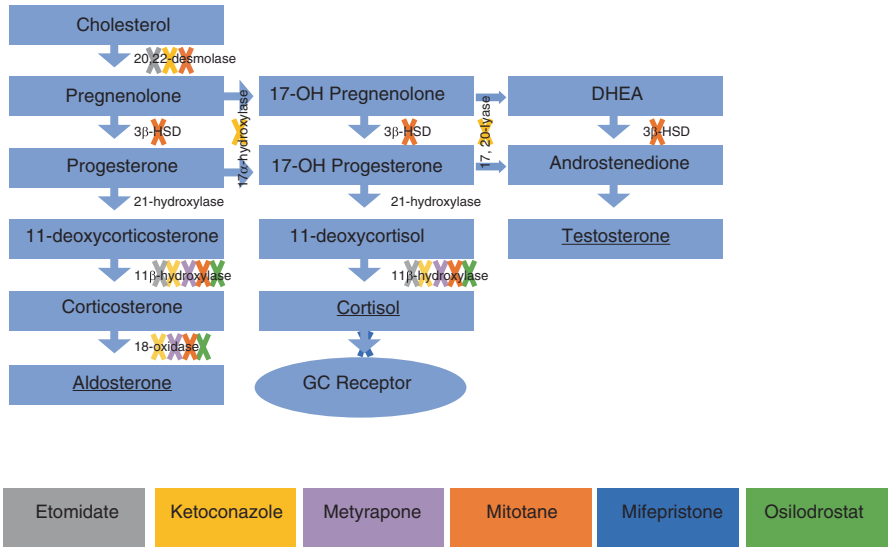

Fig. 20.1 Cortisol synthesis inhibitors and receptor blockers. (Adapted from: Sanchez Escobar J, Ravikumar A, and **Levine, AC.** Fig. 10.3 in "Benign Adrenal Cushing's Syndrome: Updates on Overt and Mild Hypercortisolism" in "Adrenal Disorders: Physiology, Pathophysiology and Treatment" Contemporary Endocrinology Series, Poretsky L (Series Editor), **Levine, AC (Edition Editor)**, Humana Press, 2018, ISBN 978-3-319-62470-9)

short half-life, it needs to be dosed three to four times daily. The main side effects that may limit therapy are hypertension and hypokalemia as it induces elevations in 11-deoxycorticosterone that has mineralocorticoid effects. Also, since adrenal androgens do not require the 11β-hydroxylase enzyme, the drug can cause hirsutism and other hyperandrogenic signs and symptoms in females with long-term use.

Ketoconazole inhibits several enzymes in the cortisol synthesis pathway. Since it works at multiple enzymatic steps, the result is improvements in metabolic outcomes such as BP, glucose tolerance, and hypokalemia. It reduces 24-hour UFC values in up to 73% of patients, with 49% having normalization preoperatively [39]. Ketoconazole also acts rapidly and has been reported to lower cortisol levels within a few days. The limiting factor is potential hepatotoxicity at high doses.

Osilodrostat is a newer 11β-hydroxylase inhibitor that has a longer half-life than metyrapone. In preliminary studies, it was noted to lower cortisol levels in patients with Cushing's syndrome dramatically within weeks, including in one case of ectopic ACTH [40].

When monotherapy is not effective, combination therapy can be considered. In a retrospective study of 14 patients with EAS treated with the combination of metyrapone and ketoconazole, the median 24-hour UFC decreased from 40 to 3.2 times the upper limit of normal in one week and normalized in 73% of patients [41]. In a prospective cohort study of seven patients with occult or metastatic EAS, patients were treated with mitotane, metyrapone, and ketoconazole combination therapy as

an alternative to rescue adrenalectomy. There was an acute and significant lowering of 24-hour UFC in one to three days after initiation of triple therapy to normal levels in five patients [42].

Other medical options include mifepristone (a glucocorticoid receptor antagonist), mitotane (a steroidogenesis inhibitor and adrenolytic), somatostatin receptor agonists, and dopamine receptor agonists. However, these therapies have been less well-studied as agents to acutely lower cortisol levels in patients with severe, life-threatening hypercortisolism. For metastatic disease, chemotherapy has to be considered, although it is preferable to manage the hypercortisolism prior to its initiation.

What Are the Perioperative Risks and How Should They Be Addressed? What Are the Considerations in Determining the Type of Surgery?

The most important perioperative risks to address are hypokalemia, hypertension, thromboembolism, and infection. These risks are decreased by the use of cortisol-lowering drugs as in the prior section but also have their own sets of therapies.

Hypokalemia occurs in up to 70% of patients with EAS and can result in life-threatening arrhythmias if not corrected. The mechanism of action involves the direct stimulation of the mineralocorticoid receptor (MR) by cortisol, which at high levels overwhelms the ability of 11β hydroxysteroid dehydrogenase-2 (11β HSD-2) to inactivate cortisol to cortisone, leading to cortisol activation of the MR in the kidney [43]. It is also postulated that ACTH itself inhibits 11β HSD-2 directly. The MR antagonist spironolactone is often used as an adjunct to cortisol-lowering therapies at doses as high as 100–300 mg/day to block cortisol effects at the MR. Potassium levels must also be monitored frequently and replaced with aggressive supplementation and monitoring.

Hypertension occurs in over 80% of patients with EAS. The mechanisms are multifold and include the direct mineralocorticoid activity of cortisol, activation of the renin-angiotensin system, increased cardiac output, and enhanced peripheral and renovascular resistance [44]. Cortisol-lowering therapies may alleviate the hypertension, but additional therapies include MR antagonists, ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers.

Elevated levels of cortisol in CS lead to a hypercoagulable state with an increased incidence of thromboembolism. In a population-based cohort study of 343 CS patients, the hazard ratio was 2.6 for increased risk of venous thromboembolism, 3.7 for myocardial infarction, and 2 for stroke [45]. These complications, as well as pulmonary thrombosis, have been described in patients with EAS. Cortisol activates the coagulation pathway by augmenting procoagulant factors VIII and IX and von Willebrand factor complex, impairing fibrinolysis, and increasing platelet aggregation. Though there are no specific studies on EAS, it is likely that the underlying malignancy responsible for the ectopic ACTH may further induce a

thromboembolic state. Postoperatively, the risk of venous thromboembolism in patients with CS due to any etiology is up to 5.6% and can extend to 30–60 days postoperatively, which is comparable to the risk after total hip or knee replacement on routine thromboprophylaxis [46, 47]. Though no official guidelines exist on anticoagulation for CS patients undergoing surgery, a retrospective study showed that postoperative prophylactic anticoagulation with two weeks of heparin reduced the risk of thromboembolic events from 20% to 6% [48]. Even in patients with successful surgical outcomes, long-term anticoagulation therapy should be considered as there is a demonstrated increased risk for thromboembolism and stroke in patients for as long as 1–21 years after remission [49].

The risk of infection is related both to the severity of hypercortisolism and the degree of immunosuppression [50]. Patients with CS are at risk for opportunistic infections due to bacteria, viruses, and fungi like the *Pneumocystis* family causing pneumonia. Due to the serious risk of the latter, the Endocrine Society guidelines recommend trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis carinii* or *jirovecii* in cases of severe hypercortisolism [32].

The surgical approach to bilateral adrenalectomy is primarily laparoscopic instead of open given advances in technology and can be done via an anterior or retroperitoneal approach. In addition, it can be done as a staged procedure depending on patient's prior surgical history and comorbidities.

What Is the Postoperative Management for Patients Who Have Undergone Bilateral Adrenalectomy?

Bilateral adrenalectomy eliminates both endogenous glucocorticoid and mineralocorticoid synthesis, and thus both types of replacement will be needed lifelong postoperatively. Hydrocortisone is the preferred agent for glucocorticoid replacement given its physiology and short-acting nature, and fludrocortisone is the only agent available for mineralocorticoid replacement. Initially stress doses of hydrocortisone are required with a quick taper to maintenance doses. With doses above 100 mg/day, fludrocortisone is not needed in the immediate postoperative period but must be added upon discharge.

Hydrocortisone doses should be tailored to the patient's symptoms, and fludrocortisone titrated to the patient's electrolyte levels and BP.

Multiple-Choice Questions

1. A 36-year-old male presents with new-onset hypertension, hyperlipidemia, insomnia, and weight gain of 45 lbs. in two months. He reports no prior steroid use. On physical exam, his BP is 161/94, BMI is 36 kg/m^2, and he has round facies, violaceous striae, and lower extremity edema. His initial labwork shows ACTH 163 pg/mL (<50), morning cortisol 31 μg/dL (<22), and potassium 2.8 mEq/L (3.5–5.2). Subsequent testing showed a 24-hour UFC of 285 μg/24 h

(<50) and failure to suppress cortisol with a HDDST. MRI of the pituitary did not show any lesions. IPSS did not demonstrate lateralization or step-up from the pituitary to periphery.

What is the best next step in management?

(a) Localization with somatostatin receptor-based imaging (i.e., ^{68}Ga-DOTATATE PET/CT)
(b) Abdominal CT to rule out adrenal tumor
(c) CRH stimulation test
(d) Treatment with pasireotide

2. The following are correct about EAS *except:*

(a) The most common primary tumors causing EAS arise from the lung.
(b) False positives on the dexamethasone suppression tests can occur with estrogen therapy, acute physical or emotional stress, and obesity.
(c) Many ectopic ACTH-secreting tumors express somatostatin receptors.
(d) High-dose dexamethasone suppression test distinguishes EAS from eutopic Cushing's with 100% sensitivity and specificity.

3. What are the risks that need to be emergently addressed in patients with severe hypercortisolism due to EAS?

(a) Hypokalemia
(b) Infection
(c) Thromboembolism
(d) Severe hypertension
(e) All of the above

4. A 53-year-old female with newly diagnosed poorly differentiated pancreatic neuroendocrine tumor with peritoneal deposits is admitted from clinic with new onset HTN and metabolic alkalosis with venous blood gas pH 7.52 (7.33–7.43) and bicarbonate 45 mEq/L (22–30). She was suspected to have EAS based on biochemical evaluation showing ACTH 101.8 pg/mL (<50), AM cortisol 28.8 μg/dL (<22), and inability to suppress cortisol with HDDST. Her clinical course was complicated by hypokalemia to 2.3 mEq/L (3.5–5.2), which responded with potassium chloride repletion and spironolactone therapy. ^{68}Ga-DOTATATE PET/CT (somatostatin receptor imaging) showed abnormal tracer avid uptake in a mediastinal lymph node.

The following options might be considered to treat her hypercortisolism while awaiting treatment of her underlying metastatic malignancy with chemotherapy:

(a) Ketoconazole
(b) Bilateral adrenalectomy
(c) Metyrapone
(d) All of the above

5. Patients who undergo bilateral adrenalectomy for severe hypercortisolism from EAS are at risk for all the following *except*:

   (a) Glucocorticoid deficiency
   (b) Mineralocorticoid deficiency
   (c) Nelson's syndrome

6. Which is the most useful clinical parameter in determining maintenance hydrocortisone dosage after bilateral adrenalectomy?

   (a) AM ACTH and cortisol after holding the AM dose of hydrocortisone
   (b) 24-h UFC
   (c) Patient's signs and symptoms (weight, appetite, energy level)
   (d) BP

Answers

1. (a)
2. (d)
3. (e)
4. (d)
5. (c)
6. (c)

Lessons Learned

EAS can be challenging to diagnose and treat especially if cases of severe, life-threatening hypercortisolism. Certain features in the clinical history such as prominent catabolic signs and symptoms, rapid onset, and profound hypokalemia can direct the diagnosis toward EAS. However, the diagnosis is confirmed biochemically with often significant elevations in ACTH and cortisol (typically measured by the 24-hour UFC) and by a negative IPSS and localization of a suspect tumor on CT, PET/CT, or somatostatin-based nuclear imaging. When severe hypercortisolism occurs as a consequence of EAS, it should be treated as an endocrine emergency with prompt medical stabilization as a bridge to surgical management. Life-threatening complications of severe hypercortisolism include severe hypertension, heart failure, hypokalemia, thromboembolism, gastrointestinal hemorrhage, hyperglycemia, infection, and altered mental status. Etomidate, metyrapone, ketoconazole, and mifepristone are agents to consider for acute lowering of cortisol levels, but ultimately if a primary tumor is not found, bilateral adrenalectomy may be necessary. After bilateral adrenalectomy, glucocorticoid and mineralocorticoid therapy must be immediately administered. The prompt recognition and management of severe hypercortisolism in cases of ectopic ACTH are essential in order to prevent morbidity and mortality in this rare endocrine emergency.

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Part VI
Primary Hyperparathyroidism

Chapter 21
Primary Hyperparathyroidism

Claudio Marcocci

Calcium in the Body

The calcium content of the adult body is approximately 1 kg, 99% of which is stored in the mineral phase of bone and the remaining is located in the extracellular fluid and soft tissues.

Calcium in Blood

The concentration of serum calcium ranges between 8.4 and 10.4 mg/dL (2.1–2.6 mmo/L), approximately half is in the ionized form (Ca^{2+}), and the remaining half is bound to protein (45%, mostly albumin) or complexed to anions, such as phosphate or citrate [1].

Total serum calcium is commonly measured in clinical practice and its concentration may vary when protein concentrations, especially albumin, fluctuate. Dehydration and hemoconcentration may also increase serum albumin and falsely elevate total serum Ca values. The following formula can be used to obtain the corrected total serum calcium:

$$\text{Corrected total calcium} = \text{total calcium}\left(\text{mg / dL}\right) + 0.8 \times \left[4 - \text{serum albumin mg / dL}\right)]$$

Variations in blood pH can change the equilibrium constant of the albumin-Ca complex, even when serum albumin concentration is normal: acidosis reduces and

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alkalosis increased the binding. Ca^{++} should be measured when major shift in serum protein or pH occurs.

Calcium in the Cell

The concentration of calcium in the cytoplasm is about 10^{-6} M, whereas its concentration in the ECF is approximately 10^{-3} M, thus favoring the calcium entry into the cell, which is also favored by a negative cell interior. The cell uses several mechanisms to defend against these chemical and electrical gradients across the plasma membrane in order to preserve viability. In addition, intracellular calcium bound to proteins in the cytoplasm, endoplasmic reticulum, and mitochondria can be mobilized to maintain cytoplasmic calcium levels and create pulsatile peaks of Ca^{2+} which mediate membrane receptor signaling.

Calcium in Bone

The majority of skeletal calcium is located in the mineral phase of bone as hydroxyapatite [$Ca_{10}(PO4)_6(OH)_2$]. The hydroxyapatite crystal serves as a source of calcium for a variety of calcium-dependent biological systems and contributes to maintain blood calcium within the normal range.

Regulation of Calcium Homeostasis

Three hormones are involved in the control of calcium homeostasis: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], and fibroblast growth factor 23 (FGF23) [2].

Minimal changes of extracellular fluid concentrations of Ca^{2+} are sensed by the parathyroid calcium-sensing receptor (CaSR), and the PTH secretion is adjusted accordingly [3].

A decrease in ECF calcium leads to reduced activation of the parathyroid CaSR, which leads to an increase in PTH production and secretion [4, 5]. PTH, over the course of minutes, increased calcium reabsorption in the cortical thick ascending limb of the Henle's loop and distal convolute tubule of the kidney. Over the course of several hours to days, PTH enhances osteoclastic bone resorption and liberates both calcium and phosphate from the skeleton. PTH stimulates the renal conversion of 25(OH) to the active sterol 1,25$(OH)_2$D, likely over several hours, which in turn will augment intestinal calcium absorption. PTH has also increase the release of FGF23 from mature osteoblasts and osteocytes. More prolonged hypocalcemia and exposure to elevated PTH may also result in 1,25$(OH)_2$D-mediated release of

calcium and phosphate from the bone. The net effect of the increased reabsorption of filtered calcium along the nephron, of the mobilization of calcium from bone, and of the increased absorption of calcium from the gut is to restore the extracellular calcium to normal and to inhibit further production of PTH and $1,25(OH)_2D$. Additionally, FGF23 can be released from the bone by $1,25(OH)_2D$ and can in turn reduce $1,25(OH)_2D$ concentrations. FGF23 has also been reported to decrease PTH production, therefore further ensuring that Ca homeostasis is restored.

An increase of the extracellular calcium is followed by the opposite sequence of events. A short-term increase leads to an increase in the cleavage of PTH (1–84), a decreased secretion of stored PTH from secretory vesicles, and when long-lasting a suppression of expression and transcription of the PTH gene. 1,25(OH)2D production in the kidney is decreased. In addition, calcium activation of the CaSR in the cortical thick ascending limb leads to hypercalciuria, a mechanism of renal calcium handling independent of PTH. Thus, suppression of PTH release and $1,25(OH)_2D$ synthesis results in reduced renal tubular Ca reabsorption, decreased skeletal Ca release, and decreased intestinal Ca absorption, resulting in normalization of the elevated ECF Ca.

PTH secretions is also regulated by serum $1,25(OH)_2D$, phosphate, and FGF23 [5]. $1,25(OH)_2D$ decreases the transcription of the PTH gene and PTH secretion. Hyperphosphatemia (as in chronic kidney failure) stimulates PTH synthesis and secretion and parathyroid cell proliferation, either directly or by lowering plasma Ca^{2+} due to its binding to phosphate. In addition, hyperphosphatemia stimulates the secretion of FGF23 by osteoblast/osteocytes. The main effect FGF23 is to increase phosphate excretion and suppress the renal 1α-hydroxylase enzyme. In addition, FGF23 acts directly, in a Klotho-dependent fashion, on the parathyroid cell inhibiting PTH secretion.

Primary Hyperparathyroidism

Hyperparathyroidism (HPT) may occur as a primary disorder of the parathyroid gland where PTH secretion is increased or abnormally elevated in the face of PTH-induced hypercalcemia (primary HPT, PHPT) or as a compensatory response to hypocalcemia or peripheral resistance to PTH (secondary HPT, SHPT). Finally, HPT may occur in setting of previous SHPT, when PTH secretion continues despite the correction of the triggering cause (tertiary HPT), as in end-stage chronic kidney disease.

PHPT is the most common endocrine disorder after thyroid diseases and diabetes and the most frequent cause of hypercalcemia in the general population [6, 7].

The incidence varies according to geographic areas and assessment measures; recent data in the United States indicate an incidence of 79.6 per 100,000 person-years in women and 35.6 per 100,000 person-years in men of all races, with the highest rate among blacks. The incidence peaks in the sixth decade of life. The prevalence ranges between 1 and 7 cases per 1000 adults. Most cases occur in

women (with a female-to-male ratio of 3:1), but there is no sex difference before the age of 45 years. PHPT is rare in children and adolescents.

PHPT is most often caused by a single adenoma (80–85%) and less frequently by multiple gland disease (10–15%) or carcinoma (less than 1%). It mainly occurs as a sporadic disease (90–95%) or may be part of hereditary disorders [multiple endocrine neoplasia (MEN) types 1, 2A, and 4, familial isolated hyperparathyroidism (FIHPT), and hyperparathyroidism–jaw tumor syndrome (HPT-JT)]. Multigland involvement is more common in hereditary cases, particularly MEN1.

Clinical Presentation

In Western countries, the clinical profile has shifted from a symptomatic disease characterized by hypercalcemic symptoms, kidney stones, overt bone disease (osteitis fibrosa cystica, fragility fractures) to one with absent or nonclassical manifestations (asymptomatic PHPT), which include subtle cardiovascular abnormalities and psychological and cognitive symptoms [6].

In the last 20 years, a new variant of PHPT has been identified, namely, patients with, in repeated testing, increased serum PTH in the absence of hypercalcemia (also by measurement of ionized calcium) or other causes of secondary PHPT (normocalcemic PHPT) [8]. This condition has been typically found in individuals evaluated for skeletal health, in whom PTH was measured even in the absence of hypercalcemia. This biochemical signature may represent an early phase of classical hypercalcemic PHPT, when PTH elevation precedes the occurrence of hypercalcemia.

Evaluation and Diagnosis

The finding of confirmed, mildly increased albumin-corrected serum calcium on routine blood testing in asymptomatic or mildly symptomatic (weakness and easy fatigability, anxiety, and cognitive impairment) individuals or in postmenopausal women investigated for osteoporosis is typically the first clue to the diagnosis of PHPT. The next step in the differential diagnosis would be the measurement of plasma PTH: the finding of abnormally increased serum calcium together with increased or inappropriately normal PTH is virtually diagnostic of PHPT. Exceptions to this rule are the use of lithium or thiazides, tertiary hyperparathyroidism of end-stage renal failure, and familial hypocalciuric hypercalcemia. Serum phosphate is normal or in the low-normal range in mild PHPT and low in severe cases. A low or undetectable PTH level in a hypercalcemic patient rules out the diagnosis of PHPT. Twenty-four-hour urinary calcium should also be measured, and if greater than 400 mg, a more extended evaluation of the stone risk profile is recommended [9]. Evaluation of the calcium-to-creatinine clearance ratio should be performed in

selected cases to exclude familial hypocalciuric hypercalcemia (FHH), which is suggested by a value of less than 0.01.

Hereditary forms of PHPT should be sought in young patients and in those with a family history of hypercalcemia and/or neuroendocrine tumors. Serum calcium should be measured in first-degree relatives, and genetic tests performed as appropriate. Parathyroid cancer should be suspected in individuals, especially males, with marked hypercalcemia, a palpable neck mass, and markedly elevated (3–10 times the upper normal value) plasma PTH concentration.

All patients with a confirmed diagnosis of PHPT, even those with no history of nephrolithiasis, should undergo renal ultrasound, since silent kidney stones are common in patients with asymptomatic PHPT. BMD by dual-energy X-ray absorptiometry (DXA) should be measured at the lumbar spine, hip, and distal forearm. It is typically low at the one-third distal radius, a site of enriched cortical bone, but a few patients may show predominant cancellous bone involvement, as documented by low BMD at the lumbar spine. The involvement of the trabecular compartment is also confirmed by a lower trabecular bone score (TBS) at the lumbar spine. Vertebral imaging by X-ray or DXA (vertebral fracture assessment, VFA) should also be routinely performed to detect silent vertebral deformities, since vertebral fracture risk is increased in asymptomatic patients.

Neck imaging (ultrasound and sestamibi scanning) has no value in the diagnosis of PHPT, but it is a useful tool for localizing the abnormal parathyroid gland in patients selected for parathyroidectomy (PTx). Sestamibi has the advantage of localizing ectopic parathyroid glands outside the neck. The 4D computerized tomography protocol has recently emerged as a useful tool.

Natural Course

The natural course of PHPT depends upon its severity. Worsening usually occurs in symptomatic patients not undergoing PTx. Conversely, studies of most patients with asymptomatic PHPT, particularly if mild, have shown stability of serum calcium, PTH, creatinine, urinary calcium, and BMD for up to 8 years [10]. Progression of the disease occurs in about one-third of patients, particularly in those aged less than 50 years.

Management

The aim of treatment is to remove all hyperfunctioning parathyroid tissue, normalize biochemical abnormalities, improve BMD, and decrease the risk of nephrolithiasis and fractures.

Surgical Management

PTx, with removal of all hyperfunctioning parathyroid tissue, is the only cure of the disease. It should be considered in all patients and recommended in those with symptomatic PHPT and in those with asymptomatic PHPT who met the criteria for surgery established by international guidelines [9, 11] (Table 21.1).

Patients selected for surgery should be referred to an experienced parathyroid surgeon. A minimally invasive approach can be offered to most patients. Intraoperative PTH monitoring may be helpful in this setting. The "classical" approach, namely, bilateral neck exploration, should be preferred in hereditary cases since multigland involvement is common. When parathyroid carcinoma is suspected, a more extended surgical approach is recommended, in which an "en bloc" resection of the parathyroid lesion together with the ipsilateral thyroid lobe with clear gross margins and the adjacent structures is performed. In experienced

Table 21.1 Guidelines for the management of patients with asymptomatic primary hyperparathyroidism

Measurement	Criteria for parathyroidectomy	Surveillance without surgery	Indication for parathyroidectomy during surveillance
Serum calcium	>1.0 mg/dL (0.25 mmol/L) above upper limit of normal	Annually	>1.0 mg/dL (0.25 mmol/L) above upper limit of normal
Renal	(a) eGFR <60 mL/min (b) 24-h urinary calcium >400 mg (>10 mmol) and increased stone risk by biochemical stone risk analysis[a] (c) Nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	(a) eGFR annually, if renal stone is suspected (b) 24-h urinary biochemical stone risk analysis[a] (c) Renal imaging by X-ray, ultrasound, or CT	(a) eGFR <60 mL/min (b) Detection of nephrolithiasis or nephrocalcinosis
Skeletal	(a) BMD by DXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or 1/3 distal radius[b] (b) Vertebral fractures by X-ray, CT, MRI, or VFA	(a) BMD every 1–2 years (3 sites) (b) X-ray of VFA if clinically indicated (e.g., height loss, back pain)	(a) BMD T-score at any site < −2.5 or the finding of a significant decrease of BMD (even if the T-score is not less than −2.5)[c] (b) Clinical fractures or morphometric vertebral fractures, even if asymptomatic
Age	<50 years	Not applicable	Not applicable

Modified from Bilezikian et al. [9]

[a]Evaluation of additional risk factors for nephrolithiasis, available by many laboratories

[b]The use of Z-score is recommended in premenopausal women and men younger than 50 years

[c]Greater than the least significant change, as defined by the International Society for Clinical Densitometry [12]

hands PTx is successful in up to 95–98%, with a low rate (1–3%) of complications (laryngeal nerve injury and less frequent permanent hypocalcemia). A single, benign chief-cell adenoma is usually found at histology. When histology is equivocal or suggests a possible malignancy, molecular studies may be of help. Successful surgery is followed by normalization of biochemical parameters and improvement of BMD, promptly at the lumbar spine and hip and lately at the radius. The rate of nephrolithiasis decreases. Recurrence of PHPT is rare in patients with sporadic PHPT, but more common in familial cases unless total or near-total PTx is performed as initial surgery. PTx is a reasonable option also for patients with sporadic asymptomatic PHPT who do not met the surgical criteria since randomized clinical trials have shown a benefit from surgery, not only because it normalizes serum calcium and PTH but also because it improves BMD and quality of life (QoL). Individual counseling addressing the benefits and risks of PTx is mandatory, and the preference of the patients should be taken into account.

Nonsurgical Management

As mentioned before, about 30–40% of patients with PHPT do not meet the criteria for surgery. These patients, as well as those who decline surgery or have contraindications to surgery, need to be monitored.

Monitoring

PHPT remains stable in many patients with asymptomatic PHPT followed without surgery for up to 8–9 years, but progression of the disease may occur in up to one-third of patients [10].

An adequate calcium intake (preferably with food), appropriate for age and sex as in the general population, should be recommended. Hypovitaminosis D should be corrected using cholecalciferol 800–1000 IU daily; or equivalent doses calculated on this daily dose can also be used weekly or monthly, with a target serum 25OHD > 20 ng/mL or 30 ng/mL, as suggested by some guidelines.

General principles for monitoring and indication to advise surgery are reported in the Table 21.1.

Parathyroid surgery should be recommended if one of the following criteria is met during observation: (1) serum calcium concentration greater than 1 mg/dL above the upper normal limit; (2) creatinine clearance less than 60 mL/min; (3) detection of nephrocalcinosis or kidney stones; (4) BMD T-score at any site less than −2.5 or the finding of a significant (greater than the least significant change as defined by the International Society for Clinical Densitometry [12]) decrease of BMD, even if the T-score is not less than −2.5; and (5) clinical fractures or morphometric vertebral fractures, even if asymptomatic.

Medical Treatment

No medical treatment is currently available to cure PHPT, and if PTX is suggested and surgery is not contraindicated, medical treatment should not be considered as a valuable alternative [11]. Conversely, if there is significant risk for surgery, prior surgery in experienced hands is failed, or the patient is unwilling to undergo PTx, medical treatment could be considered, and treatment should be guided by the aim of therapy.

Antiresorptive therapy (bisphosphonates and in selected cases also denosumab) is effective in improving bone mineral density at lumbar spine and hip, but less effective at the distal radius. No significant effects are seen on serum calcium and PTH. The calcimimetic cinacalcet may be considered in patients in whom the aim of treatment is to reduce serum calcium concentration. It has been shown to decrease and often normalize serum calcium levels across a broad range of disease severity, including patients with parathyroid carcinoma, with modest effects on PTH.

Combined therapy with antiresorptive drugs and cinacalcet may be considered when the aim is both to increase BMD and decrease serum calcium.

Pregnancy

Women with mild elevation of calcium PHPT should be managed conservatively, mostly by hydration. In cases with progressive increase of serum calcium, PTx in the second trimester and cinacalcet may be considered.

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Chapter 22
Cinacalcet Use in Primary Hyperparathyroidism

Elisa Dinoi, Laura Pierotti, Laura Mazoni, Filomena Cetani, and Claudio Marcocci

Objectives

- Evaluation of a patients with recurrent primary hyperparathyroidism (PHPT).
- Therapeutic options in a patient with recurrent PHPT after parathyroidectomy.
- Cinacalcet handling to control serum calcium.

Case Presentation

We report the case of a 44-years-old man with a diagnosis of primary hyperparathyroidism (PHPT), who underwent left inferior parathyroidectomy (PTx) (histology, chief cell hyperplasia) with subsequent normocalcemia for several years. Then, the patient was lost to follow-up. Twelve years later PHPT recurred (calcium 15 mg/dL, PTH 270 pg/mL) with gastrointestinal manifestations (nausea, vomiting) and collapse. A left and right superior PTx was performed, but hypercalcemia persisted (histology, chief cell hyperplasia).

At this time (55 years old) the patient was referred to our center. Physical examination revealed obesity (BMI 31 kg/m^2) and normal vital signs. Blood tests

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confirmed the persistence of PHPT with serum calcium of 12.2 mg/dL (normal range 8.4–10.2) and PTH of 118 pg/mL (normal range 8–40).

Neck ultrasound showed a nodular lesion (5 × 12 mm) next to the right thyroid lobe suspicious for hyperplastic parathyroid gland.

The single-photon emission computed tomography (SPECT) showed an uptake at right inferior thyroid lodge. Abdominal ultrasound was negative for nephrolithiasis and nephrocalcinosis and bone mineral density by DXA at lumbar spine and femur, and one-third distal radius was normal.

The metachronous parathyroid multiglandular involvement and the young age of the patient were suggestive of a hereditary form of PHPT. Therefore, the patient underwent a pituitary MRI that revealed a pituitary microadenoma (2 mm) and abdomen computed tomography that was negative for lesions. Pituitary hormones and neuroendocrine markers were normal. Genetic testing for multiple endocrine neoplasia (MEN) type 1 (MEN1) and type 4 (MEN 4) syndrome was negative. First-degree relatives had normal serum calcium values.

Discussion

PHPT is caused by excessive synthesis and secretion of PTH by one or more parathyroid glands. It occurs as sporadic disease (90%) or as familial (10%). Among the latter, MEN1, type 2A (MEN2A), MEN4, and the hyperparathyroidism-jaw tumor syndrome (HPT-JT) are caused by known germline genetic mutations and are associated with a broad spectrum of endocrine and nonendocrine tumors [1]. Because of the underlying genetic basis, these diseases may have different clinical features compared to the sporadic counterparts.

The most common parathyroid tumor is adenoma (80–85%), a benign lesion that typically involves one single parathyroid gland, whereas atypical adenoma (APA) and carcinoma (PC) are rarer (1–2%) being the latter the rarest parathyroid tumor. In contrast with sporadic PHPT, hereditary PHPT is often associated with multiglandular parathyroid involvement namely adenomas or four-gland hyperplasia.

Nowadays, in about 80% of the patients, the disease is discovered by routine blood testing.

Signs and symptoms of PHPT, when present, are mainly due to hypercalcemia and renal and bone involvement.

PTx is the only therapeutic procedure able to cure PHPT. Surgery should be considered in all symptomatic patients and also in asymptomatic patients who meet surgical criteria developed at latest International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism [2]. The cure rate in experienced hands is up to 95% [3].

Asymptomatic patients who do not meet surgical criteria can be followed safely without surgery, at least for a period of years [2].

Medical therapy can be an option for patients who satisfy surgical guidelines, but do not undergo surgery for any of the subsequent reasons: (i) patients who are

unwilling to undergo surgery; (ii) increased risk of surgery (comorbidities, anesthetic risk); (iii) inoperable carcinoma; (iv) therapy in preparation of PTx; and (v) failed PTx in experienced hands or recurrent hypercalcemia.

Two therapeutic options are available: antiresorptive agents and cinacalcet.

Antiresorptive agents (bisphosphonates and in selected cases denosumab) are a valid option to decrease bone remodeling and improve bone mineral density but have neutral effect on serum calcium and PTH levels. They should be considered in patients (i) with fragility fracture, independently of whether submitted or not to PTx, and (ii) with a T-score < -2.5 at any site either if unable or unwilling to undergo PTx or 1–2 years after successful surgery.

The calcimimetic cinacalcet (Sensipar®) is a positive allosteric modulator of the calcium-sensing receptor (CaSR) that reduces serum calcium levels and, to a lesser extent, PTH secretion. Cinacalcet may be considered in patients in whom the aim of treatment is to reduce serum calcium concentration.

Combined therapy with cinacalcet and bisphosphonates may be considered when the aim is both to decrease serum calcium and increase BMD. The former decreases serum calcium but has neutral effects on BMD, and the latter decreases bone remodeling and improves BMD but has no effect on serum calcium. A few studies including a small number of patients have evaluated the efficacy of the combined therapy [4–6].

Cinacalcet significantly reduces serum calcium in almost all patients with PHPT and normalizes it in about 2/3. It is equally effective in normalizing serum calcium in a wide range of PHPT disease severity, ranging from asymptomatic patients to patients with symptomatic disease, as well as in sporadic and familiar forms [6–8]. This treatment normalizes PTH level in less than 10% of the patients, and changes in mean PTH are not significant. Serum phosphate levels significantly increase after cinacalcet treatment [9]. Cinacalcet has also been shown to be useful in reducing calcium levels in patients with parathyroid carcinoma, but its use is limited by frequent side effects occurring at high doses. Furthermore, at variance with other calcium-lowering therapies, this agent can be used in patients with renal impairment that is a common complication in those with longstanding parathyroid cancer. Therefore, cinacalcet can be an option for the management of intractable hypercalcemia in patients with inoperable disease [10, 11].

The starting dose is 30 mg once or twice daily and should be titrated every 1–4 weeks to a maximum dose of 90 mg QID, according to serum calcium levels during the previous weeks. After maintenance dose is reached, serum calcium remains remarkably stable [12].

The most common side effects are gastrointestinal symptoms, namely, nausea and vomiting, that can be successfully controlled with H_2 receptor antagonists, in most cases. Hypocalcemia occurs only in few patients and it is often mild and asymptomatic [9]. In this case the daily dose should be reduced, or treatment withhold and eventually restarted using a lower dose.

Our patient had persistent hypercalcemia despite multiple surgical procedures; therefore, taking into account the risk associated with further surgery (laryngeal nerve damage and permanent hypoparathyroidism), we decided to give up surgery

Table 22.1 Biochemical data of the patient during therapy with cinacalcet

Cinacalcet dosage	Total serum calcium mg/dL (8.6–10.2)	Ionized calcium mmol/L (1.13–1.32)	PTH pg/mL (8–40)
30 mg/die for 10 days	12.2	1.63	118
30 mg × 2/die for 10 days	11.6	1.57	79
60 mg × 2/die for 10 days	10.7	1.42	123
60 mg × 3/die for 10 days	10.2	1.34	71
60 mg × 3/die for 10 days	9.7	1.25	61
60 mg × 3/die end follow up	9.9	1.29	62

and to administer cinacalcet. Treatment was started with a dose of 30 mg once daily, and cinacalcet was progressively titrated up to the dose of 60 mg TID. A progressively decline up to normalization of serum calcium (9.7 mg/dL) and a reduction of PTH (61 pg/mL) were observed. The patients had no gastrointestinal side effects, and the biochemical control persisted during long-term follow up (Table 22.1).

Lesson Learned

- Parathyroidectomy is the only definitive cure of PHPT.
- Cinacalcet is approved to decrease serum calcium in patients with moderate to severe PHPT who meet surgical criteria but are not candidate to PTx.
- Cinacalcet therapy decreases and often normalizes serum calcium and increases serum phosphorus in patients with PHPT of different etiologies and severity. The effect on plasma PTH is less pronounced.
- Cinacalcet has no effects on bone health.
- The dose should be titrated every 1–4 weeks, according to serum calcium levels during the previous weeks and the side effects.
- Cinacalcet has been shown to be effective both in sporadic and familial form of PHPT.

Questions

1. What is the first cure for the treatment of PHPT?

   (a) Parathyroidectomy
   (b) Antiresorptive agents
   (c) Cinacalcet
   (d) Antiresorptive agents + cinacalcet

2. Cinacalcet has an effect in?

   (a) Reducing serum calcium
   (b) Increasing phosphate
   (c) Improving BMD
   (d) (a) + (b)

3. In which of these conditions is it indicated to start therapy with cinacalcet?

   (a) Asymptomatic patient with mild PHPT
   (b) Patient with severe PHPT waiting for surgery
   (c) Patient with symptomatic PHPT not eligible for surgery
   (d) (b) + (c)

4. Which of these is the most frequent side effect of cinacalcet?

   (a) Hypocalcemia
   (b) Gastrointestinal disorders
   (c) QT prolongation
   (d) Foot edema

Answers to Questions

1. (a) Parathyroidectomy
2. (a) Reducing serum calcium
3. (b) + (c) Patient with severe PHPT waiting for surgery, Patient with symptomatic PHPT not eligible for surgery
4. (b) Gastrointestinal disorders

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Chapter 23
A Case of Apparently Sporadic Primary Hyperparathyroidism Carrying a Germline Mutation of *CDC73* Gene

Laura Mazoni, Matteo Apicella, Filomena Cetani, and Claudio Marcocci

Objectives

- Clinical features which might prompt mutational analysis of genes involved in the pathogenesis of primary hyperparathyroidism
- Focus on an uncommon case of primary hyperparathyroidism
- Approach to a case of potentially familial/syndromic case of primary hyperparathyroidism
- Choice of the appropriate surgical approach in selected cases (familial, suspicion of parathyroid carcinoma)

Case Presentation

A 30-year-old man was referred to our outpatient clinic for evaluation of recurrent nephrolithiasis and muscle weakness. The medical history was notable for recurrent bilateral nephrolithiasis since the age of 25 yrs. Moderate hypercalcemia was found at routine evaluation for kidney stones. Further investigations lead to the diagnosis of primary hyperparathyroidism (PHPT) (Table 23.1). Family history was uneventful. Neck ultrasound revealed three hypoechoic lesions consistent with enlarged

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Table 23.1 Biochemical data

Parameter	Results	Range
Albumin corrected calcium	13.1 mg/dl,	(8.6–10.2)
Creatinine	0.68 mg/dl	(0.7–1.20)
Phosphate	1.7 mg/dl	(2.7–4.5)
Magnesium	1.92 mg/dl	(1.73–2.26)
Ionized serum calcium	1.88 mmol/l	(1.13–1.32)
PTH	1391 pg/ml	(13–65)
25(OH)D	11.8 ng/ml	(30–100)
Osteocalcin	>200 ng/ml	(6.8–34)
BSAP	>75 mcg/l	(2–15)
24-h urinary calcium	450 mg/24 h	(100–321)
24-h urinary creatinine	1256 mg/2 h	(1040–2350)
24-h urinary phosphate	720 mg/24 h	(400–1300)
Creatinine clearance	134 ml/min	(71–151)

parathyroid glands. The ^{99m}Tc-MIBI planar scintigraphy showed a bilateral uptake in the lower thyroid lobes. Bilateral nephrolithiasis was confirmed at renal ultrasound, and bone mineral density by DXA showed a severely low bone mass.

The patient underwent right superior and inferior and left superior parathyroidectomy (PTx).

Histology showed chief cells hyperplasia in left glands and atypical adenoma in the right inferior gland.

Six months after surgery, a persistence of PHPT was evident with a serum calcium of 11.4 mg/dl and PTH of 724 pg/ml. Neck ultrasound revealed a hypoechoic lesion localized under the left lobe of the thyroid (11 × 11 × 20 mm) that showed an uptake at ^{99m}Tc-MIBI scintigraphy. No other endocrine lesions were present. The patient underwent left inferior PTx. Histology revealed an atypical adenoma.

After surgery the patient developed hypoparathyroidism; thus he started replacement therapy with calcium and calcitriol. During the follow-up, a good control of serum calcium and phosphate was achieved, whereas the 24-h urinary calcium persisted elevated with a progressive reduction of renal function. For this reason, the patient started thiazide diuretics with a reduction of 24-h urinary calcium and improvement of nephrolithiasis.

Review of How the Diagnosis Was Made

Primary hyperparathyroidism (PHPT) is a common endocrine disease which occur more frequently in female (female-to-male ratio of 3:1); however there is no sex difference before the age of 45 years. PHPT is mostly a sporadic disorder. Hereditary forms account for about 5–10% of cases and include multiple endocrine neoplasia (MEN) types 1, 2A, and 4, hyperparathyroidism-jaw tumor (HPT-JT) syndrome,

familial isolated PHPT, familial (benign) hypocalciuric hypercalcemia (FHH), and neonatal severe PHPT (NSHPT) [1]. These disorders are inherited with a classic Mendelian pattern, and the main genes responsible for the syndromes have been identified in the majority of families. Almost 10% of patients with sporadic PHPT and less than 45 years present a de novo germline mutation of MEN1 (20–30%) and, less frequently, *CDC73* or *CASR* genes [2].

Genetic analysis for germline mutations is indicated in a patient with PHPT in the following conditions [3]:

1. Patient younger than 45 years
2. Multiglandular parathyroid disease
3. Histology suggestive of parathyroid carcinoma or atypical parathyroid adenoma
4. Index case with two or more MEN syndrome-associated endocrine tumors
5. First-degree relative of a known mutation carrier

The identification of a germline mutation is of great importance for several reasons, namely, (i) to confirm the diagnosis, (ii) to screen for associated lesions, (iii) to perform a familial screening, and (iv) to guide the optimal surgical approach because of multiglandular disease and the increased risk of malignancy associated with the *CDC73* mutation.

Taking into account the young age of the patient, multiglandular parathyroid involvement, and histology, a genetic analysis of *MEN1* and *CDC73* genes was carried out. A germline mutation of the *CDC73* gene leading the substitution of a guanine to an adenine at splicing donor site of intron 3 was identified. The genetic screening in the first-degree relatives was negative, indicating a de novo mutation.

CDC73 is a tumor suppressor gene encoding for a nuclear protein called parafibromin. It has a role in the regulation of cellular cycle through a downregulation of cyclin D1 expression and interaction with β-catenin promoting gene transcription [4]. The large majority (75%) of patients harbor *CDC73* germline mutations in the coding regions. Large deletions are not uncommon and account for as many as one-third of all mutations [5]. *CDC73* mutations are also responsible in some FHIP families. *CDC73* somatic mutations are found in 70% or patients with PC. Interestingly, up to 20% of cases with apparently sporadic PC carry a germline mutation of *CDC73*, thus representing an occult HPT-JT or another syndromic variant [6].

HPT-JT is a rare autosomal dominant syndrome that can be associated with different manifestations. PHPT is present in 95% patients with HPT-JT, usually caused by a single gland involvement, but multiglandular involvement can occur in up to 1/3 of cases. The histology often revealed features of atypical parathyroid adenoma, namely, solid growth pattern, fibrous bands, and cellular atypia [7]. Parathyroid carcinoma can occur in up to 20% [8]. The clinical manifestations of PHPT usually develop in the early adulthood, but cases diagnosed in childhood have been reported [9]. Ossifying fibromas of the mandible or maxilla are present in 30–40% of subjects, and 15% of HPT-JT cases are associated with renal lesions, mostly simple cysts. In female patients, uterine tumors (endometrial hyperplasia, polyps, adenofibroma, etc.) are common, being present in 60–70% cases. Other neoplasias have

also been reported, specifically testicular tumor, pancreatic carcinoma, and thyroid adenoma [10] .

The diagnosis of FIHP requires the presence of at least another familial member with surgically proven PHPT and the absence of other features of syndromic forms of PHPT. FHIP is inherited in an autosomal dominant fashion, and different gene mutations have been reported, namely, MEN1 (up to 25%), *GCM2* (in up to 20%) *CASR* (in up to 18%), and *CDC73* (in up to 7%) [8].

Parathyroidectomy is the only cure of PHPT, and in recent years a mini-invasive surgical approach has been developed and represents the most common approach in sporadic PHPT. This approach is not indicated in the suspicion of familial forms and when parathyroid carcinoma is suspected, where an "en bloc" resection (parathyroid and ipsilateral thyroid lobe asportation) should be performed [11].

The identification of germline mutation of the *CDC73* gene in our patient prompted us to review the initial histology, which confirmed the diagnosis of atypical parathyroid adenoma, and to early search for mutation in the first-degree relatives because of the potential risk of parathyroid cancer. The potential risk of parathyroid carcinoma prompted us to perform a more radical surgical approach and remove the residual parathyroid gland.

Lessons Learned

1. About 10% of apparently sporadic cases of PHPT diagnosed before the age of 45 year can be due to a germline mutation of *MEN1*, *GCM2*, *CDC73*, or *CASR* genes.
2. A genetic analysis should be performed in the following setting: (i) patients with PHPT younger than 45 years, (ii) a first-degree relative (s) of a known mutation carrier; (iii) index case with two or more MEN syndrome-associated endocrine tumors; (iv) diagnosis of multiglandular disease; and (v) histological diagnosis if parathyroid carcinoma or atypical parathyroid adenomas.
3. HPT-JT is a rare condition and should be suspected when PHPT occurs in young age and is associated with ossifying fibromas of the mandible, renal lesions, or other tumors.
4. Surgical approach of PHPT in HPT-JT should be established based on the risk of PC and the multiglandular involvement.

Questions

1. Which genes are more commonly involved in sporadic PHPT?

   (a) *MEN1* and *CDC73* gene
   (b) *MEN1*, *CDC73*, and *CDKN1B* gene
   (c) *MEN1*, *CDC73*, and *CASR* gene
   (d) *RET*, *CDC73*, and *CDKN1B* gene

2. The CDC73 gene is?

   (a) A proto-oncogene encoding for a nuclear protein called parafibromin
   (b) A proto-oncogene encoding for a nuclear protein called menin
   (c) A tumor suppressor encoding for a nuclear protein called menin
   (d) A tumor suppressor encoding for a nuclear protein called parafibromin

3. *CDC73* mutations are associated with

   (a) Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism (FIHP), and parathyroid carcinoma (PC)
   (b) Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, parathyroid carcinoma (PC), and familial hypocalciuric hypercalcemia (FHH)
   (c) Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism (FIHP), and familial hypocalciuric hypercalcemia (FHH)
   (d) Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism (FIHP), and neo-natal severe hyperparathyroidism (NSHPT)

4. Besides ossifying fibromas and renal lesions, which of the following is the most common tumor associated with HPT-JT?

   (a) Colorectal polyps
   (b) Uterine tumors
   (c) Pituitary adenoma
   (d) Breast fibroadenoma

Answers to Questions

1. (c) *MEN1*, *CDC73*, and *CASR* gene
2. (d) A tumor suppressor encoding for a nuclear protein called parafibromin
3. (a) Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, familial isolated hyperparathyroidism (FIHP), and parathyroid carcinoma (PC)
4. (b) Uterine tumors

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Chapter 24
Challenges in the Preoperative Localization of Hyperfunctioning Parathyroid Tissue in a Patient with Primary Hyperparathyroidism

Matteo Apicella, Laura Mazoni, Filomena Cetani, and Claudio Marcocci

Objectives

- Role of preoperative localization of abnormal parathyroid gland(s)
- First-line parathyroid imaging studies
- Doubtful or negative parathyroid localization studies question the diagnosis of primary hyperparathyroidism?
- Second-line and novel parathyroid imaging studies

Case Presentation

A 56-year-old woman came to our attention in 2016 for evaluation of recently diagnosed primary hyperparathyroidism (PHPT), after an episode of renal colic. A renal ultrasound showed a 9-mm stone in the left kidney. The medical history was relevant for type 2 diabetes mellitus treated with metformin, obesity (BMI 31 Kg/m^2), arterial hypertension, and chronic kidney disease stage IIIa (eGFR CKD-EPI 53 ml/min).

The Table 24.1 shows the patient's biochemical data.

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Table 24.1 Baseline biochemical data

Tests	Results	Reference range
Albumin-adjusted calcium	12.1–11.9 mg/dl	(8.6–10.2)
Phosphate	2.3–2.1 mg/dl	(2.5–4.5)
PTH	111–146 pg/ml	(8–40)
25(OH)Vitamin D	26.9 mcg/ml	(30–100)
Magnesium	2.1 mg/dl	(1.7–2.5)
Ionized calcium	1.63–1.60 mmol/l	(1.13–1.32)
creatinine	1.4 mg/dl	(0.7–1.2)
24-h urinary calcium	638–425 mg/24 h	(100–320)
24 hours urinary creatinine	1210–1100 mg/24 h	(1040–2350)

The patient met several criteria for surgical treatment: symptomatic nephrolithiasis, serum calcium was greater than 1 mg/dL above the upper limit of the normal range, a chronic kidney disease with eGFR <60 ml/min, bone mineral density by DXA at lumbar spine, hip and radius showed osteoporosis at one-third distal radius (T-score −2.8).

Surgical treatment was advised to the patient, and the minimally invasive video-assisted parathyroidectomy (PTx) proposed, being routinely used in our hospital in non-familial forms of PHPT. Therefore, parathyroid imaging studies were planned. Neck ultrasound (US) performed by an expert operator showed a small multinodular goiter, with no evidence of enlarged parathyroid gland/s. A single-photon emission computed tomography (SPECT)/CT with Technetium-99m sestamibi (^{99m}Tc-MIBI) did not show hyperaccumulation of the tracer referable to hyperfunctioning parathyroid glands. Because of the negative imaging studies, the surgical plan was changed, and a bilateral neck exploration was proposed to the patient, who refused surgery. Medical treatment with the calcimimetic cinacalcet was started (30 mg BID). Treatment was well tolerated, and serum calcium declined and ranged between 10.4 and 10.8 mg/dl in the following years. Two years after, the patient experienced a new episode of renal colic, and renal ultrasound revealed a bilateral nephrolithiasis, and surgery was advised again.

At that time a novel parathyroid imaging approach, namely, the use of positron emission tomography (PET) with radiolabeled choline combined with a computed tomography (CT) without iodine contrast (18F-choline PET/CT), was shown to be of help to localized abnormal parathyroid glands [1]. The patient underwent 18F-choline PET/CT that showed an area of focal hyperaccumulation of the tracer located in the left paraesophageal area (Fig. 24.1). In consideration of the positive imaging study, the patient accepted to undergo PTx, which was performed using focused approach with the excision of the left inferior parathyroid gland. Intraoperative PTH monitoring showed a drop of PTH levels of more than 50% from baseline levels at 10 minutes after the parathyroid excision (from 118 pg/ml to 50 pg/ml). Histological examination confirmed a 1.3 x 0.6 x 0.5 cm parathyroid chief cell adenoma.

Serum calcium and PTH normalized in the following days after PTx, and remission of PHPT was confirmed during the follow-up.

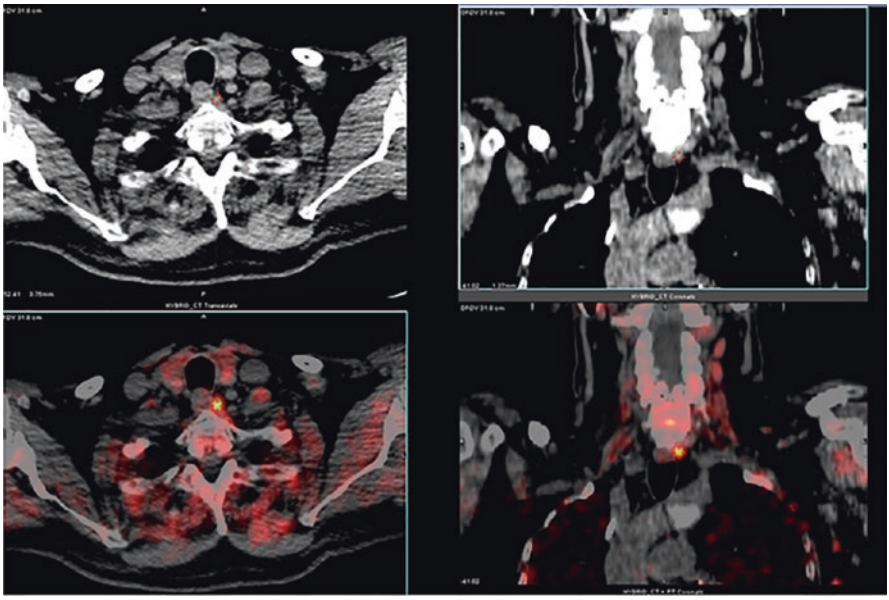

Fig. 24.1 18F-choline PET/CT showing a hyperaccumulation of the tracer in the left paraesophageal area

Discussion

PHPT is a common endocrine disease, affecting women three times more frequently than men. Nephrolithiasis, osteoporosis, and hypercalcemic symptoms are the classic disease manifestations. Surgery is the only definitive cure of the PHPT. Preoperative localization studies of the pathological gland/s are used as an aid to surgery and allow to reduce the intervention time, the surgical complications, and the risk of surgery failure [2–4].

Ultrasound (US) and SPECT/CT with ^{99m}Tc-MIBI are the standard tests performed in the pre-surgical evaluation of the PHPT. Normal parathyroid glands are not visualized with US. In PHPT, the hyperplastic parathyroid often appears as an oval-shaped hypo-anechoic lesion surrounded by a hyperechoic capsule, with a vascular hilum, located behind the thyroid lobe. US is cost-effective, does not expose to ionizing radiations, and has a good sensitivity and specificity. However, US is operator-depending and may not detect small adenomas especially of the upper parathyroid glands, as in the case described herein. Retroesophageal or retrotracheal parathyroid glands are also not visible on US. Furthermore, it should be kept in mind that the parathyroid glands can be located anywhere between the base of the tongue and the mediastinum (ectopic parathyroid glands), limiting the diagnostic power of the US.

US is often performed in combination with a scintigraphy. The tracer used in parathyroid scintigraphy is ^{99m}Tc-MIBI that electively localizes and remains in

adenomatous parathyroid cells due to the presence of the high number of mitochondria. ^{99m}Tc-MIBI scintigraphy can be performed both as planar and SPECT imaging. SPECT/CT has a better spatial resolution, allows easier visualization of retroesophageal adenomas, and, overall, has better sensitivity than planar scintigraphy. However, even this imaging technique may be not diagnostic, especially in cases of multiglandular disease (hyperplasia) and small or double parathyroid adenomas [5]. Computed tomography scanning has become more widely used with added sensitivity by employing three- dimensional technology and a fourth dimension (time) (4D-TC). The latter was first proposed by Rodgers in 2006 [6]. 4D-TC gives a very precise localization of the parathyroid adenomas, especially the single ones, but with a radiation dose of 20–28 mSv [7]. Furthermore, 4D-TC requires the administration of iodine contrast that might not be used in some conditions, namely, in patients suffering from allergy or in those with chronic kidney disease.

Another novel technique used in parathyroid imaging is the 18F-choline PET/CT. This exam is routinely performed in metastatic prostate cancer and hepatocellular carcinoma evaluation. In 2013 Quak reported for the first time the detection of a parathyroid adenoma taking up 18F-choline during a PET/CT performed on suspicion of a prostate cancer recurrence after radical prostatectomy a case of a 71-year-old patient [8]. Since then, many other authors have found similar results [9, 10]. Choline is a normal component of the cell membrane and crosses the cell membrane in a carrier-mediated manner; it is phosphorylated by a choline kinase and incorporated into the phosphatidylcholine. Cells with a high membrane turnover, as the neoplastic ones, can avidly pick up radiolabeled choline. Furthermore, the choline kinase activity has been shown to be related to PTH secretion in parathyroid adenomas, and this is a possible reason why radiolabeled choline PET is able to identify hyperfunctioning parathyroid tissue [11, 12].

In a meta-analysis of 14 studies (517 patients), Treglia et al. have shown that radiolabeled choline PET has an excellent diagnostic performance in detecting parathyroid adenomas, with a sensitivity of 95% (95% CI: 92–97%) and a positive predictive value (PPV) of 97% (95% CI: 95–98%). The authors also reported that based on literature data, radiolabeled choline PET/CT was able to detect parathyroid adenomas in a high percentage (72–91%) of patients in whom ^{99m}Tc-MIBI SPECT/CT was negative or inconclusive [13].

In another study Grimaldi et al. reported that, unlike the US and ^{99m}Tc-MIBI scintigraphy, no statistically significant correlation exists between parathyroid adenoma size and 18F-choline PET/CT findings [14]. Some, but not all, studies have also reported a strong positive correlation between the intensity of choline uptake and preoperative PTH levels. Notably, false-positive results may occur in follicular thyroid hyperplasia, differentiated thyroid carcinoma, oncocytic thyroid adenoma, and either normal or reactive lymph nodes of the central compartment [5].

In the case described herein, TC scan was not performed for the chronic kidney disease. Moreover, a potential worsening of the renal function induced by iodine contrast would have compromised the possibility of continuing to treat the patient with metformin, as well as limited the access to some other possible therapies. In agreement with the recent literature, 18F-choline PET/CT was found to be a valid

aid to localize abnormal parathyroid gland/s and may be an additional imaging technique in patients with PHPT with contraindications to TC and inconclusive or negative parathyroid conventional imaging studies.

Lessons Learned

- Preoperative localization studies of the hyperfunctioning parathyroid tissue are used as an aid to surgery and allow to reduce the intervention time, the surgical complications, and the risk of surgery failure.
- Neck ultrasound and ^{99m}Tc-MIBI scintigraphy are the conventional imaging parathyroid imaging studies; in some cases, both studies should be performed to improve the diagnostic performance.
- Negative parathyroid imaging studies should not preclude the possibility of surgical treatment of PHPT.
- When conventional imaging studies are negative or inconclusive, it is possible to carry out further investigations, including 4D-CT and 18F-choline PET/CT, the latter preferable in patients with contraindications to the iodine contrast.

Questions

1. The 18F-choline PET/CT (mark the correct)

   (a) Is a first-line imaging technique in parathyroid disease
   (b) Does not localize ectopic parathyroid glands in the mediastinum
   (c) Is a first-line imaging technique in metastatic prostate cancer
   (d) Is a now abandoned imaging technique in parathyroid disease for its danger

2. When a 18F-choline PET/CT cannot be done?

   (a) In patients with chronic kidney disease KDIGO stage >IIIa
   (b) In patients allergic to the iodized contrast
   (c) In patients with hyperglycemia
   (d) None of the above answers

3. Why is choline picked up by the hyperfunctioning parathyroid tissue?

   (a) Because it is very vascularized
   (b) Because it expresses choline kinase
   (c) Because it has low cell turnover
   (d) Because parathyroid glands are rich in mitochondria

4. Which cervical structures can capture choline giving false-positive images in the study of parathyroid adenomas?

   (a) Tracheal rings
   (b) Lymph nodes
   (c) Thyroid cysts
   (d) Paraganglia

Answers to Questions

1. (c) Is a first-line imaging technique in metastatic prostate cancer
2. (d) None of the above answers

3. (b) Because it expresses choline kinase
4. (b) Paraganglia

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Part VII
Metabolic Bone Diseases

Chapter 25
New Insights into Diagnosing Bone Diseases

Se-Min Kim and Mone Zaidi

Osteoporosis is the most common musculoskeletal disease in our aging society. In the USA alone, 40 million adults suffer from osteoporosis or low bone mass [1]. With the increased awareness of osteoporosis, we have achieved a significant leap in understanding bone physiology through advances in genetics, imaging techniques, and bioengineering. Now we have learned that bone, once believed to be a mechanical structure, interacts with not only classical endocrine organs, such as parathyroid gland, that regulate calcium and phosphate homeostasis but also with the muscle, brain, pancreas, gut, kidney, and pituitary gland. The findings of the direct skeletal effect of the sympathetic nervous system and pituitary hormones, such as follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH), are paradigm-shifting and have opened up a new chapter of integrative bone physiology [2]. Also, it has now become clear that the cells involved in skeletal remodeling, namely, osteoblasts, osteoclasts, and osteocytes, interact with each other. Studies on RANK/RANKL/OPG as a coupling mechanism between osteoblasts and osteoclasts led to a new therapeutic, anti-RANKL antibody (denosumab). Moreover, we have learned that this interaction is bi-directional where osteoclasts also influence osteoblast-driven bone formation [3].

In addition, new advanced imaging techniques have allowed us to examine bone quality beyond bone mineral density. We have become increasingly aware that the current practice of assessing the risk of fracture based solely on bone density is incomplete, as it does not provide a full picture of intrinsic bone strength. Apparently, more than 60% of fractures occur in patients with low bone density (T scores between −1.0 and −2.5) [4]. Measures of bone quality, such as microskeletal structure, bone geometry, and bone turnover, provide us with additional

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understanding of overall skeletal strength and help us to estimate a patient's risk of fracture more precisely. High-resolution peripheral quantitative CT (HR-pQCT) with resolution up to ~40 μm enables us to analyze cortical and trabecular structure separately. Trabecular bone score (TBS) is an add-on software that reads texture of existing 2D vertebral DEXA imaging, thus indirectly assessing trabecular bone structure. TBS is validated in large population studies and currently used in clinical practice. Patients with mild hyperparathyroidism and diabetes-related bone disease are great examples that highlight the critical role of understanding bone quality. Patients with mild primary hyperparathyroidism and diabetes often preserve their BMD; however, their bone quality based on TBS shows significant deterioration—this explains an increased risk of vertebral fracture in these groups of patients [5–8]. HR-pQCT also shows evidence of increased cortical porosity in patients with diabetes [9].

With these new developments, we are about to move beyond the traditional BMD-based practice. However, it is important to reemphasize that the WHO classification based on BMD (T-score) is still the gold standard for diagnosis and treatment. As an adjunctive, a clinician can use the FRAX tool, which calculates a 10-year risk of hip and major osteoporotic fracture and thus supplements BMD-based risk stratification. The FRAX tool can now incorporate the TBS score and adjust for the risk of fracture based on bone quality.

In our first case, we will present a patient with type 2 diabetes with low bone mass and discuss how to evaluate and manage diabetes-related bone disease using TBS and the FRAX tool. In this chapter, we will also present a case with high bone mass. Unlike low bone mass, high bone mass is not discussed often in clinical practice. With the emergence of next-generation DNA sequencing, we have characterized this once-undiagnosed skeletal disease—high bone mass. Patients with loss-of-function mutations in *SOST*, who express sclerostin, or missense mutation in lipoprotein-related protein (LRP) 5/6 present with significantly increased bone mass, and this observation eventually has led to the development of a new anti-osteoporotic agent, ant-sclerostin antibody (romosozumab) [10]. We will describe a case with a high bone mass concomitant with hyperparathyroidism to provide an opportunity of entertaining differential diagnosis of acquired and inherited sclerosing skeletal dysplasias.

Lastly, we will present a case of severe pediatric rickets. Rickets, which is characterized by deficient mineralization of bone, is rare in the USA. It often involves the sites of rapid bone growth that can cause significant growth delay and skeletal deformity and eventually increases the risk of fracture. We will discuss how to evaluate patients with rickets in this case that highlights the importance of early detection of the underlying condition to prevent skeletal complications that severely impair patient's well-being.

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Chapter 26
Type 2 Diabetes and Bone

Se-Min Kim, Lena Fan, and Mishaela R. Rubin

Objective

1. Understanding of the risk and pathophysiology of type 2 diabetes-related bone disease
2. Evaluation of the risk of fracture in type 2 diabetes
3. Issues to consider in treating type 2 diabetes bone disease

Case Presentation

A 72-year-old Caucasian female with type 2 diabetes (T2D) was seen at an osteoporosis research center. Her T2D was diagnosed at the age of 60 and was complicated by diabetic retinopathy. There was no history of macrovascular complications or other microvascular complications such as diabetic neuropathy or nephropathy. Her glycemic control, for which she took sitagliptin 100 mg daily and glipizide/metformin 5/500 mg two tablets twice a day, was suboptimal (A1c 8.6%). Other comorbidities included well-controlled hypertension.

Her musculoskeletal history was notable for two fractures in the past, of the right shoulder and a right rib. She recently had a dual-energy X-ray absorptiometry (DXA) scan (as below) and was referred for further evaluation due to low bone mineral density (BMD). She denied any family history of osteoporosis or

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fracture. There was no history of kidney stones. Menopause occurred during her 40s. She had never taken glucocorticoids, anticonvulsants, or anticoagulants. She did not smoke or consume alcohol. Overall, her life-style was healthy. She was independent and involved in moderate-intensity exercise at least 30 mins a day. She took calcium ~1900 mg a day through her diet and supplements and vitamin D 800 IU a day.

On exam, her height was 59.5 inches and weight 190 lb (BMI, 37.8 kg/m^2).

The remainder of her physical exam was unremarkable without any sign of Cushing's disease, hyperthyroidism, or acromegaly.

Initial laboratory evaluation showed:

- Glucose 149 mg/dL, insulin 5.5 uIU/mL (2–19.6), A1c 8.6%
- Creatinine 0.70 mg/dL (GFR 87 mL/min/1.73 m^2)
- AST and ALT 15 and 15 (U/L)
- Hb/Hct 11.2/33.7 g/dL/%
- PTH 57 pg/mL (14–64), calcium 9.8 mg/dL, albumin 4.1 g/dL, vitamin D 20 ng/mL
- TSH 1.44 mIU/L

Her most recent DXA (Horizon) showed:

- Lumber spine 1.057 g/cm^2 (T-score 0.1, Z-score 2.4)
- Femoral neck 0.840 g/cm^2 (T-score −0.1, Z-score 1.9)
- Total hip 0.985 g/cm^2 (T-score 0.4, Z-score 2.0)
- 1/3 radius 0.598 g/cm^2 (T-score −1.6, Z-score 0.7)

Skin autofluorescence, a measure of advanced glycation end products (AGEs) by the AGE Reader: 2.8 (within 1SD of age-matched normative reference).

Lessons to be Learned

The Risk of Fracture and Pathophysiology of T2D-Related Bone Disease

About one in ten Americans have diabetes, and approximately 90–95% of them have type 2 diabetes (T2D) [1]. In addition to its well-recognized macro- and microvascular complications, T2D also impairs skeletal health and substantially increases the risk of fracture. In the Women's Health Initiative Cohort, women with T2D had a significantly increased risk of fracture at multiple sites: hip, humerus, foot, ankle, and spine [2] Meta-analyses also demonstrated that the risk of hip fracture and vertebral fracture is ~34% and ~35% higher in patients with T2D, respectively [3, 4]. Importantly, fractures in T2D are associated with worse prognosis and higher mortality as compared to non-diabetic individuals [4].

The fracture in T2D is a multifactorial process. First, patients with T2D have a higher risk of falls. T2D-related complications such as retinopathy, neuropathy, or

sarcopenia impair vision and balance. The risk of hypoglycemia with insulin use is a strong risk factor for fall and fracture [1, 5, 6]. Often, patients with T2D tend to be older and have other underlying comorbidities such as hypertension, congestive heart failure, and cerebral vascular disease, which directly or indirectly increase the risk of fall.

Importantly, the fracture risk is still high even with the adjustment for fall risk, which suggests impaired bone integrity in T2D [1]. Bone mineral density by DXA is typically elevated in T2D (see Evaluation); thus factors that DXA does not capture are thought to increase diabetic bone fragility. For example, chronic hyperglycemia and insulin resistance, hallmarks of T2D, negatively impact skeletal health. Advanced glycation end product (AGE) accumulation such as pentosidine in skeletal tissue is associated with an increased propensity of fracture [7]. AGEs form cross-links that increase the stiffness of bone collagen, thus reducing its ability to absorb stress, and impair osteoblast and osteoclast function [8]. In T2D patients, urine pentosidine levels predicted the incidence of clinical fractures [9], and higher skin AGEs, measured by skin autofluorescence (SAF), were associated with lower bone material strength, a measure of resistance to microfractures [10]. Another key determinant of bone quality that is affected in T2D is bone turnover [11]. Both bone formation markers (procollagen type I amino-terminal pro-peptide (P1NP) and osteocalcin (OCN)) and the bone resorption marker (C-terminal telopeptide (CTx)) were suppressed in T2D subjects as compared to controls [12]. Sclerostin, a strong inhibitor of bone formation, was upregulated in the skeletal tissue of T2D patients [13]. Histomorphometric analysis with tetracycline double-labeling confirms significantly decreased bone formation and reduced mineralizing surface [12]. Furthermore, low bone formation is more prominent in patients with poor glycemic control or microvascular complications [14]. Taken together, these data suggest that aspects of bone quality – including material properties that are altered by AGE accumulation and dynamic properties that are altered by suppressed bone remodeling – are key contributors to diabetic bone fragility.

Advanced imaging techniques have provided us with greater insight into microarchitectural changes in T2D. High-resolution peripheral quantitative computed tomography (HR-pQCT), which provides a three-dimensional image resolved to 60 μm, shows cortical deficits in T2D subjects, with decreases in cortical volumetric bone density (vBMD) and increases in cortical porosity [15, 16]. Microvascular complications and decreased skeletal blood flow might relate to increased cortical porosity. T2D patients with microvascular complications or peripheral vascular disease with decreased transcutaneous oxygen tension show significantly higher cortical porosity [17, 18]. Overall, the microarchitectural changes, accumulated AGEs, low bone turnover, and osteoblast dysfunction result in impaired biomechanical properties of bone. In vivo microindentation, which directly assesses the mechanical resistance of cortical bone, showed lower bone material strength in postmenopausal T2D as compared to non-diabetic controls [10, 19, 20].

Evaluation of Diabetes-Related Bone Disease

Despite the well-documented risk of fracture in T2D, it is often under-recognized in clinical practice. Unfortunately, our mainstay diagnostic tool, dual-energy X-ray absorptiometry (DXA), which measures areal bone density (aBMD), does not capture deficits in microarchitecture, bone turnover, or bone material properties, the likely mechanisms for T2D-related bone fragility. As a result, measuring aBMD underestimates fracture risk in T2D. A meta-analysis including 15 observational studies showed that aBMD in T2D is significantly higher at the femoral neck, hip, and spine, despite the risk of fracture being high [21]. Indeed, the expected fracture risk based on aBMD in T2D is much lower than the observed risk of fracture [22, 23]. The well-established Fracture Risk Assessment Tool (FRAX) also underestimates the risk of fracture in T2D.

Several approaches have been advanced for a better understanding of fracture risk in T2D. A study that analyzed three large cohorts showed that the fracture risk in T2D can be adjusted by subtracting the femoral neck (FN) T-score by 0.3 and 0.5 SD in men and women, respectively [24]. Using the FRAX tool, a practitioner can use (1) rheumatoid arthritis as a proxy, or (2) increase age by 10 years, or (3) reduce the FN T-score by 0.5 SD if BMD is available or (4) add trabecular bone score (TBS) for adjustment [25]. Trabecular bone score (TBS) is an add-on software that measures the texture of trabecular bone structure using the lumbar spine DXA imaging and generates a unitless score (Fig. 26.1). A lower TBS score was an independent predictor of fracture in patients with diabetes even when BMD was normal [26]. TBS adjustments can enhance the performance of the FRAX tool in general,

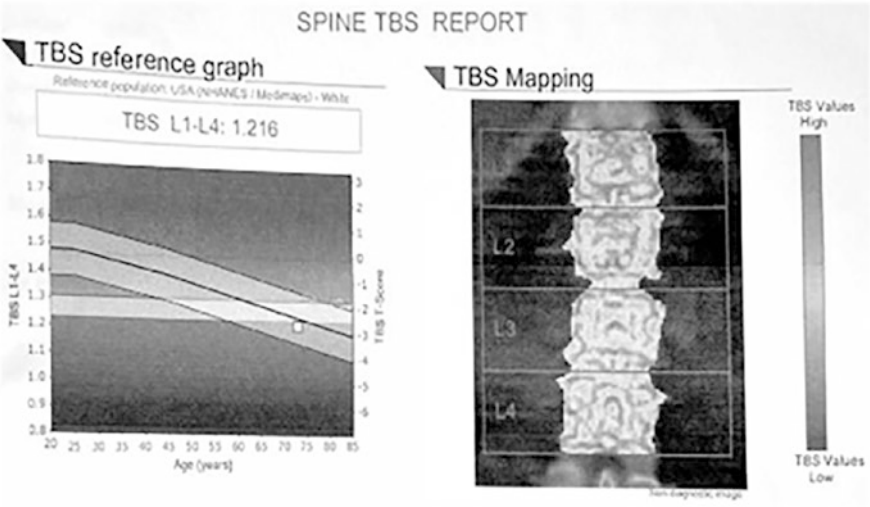

Fig. 26.1 Trabecular bone score (TBS)
Decreased TBS was noted. TBS ≥1.35 is considered to be normal; TBS between 1.20 and 1.35 is considered to be consistent with partially degraded microarchitecture; and TBS ≤1.20 defines degraded microarchitecture [27]

Table 26.1 FRAX adjustments in T2D

	10-year MOF (%)	10-year Hip fx (%)
Without adjustment	11	0.7
TBS-adjusted	12	0.9
With reduction of T-score 0.5 SD (FN BMD)	12	1.0
Age increased by 10	12	1.6
With rheumatoid arthritis as a proxy	14	1.0

and a TBS-adjusted FRAX score would be a better predictor of the risk of fracture in T2D (Fig. 26.1) [25]. In our case, the patient's DXA showed that T-score was −0.1 at the femoral neck and 0.1 at the lumbar spine, and her 10-year major osteoporotic fracture (MOF) and hip fracture (HF) risks were 11% and 0.7%, respectively. The adjusted risks are calculated in Table 26.1. Although this patient's adjusted FRAX scores remained less than 20% for MOF and less than 3% for HF, in other patients, the adjustments to FRAX might lead to meeting criteria for treatment.

Treatment of Diabetes-Related Bone Disease

T2D patients are less likely to be treated despite the increased risk of fracture [28]. Post hoc analyses of currently available treatments (bisphosphonates, raloxifene, denosumab, teriparatide, and abaloparatide) demonstrated similar anti-fracture efficacy in T2D patients as compared to non-diabetic patients [29–32]. Anti-resorptive treatment may seem counterintuitive given the low bone turnover in T2D, which theoretically increases the risk of osteonecrosis of the jaw or atypical femur fracture, yet safety data have not shown an increased risk of side effects with anti-resorptives in T2D [33]. Poor glycemic control appears to be associated with an increased risk of fracture, in particular at HbA1c levels that are greater than 8% [34]. Fall prevention is extremely important in patients with diabetes complications and in those on insulin and at risk for hypoglycemia. Certain oral hypoglycemic medications, namely, thiazolidinediones and canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, have shown an association with increased risk of fracture and, therefore, should be used with caution in T2D with a higher risk of fracture [35–37]. Currently, there is no specific guideline for when to initiate anti-osteoporosis medication in a T2D patient with low bone mass. The general consensus is to follow the guidelines for patients without T2D, namely, to treat patients with a T-score below −2.5 in the spine, femoral neck, total hip, or 33% radius (after adjusting the T-score downward by 0.5 SD for women). The consensus is also in the USA, to treat if the FRAX score for hip fracture or major osteoporotic fracture is above 3% or 20%, respectively (after implementing one of the possible FRAX adjustments). In our case, the TBS-adjusted FRAX scores were 0.9% and 12% (Table 26.1), which were below the pharmacological treatment threshold. Therefore, the patient was counseled to ensure adequate calcium and vitamin D intake and

continues her active and healthy lifestyle with limiting alcohol consumption, avoiding cigarette smoking, and performing weight-bearing and balance exercises. She was also advised to continue seeing her diabetologist for better glycemic control and her ophthalmologist for managing her diabetic retinopathy to preserve her visual acuity.

Questions

1. What's the estimated risk of hip fracture in type 2 diabetes patients?

   A. 5% higher
   B. 10% higher
   C. 30% higher
   D. 50% higher
   E. 70% higher

2. What's the characteristic skeletal presentation of type 2 diabetes-related bone change?

   A. Decreased bone turnover
   B. Stable or increased areal bone mineral densities
   C. Increased cortical bone porosity
   D. Decreased low bone material strength
   E. All of the above

3. How can the FRAX tool be adjusted and enhanced to predict the fracture risk of T2D?

   A. Reduce FN T-score by 0.5
   B. Increase age by 10
   C. Use rheumatoid arthritis as a proxy
   D. Adjust with trabecular bone score (TBS)
   E. All of the above

4. Which anti-diabetic medication potentially increases the risk of fracture?

   A. Metformin
   B. Insulin
   C. Actos
   D. Canagliflozin
   E. Liraglutide

Answers

1. (C)
2. (E)
3. (E)
4. (B), (C), (D)

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Chapter 27
Hypercalcemia and High Bone Mineral Density

Hirotaka Miyashita, Se-Min Kim, and John G. Graham

Objective

1. Overview of hypercalcemia
2. Evaluation of a complex case of hypercalcemia
3. Differential diagnosis of high bone density

Case Presentation

A 69-year-old woman was evaluated for hypercalcemia. The clinical history was notable for developmental disability and uncontrolled type 2 diabetes mellitus for which she took insulin and oral hypoglycemics. With further chart review, the patient was found to have had intermittently elevated serum calcium levels for at least 16 years fluctuating between 9.6 and 11.9 mg/dL (8.5–10.5). She had once been on hydrochlorothiazide, but the medication was stopped when hypercalcemia was noted. She denied a history of fracture, nephrolithiasis, and endorsed adequate dietary calcium intake. She is a non-smoker and does not use alcohol. She denies a family history of fractures, although her mother had unspecified "calcium issues."

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The physical exam was unremarkable: height 5′2″ and weight 220 lbs (BMI 40.24 kg/m^2).

Her laboratory data were as follows:

Initial Labs
- CBC: nml
- Total serum calcium: 10.1 mg/dL (8.5–10.5)
- Albumin: 4.0 g/dL (3.5–4.9)
- Serum creatinine: 1.21 mg/dL (0.50–1.10)
- Intact PTH: 341 (10–65 pg/mL)
- Alkaline phosphatase: 132 U/L (38–126)
- Vitamin D 25(OH): 16.9 ng/mL (30–100)
- Hb A1c: 9.8%

Follow-up Labs
- Total serum calcium: 11.5 mg/dL (8.5–10.5)
- Albumin: 2.7 g/dL (3.5–4.9)
- Serum creatinine: 1.11 mg/dL (0.50–1.10)
- Intact PTH: 154 (10–65 pg/mL)
- Alkaline phosphatase: 77 U/L (38–126)
- Spot urine calcium: = <2.00
- Vitamin D 25(OH): 41 ng/mL (30–100)

Neck ultrasound demonstrated multinodular goiter without a distinct parathyroid adenoma.

Dual-Energy X-Ray Absorptiometry (DXA) (Fig. 27.1)
- Femur neck (FN): 1.317 g/cm^2 (T-score 3.8, Z-score 5.4)
- Lumbar spine (LS 1–4): 1.655 g/cm^2 (T-score 5.5, Z-score 7.5)

Lessons to Be Learned

Overview and Evaluation of Hypercalcemia

The etiology of hypercalcemia can be classified into two categories: PTH mediated and non-PTH mediated. Examples of PTH-mediated hypercalcemia include primary hyperparathyroidism, tertiary hyperparathyroidism, and familial hypocalciuric hypercalcemia (FHH). Most cases of primary hyperparathyroidism are sporadic, but there are inherited syndromes to cause primary hypercalcemia, such as multiple endocrine neoplasia syndrome (MEN) and familial isolated hyperparathyroidism. Primary hyperparathyroidism accounts for approximately 90% of hypercalcemia in an outpatient setting [1]. Tertiary hyperparathyroidism occurs in patients with advanced and prolonged renal failure. Renal failure causes phosphate retention, decreased serum free calcium, and 1,25-$(OH)_2$D concentration, leading to parathyroid hyperplasia. Eventually, autonomous overproduction of PTH results in hypercalcemia. Familial hypocalciuric hypercalcemia (FHH) is a non-pathologic condition caused by several

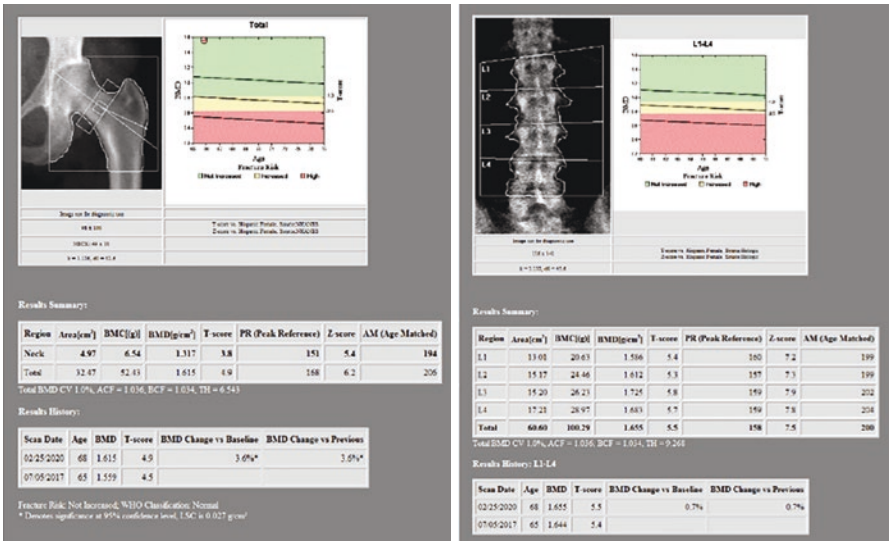

Fig. 27.1 DXA showed significantly elevated bone density in the axial bones

inactivating mutations in genes encoding calcium-sensing receptor (CASR), leading to inappropriately high PTH secretion and increased renal resorption of calcium [2].

PTH-independent hypercalcemia can be caused by different etiologies. In an acute hospitalization setting due to hypercalcemia, about 50% of the cases are accounted for malignancy. Malignancy-associated hypercalcemia occurs from mainly four different mechanisms. PTH-related protein (PTHrP) secretion by squamous cell carcinomas and direct local osteolytic bone resorption by skeletal involvement of breast cancer, multiple myeloma, or lymphoma are the majority of the cases. Rarely, ectopic PTH secretion or active 1,25-$(OH)_2$D secretion also causes hypercalcemia [3]. Also, several endocrine disorders can cause hypercalcemia. Hyperthyroidism increases bone turnover, and [4] pheochromocytoma can rarely secrete PTHrP [5]. Adrenal insufficiency is another uncommon cause of hypercalcemia that is caused by increased bone resorption, volume contraction, and increased renal calcium resorption in patients.

Other causes of non-PTH mediated hypercalcemia include milk-alkali syndrome, which may account for up to 10% of hypercalcemia. It is mainly caused by oversupplement of calcium and vitamin D especially in the elderly with decreased renal clearance [6]. Vitamin A, thiazide diuretics, lithium, PTH or PTHrP analogs, and theophylline also can cause hypercalcemia. Finally, prolonged immobilization increases bone resorption resulting in hypercalcemia.

A step-wise process to elucidate the cause of hypercalcemia starts with complete medication reconciliation. The cornerstone to differentiate causes of hypercalcemia is the measurement of intact PTH to determine if the process is PTH-dependent. Increased or inappropriately normal (>20 pg/ml) PTH in the setting of elevated calcium confirms PTH-mediated hypercalcemia [7]. History of end-stage renal failure with dialysis or renal transplantation suggests tertiary hyperparathyroidism.

The similar biochemical snapshot of hyperparathyroidism with normal PTH and FHH can be challenging to differentiate. The clinicians should be aware that FHH is a rare condition (1:10,000–1:100,000), but misdiagnosis as primary hyperparathyroidism can result in unnecessary surgery. Family history can provide a cue. Measuring 24-hour urine calcium excretion is helpful as patients with FHH are expected to have decreased fractional excretion of calcium ([24-hr urine Ca x serum Cr] / [24-hr urine Cr x serum Ca] $\leq$0.01), although recent data suggested that 20–35% of FHH had fractional excretion of calcium above >0.01 [2]. Lastly, gene sequencing analysis for the calcium-sensing receptor (CASR) is commercially available.

If intact PTH is suppressed, PTH-independent hypercalcemia is suspected. PTHrP, 25-(OH)D, and 1,25-$(OH)_2$D should be measured. If PTHrP is elevated, humoral malignancy-associated hypercalcemia should be suspected. 1,25-$(OH)_2$D elevation suggests endogenous overproduction from lymphoma or granulomatous disease. Vitamin D toxicity presents with elevated 25-(OH) D elevation with normal 1,25-$(OH)_2$D. If all are negative, multiple myeloma should be excluded with immunofixation.

In our case, intact PTH was elevated, but total serum calcium was within the normal limit. It is challenging to differentiate normocalcemic primary hyperparathyroidism with concomitant vitamin D deficiency from secondary hyperparathyroidism from vitamin D deficiency. Patients with vitamin D deficiency are expected to normalize PTH levels after vitamin D repletion. Vitamin D should be carefully repleted especially in those with suspected primary hyperparathyroidism like our case, as overt hypercalcemia and hypercalciuria can develop. After normalization of vitamin D, her PTH stayed markedly elevated with unmasked hypercalcemia, which confirmed primary hyperparathyroidism. Elevated alkaline phosphatase reflected increased bone turnover from hyperparathyroidism.

Differential Diagnosis of High Bone Density

The patient unexpectedly showed significantly increased bone mineral density (Z-score: +7.5 and +5.4 in the lumbar spine and the femur neck, respectively) (Fig. 27.1). The first step in a case of high BMD (T score >2.5) is to exclude possible artifacts, which can be caused by, most commonly, osteoarthritic change and others like fractures, surgical implant, ectopic calcification, and gallstones [8]. Paget's disease, osteoblastic metastasis, osteomyelitis, and osseous tuberous sclerosis can present with focal increase in bone mass.

Osteosclerosis, generalized increased BMD within the axial bone, can be seen in patients with non-skeletal conditions. Hepatitis C-associated osteosclerosis, although rare, was reported [9]. Acromegaly and bone marrow disorders such as myelofibrosis and mastocytosis are also associated with osteosclerosis [8].

Inherited genetic diseases either with an increased bone formation or a decreased bone resorption can present with generalized high bone mass. The alteration of the canonical Wnt signaling pathway, which is crucial in bone formation, can cause sclerosing bone dysplasia. One of the key players in the canonical Wnt signaling pathway is sclerostin, which is secreted by osteocytes, binds to low-density lipoprotein receptor-related protein (LRP) 5/6, and negatively regulates canonical Wnt signal [10]. The loss-of-function mutation in *SOST*, which encodes sclerostin, results in sclerosteosis, a rare autosomal recessive skeletal dysplasia, characterized by excessive height, facial distortion, and hand malformation (syndactyly). Skeletal overgrowth of bones in the skull can cause cranial nerve entrapment, potentially leading to facial palsy, hearing loss, and visual impairment [11, 12]. van Buchem disease is caused by a deletion of the downstream region containing regulatory elements for *SOST* transcription [11]. It shows similar but milder skeletal presentations as compared to sclerosteosis. Thickening of skull, jaw, and long bones and cranial nerve entrapment with facial palsy can occur, but patients with van Buchem disease do not have excessive height or hand malformation. The life expectancy of van Buchem disease is normal, whereas many patients with sclerosteosis die in early adulthood [12]. A gain-of-function mutation of LRP5 or 6 also causes high bone mass phenotype [13]. Patients with LRP5 mutation can present with dysmorphic facial features like macrocephaly, frontal bossing, prominent jaw and cheekbone, but with normal height and body proportions. Mild developmental delay was also reported with LRP5 mutation [14].

The genetic conditions with impaired bone resorption also cause high bone mass phenotype. Osteopetrosis is a rare genetic skeletal disorder with a defect in the bone resorption process: osteoclast differentiation, resorptive pit formation, and osteoclast acidification. Most commonly, it arises from the mutation of genes in osteoclast acidification, namely *TCIRG1* and *CLCN7*, encoding a3 subunit of the vacuolar proton pump and chloride voltage-gated channel7, respectively [15]. A rare autosomal recessive form of osteopetrosis due to the mutation in the carbonic anhydrase II (*CA2*) gene can present with renal tubular acidosis, nephrolithiasis, nephrocalcinosis, basal ganglia calcification, and cognitive dysfunction [16]. Pycnodysostosis is another genetic disorder with impaired bone resorption. The mutation in *CTSK*, which encodes cathepsin K that is responsible for type 1 collagen cleavage and bone matrix degradation, can develop a high bone mass [17]. Patients with pycnodysostosis manifest with short stature, craniofacial malformation, brittle bone, but also extra-skeletal manifestations such as hepatosplenomegaly and hypopituitarism.

In our case, she did not have a history of hepatitis C or bone marrow disorders. Her height was about 27% based on the US adult height distribution, and the exam showed no other skeletal feature including craniofacial or hand malformation. Of note, her previous head CT noted a rather dense calvarium. Primary hyperparathyroidism can present with osteosclerotic lesions; however, it's very rare and focal [18]. Our patient likely had two different pathologies-inherited sclerosing skeletal dysplasia and primary hyperparathyroidism. She showed a high bone mass despite catabolic action from concomitant hyperparathyroidism. Given the normal

height, the absence of other skeletal and facial malformation, and mild cognitive dysfunction, activating LRP5 gene mutation was suspected, but the genetic testing was not performed.

Questions

1. Familial hypocalciuric hypercalcemia is mostly caused by the mutations of which gene?

   A. *RET*
   B. *GCM2*
   C. *CCND1*
   D. *CASR*

2. Which laboratory finding in patients with hypercalcemia is most compatible with primary hyperparathyroidism?

   A. Elevated serum intact PTH with low urine calcium excretion
   B. Elevated serum intact PTH with high urine calcium excretion
   C. Low serum intact PTH with low urine calcium excretion
   D. Low serum intact PTH with high urine calcium excretion

3. The mutation of which gene is least related to osteosclerosis?

   A. *GATA3*
   B. *TCIRG*
   C. *SOST*
   D. *LRP5*

4. Which finding is most compatible with patients with van Buchem disease?

   A. Elevated bone mineral density, excessive height
   B. Elevated bone mineral density, normal height
   C. Low bone mineral density, excessive height
   D. Low bone mineral density, normal height

Answers

1. (D) *CASR* encodes calcium-sensing channel, and it is expressed in the parathyroid gland and kidney. The mutation of *CASR* causes elevated urinary resorption of calcium and inappropriate secretion of PTH, causing low urine calcium and elevated serum calcium. The mutations of *RET*, *GCM2*, and *CCND1* are related to multiple endocrine neoplasia type 2A, hypoparathyroidism, and sporadic hyperparathyroidism, respectively.
2. (B) The cornerstone to diagnose hypercalcemia is the level of intact PTH. Elevated intact PTH suggests PTH-medicated hypercalcemia, which includes primary and tertiary hyperparathyroidism and FHH. Low urinary excretion of calcium is suggestive of FHH.
3. (A) The mutations of *TCIRG*, *SOST*, and *LRP5* are related to osteopetrosis, sclerosteosis, and *LRP5* high bone mass, all of which cause osteosclerosis. The

mutation of *GATA3* is known as the cause of Barakat syndrome, a hereditary disease characterized by the triad of hypoparathyroidism, sensorineural hearing loss, and renal disease.

4. (B) The findings of van Buchem disease include generalized elevated bone mineral density with relatively normal height. Elevated height is suggestive of sclerosteosis rather than van Buchem disease.

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Chapter 28
Rare Presentation of Severe Pediatric Rickets

Cemre Robinson, Tony Yuen, and Mone Zaidi

Objective

1. Recognize a rare etiology of severe rickets
2. Evaluation of rickets and its broad differential
3. Review of primary hyperparathyroidism which is rare in the pediatric population

Case Presentation

A 12-year-old Bangladeshi girl was evaluated for severe rickets. The clinical history is notable for acquired rickets with the onset of symptoms at age 9. Previously, she was a healthy young girl without any bony deformities or bowing. Gradually over 3 years, the patient developed worsening bilateral genu valgum of her knees and was referred to orthopedics. Plain X-ray imaging of her legs demonstrated marked bilateral knee valgus deformity around 25–30 degrees (Fig. 28.1). Topogram of both lower extremities revealed leg length discrepancy with the right leg measuring 74.8 cm and the left leg measuring 73.8 cm. She underwent bilateral medial distal femur and proximal tibia hemiepiphysiodesis without any clinical improvement. In addition to severe genu valgum, she developed worsening muscle weakness, pain around her knees, fatigue with prolonged walking and climbing stairs, weakness of her arms when carrying objects, and loss of balance with ambulation. She disclosed constipation and

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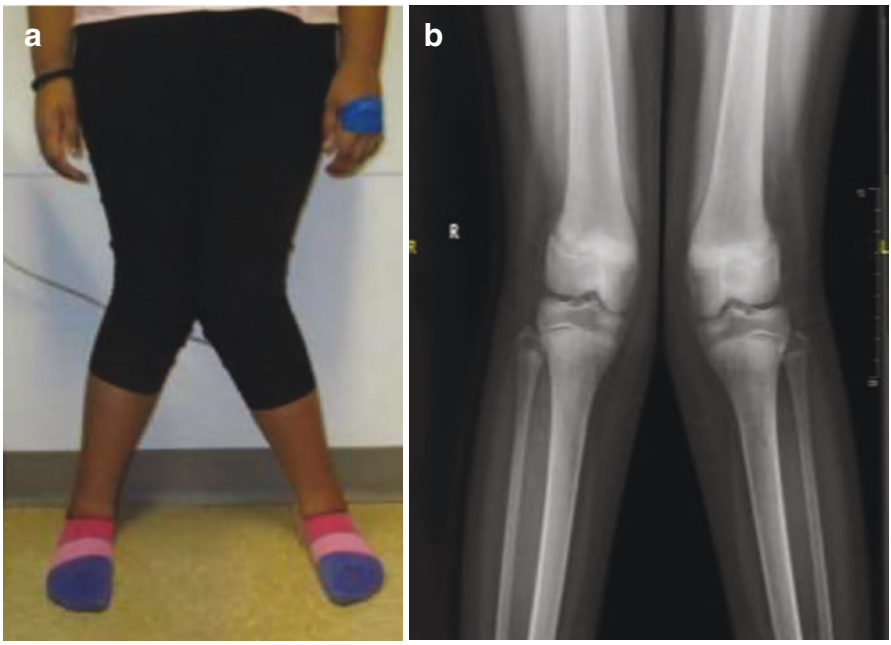

Fig. 28.1 (**a**) Severe bilateral genu valgum on physical exam. (**b**) Standard anteroposterior (AP) weight-bearing X-ray of lower extremities demonstrating bilateral knee valgus deformity around 25–30 degree

occasional abdominal pain as well as increased thirst. No history of fractures, renal stones, dental abscesses, or premature loss of deciduous teeth was noted. She denied a history of seizure, numbness, or tingling of the extremities. In the past, she was intermittently treated for vitamin D deficiency with over-the-counter supplements, but within last year, she has not taken any multivitamin, vitamin D, or calcium supplements. Dietary calcium intake was suboptimal with only one cup of milk per day. The physical examination was unremarkable except for severe bilateral genu valgum (Fig. 28.1). No distinct neck masses were palpable.

Her laboratory data were as follows (age-appropriate reference ranges are reported in parentheses). The results were notable for hypercalcemia, elevated iPTH, hypophosphatemia, and hypercalciuria, consistent with hyperparathyroidism and severe vitamin D deficiency:

- Calcium: 12.9 mg/dL (8.9–10.4)
- Phosphorus: 3.1 mg/dL (3.3–5.1)
- iPTH: 2226 pg/mL (10–65)
- Alkaline phosphatase (ALP): 588 IU/L (134–349)
- 25-hydroxyvitamin D: 5.9 ng/mL
- Albumin: 4.6 g/dL
- Spot urine calcium to creatinine ratio was consistent with hypercalciuria.

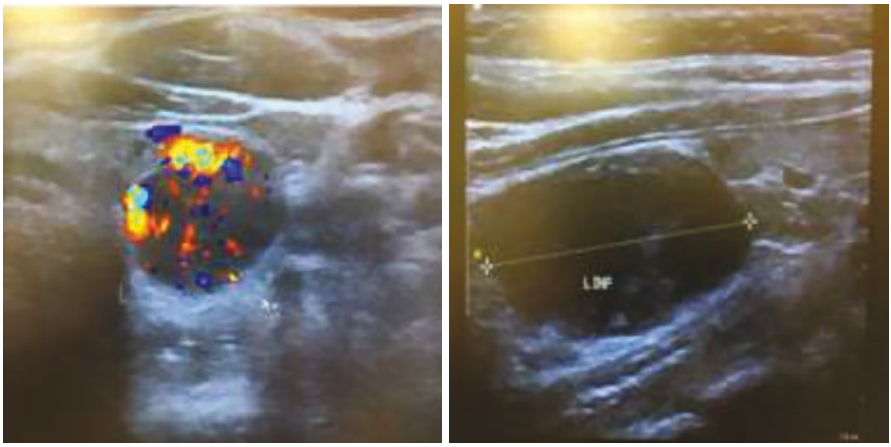

Fig. 28.2 A ~2.5 cm hypervascular parathyroid adenoma at the inferior pole of the thyroid

Bone resorption induced by PTH leads to a high bone turnover state, which is reflected in the elevated ALP level.

Neck ultrasound showed a left-sided hypervascular mass with smooth margins at the inferior pole of the thyroid, measuring 2.5 cm in maximum dimension (Fig. 28.2), suggestive of parathyroid adenoma.

In order to evaluate for potential renal and skeletal effects of prolonged hypercalcemia, renal ultrasound and dual energy X-ray absorptiometry (DXA) were obtained. Renal US was negative for nephrocalcinosis or nephrolithiasis. Baseline bone mineral density (BMD) at lumbar spine was normal with an age and height-corrected Z-score of −0.70 (normal > −2.0).

She underwent neck exploration with excision of an enlarged left inferior parathyroid adenoma, weighing 4.0 grams, and an enlarged right inferior parathyroid, weighing 0.1 grams. The histology was consistent with benign adenoma.

PTH levels normalized intraoperatively and remained normal postoperatively, but patient quickly developed symptomatic hypocalcemia, including numbness and tingling of her fingers, consistent with hungry bone syndrome. Treatment with calcium carbonate 400 mg three times daily, calcitriol 0.25 mcg twice daily, and vitamin D3 4000 IU daily was started. Calcium and calcitriol were slowly weaned off within the 1 month post-surgery according to repeat laboratory test results. Vitamin D supplement dose was reduced to maintenance 2 months post-surgery.

How the Diagnosis Was Made

Rickets is a heterogeneous bone disease clinically characterized by bowing deformities of the legs, widening of joints, and short stature [1]. The differential diagnosis of rickets in children is broad and includes many disorders of mineral homeostasis

Table 28.1 Differential diagnosis of rickets

Hypocalcemic rickets	**Normocalcemic rickets**
Elevated PTH	**Low serum phosphorus (Pi), high urine Pi**
Vitamin D deficiency	Hypophosphatemic rickets
Calcium deficiency	X-linked hypophosphatemic rickets
Vitamin D 25-hydroxylase deficiency	Autosomal dominant (AD) hypophosphatemic rickets
Malabsorption	Autosomal recessive (AR) hypophosphatemic rickets
Nephrotic syndrome	Fibrous dysplasia
Hepatic disease	Tumor induced osteomalacia
Low PTH	Fanconi syndrome
Hypoparathyroidism	**Low serum Pi, low urine Pi**
	Phosphate deficiency

Table 28.2 Differential diagnosis of hypercalcemia based on urine calcium excretion

High urinary calcium	**Other etiologies**
Hyperparathyroidism	Adrenal insufficiency
Multiple endocrine neoplasia (MEN)	Hyperthyroidism
Jansen's metaphyseal dysplasia	William's syndrome
Malignancy	Immobilization
Vitamin D intoxication	Alkalosis
Granulomatous diseases	
Low urinary calcium	
Familial hypocalciuric hypercalcemia	

(Table 28.1). The most common etiologies are hypocalcemia, hypophosphatemia, or vitamin D deficiency.

In this case, clinical history and examination, consistent with acquired rickets, provided key diagnostic clues and guided further investigations. Compared to the more common causes of acquired rickets, including nutritional deficiencies, the finding of hypercalcemia was surprising yet was crucial in making the correct diagnosis. The etiology of hypercalcemia is broad (Table 28.2) and can be classified as PTH-dependent when circulating PTH levels are elevated or inappropriately normal or PTH-independent when PTH levels are suppressed in the setting of elevated calcium. Our patient had PTH-dependent hypercalcemia evidenced by a significantly elevated PTH and hypercalcemia. Biochemically, this patient's hypercalcemia can be considered to be moderate (between 12 and 14 mg/dL) [2], yet she did not disclose many symptoms of hypercalcemia except for occasional constipation, abdominal pain, and increased thirst. We can postulate that severe vitamin D deficiency prevented serum calcium levels from raising even further.

In contrast to hypercalcemia in adults, which is accounted for by primary hyperparathyroidism (PHPT) in the majority of the cases (>90%), in children, PHPT only accounts for less than 5% of hypercalcemia [2, 3]. The estimated incidence of pediatric PHPT is 1 per 200–300,000, and its prevalence is 2–5 in 100,000 [4, 5] with a higher predominance in adolescents [4, 6]. Like in adults, most of the pediatric PHPT is caused by a single parathyroid adenoma (90%) as was the case for this patient, followed by four-gland parathyroid hyperplasia (~10%) and multi-grand disease (2 ~ 4%) [7]. Parathyroid carcinoma in children and adolescents is extremely rare with less than 1% of patients [7].

Parathyroidectomy is the treatment of choice in children with PHPT, and surgery is often curative. The preoperative identification of the parathyroid adenomas on neck ultrasonography allowed for consideration of minimally invasive parathyroid surgery instead of a conventional bilateral neck exploration. In our case, the pathology result was consistent with benign parathyroid adenoma. There is an increased risk of postoperative hungry bone syndrome in children because PHPT is generally more severe in the pediatric age group [7]. Acute hypocalcemia and hungry bone syndrome occur in approximately 50% of the cases, and persistent hypocalcemia or hypercalcemia (2–3%) has been reported as well [7]. Thus far, the patient is clinically doing well, but biochemical surveillance of serum calcium and PTH levels will be important.

Radiographically, typical features associated with PHPT such as subperiosteal resorption, brown tumors, and osteitis fibrosa cystica were lacking, and there was no evidence of fractures. Baseline DXA BMD and renal US results were reassuring without evidence of decreased BMD for age or nephrocalcinosis and/or nephrolithiasis, all of which could be complications of long-standing hypercalcemia. Repeat BMD assessment via DXA will be pursued in the future to evaluate for potential gain in bone mass postoperatively.

PHPT may occur as a hereditary familial disease or sporadically due to a de novo germline mutation in the patient [2]. There are 12 genes identified to-date in association with syndromic and non-syndromic forms of PHPT. Our patient did not have a family history of PHPT. The genetic testing panel for hereditary hyperparathyroidism was negative for the following genes: AP2S1, CASR, CDC73, CDKN1B, GNA11, MEN1, and RET, making a hereditary familial disease unlikely.

It is exceedingly rare for rickets, especially severe rickets, to be the initial presentation of PHPT. In pediatric literature, PHPT masquerading as rickets has been reported in a few case reports [4, 8–10]. This case highlights that rickets can be a rare presenting symptom of PHPT in children and illustrates the need to pursue a comprehensive laboratory workup for potential etiologies of rickets listed in Table 28.1. A thorough workup done early on in her 3-year disease course could have uncovered the correct diagnosis and would have spared the patient a severe skeletal disease burden. Future management of this patient involves further corrective orthopedic surgeries and clinical and laboratory surveillance for recurrent hyperparathyroidism of the two remaining parathyroids.

Diagnosis: Severe rickets Caused by Primary Hyperparathyroidism

Lessons Learned

- Primary hyperparathyroidism is a rare diagnosis in the pediatric population.
- Severe rickets is an uncommon presentation of PHPT in comparison to symptoms related to hypercalcemia.
- Comprehensive metabolic bone workup is indicated in the evaluation of rickets.
- Family screening and genetic testing are recommended for genes associated with PHPT.

Questions

1. Which of the following does the etiology of PHPT include?

   A. Distinct parathyroid adenomas due to germline or somatic mutations in *HPRT2* (CDC 73)
   B. Multigland hyperplasia due to germline mutations in *MENIN*, *RET*, and *CDKN1B* genes
   C. Single parathyroid adenoma that represents monoclonal neoplasm, associated with a somatic mutation in *MENIN* or *PRAD1*
   D. All of the above

2. Which of the following features can be seen in PHPT?

   A. Markedly elevated serum calcium and PTH
   B. Hypercalciuria
   C. Decreased BMD
   D. Rickets
   E. All of the above

3. Which of the following genes is not associated with PHPT?

   A. *CDKN1B*
   B. *AP2S1*
   C. *CASR*
   D. *PHEX*
   E. *RET*

4. Hereditary hypercalcemic disorders include all except:

   A. Neonatal severe primary hyperparathyroidism
   B. Osteogenesis imperfecta
   C. Multiple endocrine neoplasia
   D. Familial hypocalciuric hypercalcemia

Answers to Questions

1. (D) All of the above
2. (E) All of the above
3. (D) *PHEX*
4. (B) Osteogenesis imperfecta

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Part VIII
Endocrine Disorders in Men

Chapter 29
Introduction to Endocrine Disorders in Men

Stephen J. Winters

Introduction

The disorders that affect hypothalamic-pituitary-testicular function are diverse and can be challenging to diagnose and manage. These include ambiguous genitalia in the newborn, failure to enter puberty, and androgen deficiency and infertility in adult men. The increased willingness of men to discuss the symptoms of hypogonadism and the availability of effective well-accepted testosterone treatments have increased substantially the number of men seeking to be evaluated and treated for hypogonadism. Men may present with classical symptoms and signs of androgen deficiency or with infertility. Often the symptoms are non-specific, however, and the clinical signs of hypogonadism may be subtle or absent, depending on the severity and duration of the illness. Other than azoospermia, the semen parameters that distinguish fertile from infertile men are equally indistinct.

Careful medical history and physical examination, to include measurement of testicular size, are the essential first step in establishing a hypogonadism diagnosis. Laboratory testing should proceed in a logical, cost-effective fashion. Often, the total testosterone level is sufficient to confirm the clinical diagnosis of hypogonadism, to be followed by the measurement of LH and FSH in order to determine if the patient has primary or secondary hypogonadism. Thereafter, a rather lengthy differential diagnosis should be considered. When the total testosterone level is borderline, or is not consistent with the clinical findings, the free testosterone level should be measured, and it is important to emphasize that direct analog assays for testosterone are inaccurate, and should not be used for this purpose.

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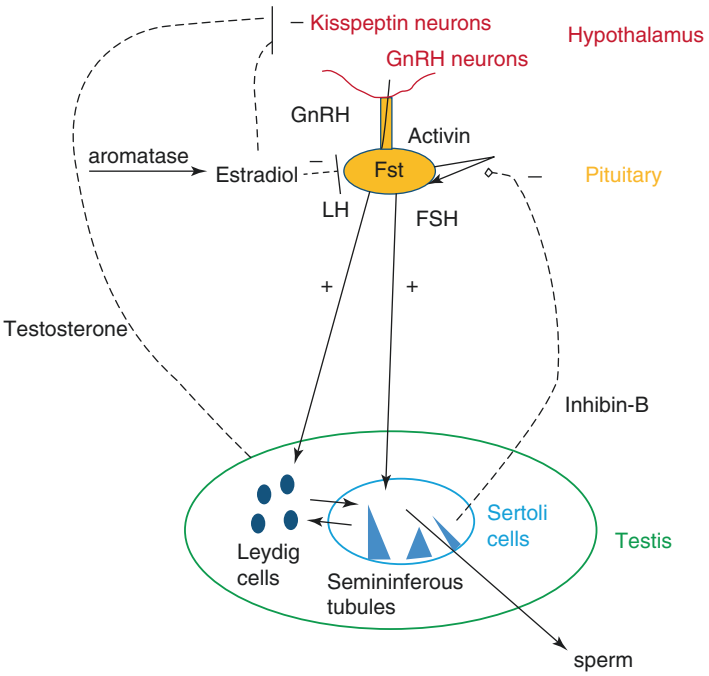

Fig. 29.1 Diagram showing feed-forward (solid lines) and feedback (dashed lines) mechanisms governing hypothalamic-pituitary-testicular function. GnRH stimulates pituitary gonadotrophs to synthesize and secrete LH and FSH. LH activates the LH/hCG receptor in Leydig cells to stimulate testosterone production, whereas Sertoli cell FSH receptors are the target for FSH. There is substantial paracrine communication between Leydig cells and Sertoli cells so that both FSH and LH are spermatogenic hormones. Testosterone activates androgen receptors throughout the body and inhibits GnRH pulsatility through effects on kisspeptin (KNDy) neurons which, in turn, regulate GnRH synthesis and secretion. Testosterone is converted to estradiol by the aromatase enzyme in adipose tissue, liver, pituitary, and the CNS and negatively regulates LH and FSH through effects on both the pituitary and NKD neurons. The selective regulation of FSH occurs in part because pituitary activin stimulates FSH transcription which is blocked by testicular inhibin-B and pituitary follistatin

In recent years, understanding of the feed-forward and feedback mechanisms (Figure1) that control testicular function has increased substantially, and studies of the human genome have added an exciting new dimension to the field. With the exponential increase in our understanding of male hypogonadism and its treatments, there are thousands of possible references for this section, and I apologize to those whose important contributions I have learned from, but are not listed due to space limitations (Fig. 29.1).

Chapter 30
Adult Onset Hypogonadism

Stephen J. Winters

Objectives

1. Learn how obesity affects testicular function
2. Be aware of pitfalls in the diagnosis of testosterone deficiency in obese men
3. List comorbidities associated with adult onset hypogonadism
4. Summarize the benefits and risks of testosterone treatment for men with adult onset hypogonadism

Case Presentation

A 38-year-old man presented with his wife because of infertility. The couple had been married for 3 yrs. Prior to the marriage, he experienced low energy, low libido, a sleep disturbance, and mood swings. He weighed 340 pounds. The AM total testosterone level was 194 ng/dL (325–1125), and the free testosterone level by direct analog assay was 7.0 pg/mL (8.7–25). PRL was 9.9 ng/ml, LH 3.8 mIU/ml (1.5–12), and FSH 6.3 mIU/ml (1.8–8.6). A pituitary MRI was normal. He was diagnosed with secondary hypogonadism and treated with a testosterone gel. He dieted and exercised, and his weight fell to 306 lbs.; his symptoms improved. The couple remained infertile and consulted with a specialist in reproductive endocrinology and infertility who found azoospermia. He was a sexually mature man with no abnormal physical findings other than obesity. The testes measured 4.6 × 2.5 cm on the right and 4.3 × 2.3 cm on the left. He was advised that testosterone treatment might

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explain his infertility, and treatment was discontinued. Ten months later his wife conceived. A follow-up total testosterone level was 246 ng/dL, and the calculated non-SHBG (bioavailable) testosterone level was 128 ng/dL (normal >110).

Review of How the Diagnosis Was Made

This middle-aged man was diagnosed with adult onset hypogonadism (AOH) and treated with testosterone. He was subsequently found to have azoospermia that reversed after testosterone treatment was discontinued. He was obese with disturbed sleep which presumably represented sleep apnea, which together with metabolic syndrome (MetS), T2DM, and NAFLD are often associated with low total testosterone levels. In these clinical conditions, low total testosterone is often explained by low SHBG, and my approach is to measure SHBG and free testosterone before beginning testosterone treatment to more definitively establish the diagnosis of testosterone deficiency. In this case, a low free testosterone level was found, but an analog direct free testosterone assay was used, and the low free testosterone and normal LH levels were thought to signify hypogonadotropic hypogonadism, perhaps due to a pituitary tumor, but no tumor was found on MRI. Hypogonadism and the MetS may occur in Cushing syndrome, acromegaly, or hemochromatosis, so these conditions should be considered in the diagnostic evaluation. The free testosterone result with this assay is inaccurate and misleading, and when the pretreatment non-SHBG (bioavailable) testosterone level was subsequently calculated (www.issam.ch/freetesto.htm) from the levels of total testosterone (194 ng/dL) and SHBG (12 nmol), the result (136 ng/dL) was within the normal range (>110 ng/dL). If this information had been known, the MRI was probably unnecessary since the patient had no clinical features of hypogonadism, no headache, or vision disturbance and his serum free thyroxine and PRL levels were normal. Diet and exercise might have been recommended rather than testosterone treatment, and azoospermia would not have developed. After stopping testosterone treatment, the AM non-SHBG testosterone level was within the reference range, and his wife conceived.

Lessons Learned

Endocrinologists are often asked to evaluate middle-aged men when a low testosterone level is found in the setting of asthenia and erectile dysfunction. This condition is generally neither classical testicular failure nor hypogonadotropic hypogonadism and has been termed “adult onset hypogonadism” [1] or “late onset hypogonadism,” a term also applied to the testosterone deficiency that occurs with aging. Both the diagnosis of AOH and its treatment remain controversial. While most guidelines require both symptoms consistent with hypogonadism and a low testosterone level, the details of the diagnostic criteria vary [2]. The testosterone level should be

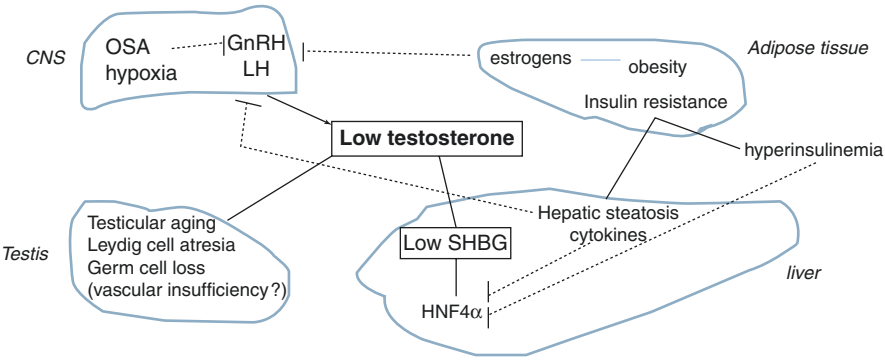


Fig. 30.1 An illustrative schema for the mechanisms for low testosterone levels in men with AOH. It highlights the complex interaction between the testis and adipose tissue, liver, and the hypothalamic-pituitary unit

checked in the morning because there is a diurnal variation which averages about 15% but can be much greater and reference ranges are usually morning values. The total testosterone level also declines slightly shortly after a glucose load [3]. Finally, low values should be confirmed.

As in this case, men with AOH are often obese and/or have type 2 diabetes, dyslipidemia, or NAFLD [4]. The cause of low testosterone in these men is multifactorial, controversial, and incompletely understood, and proposed mechanisms are diagrammed in Fig. 30.1. Low T is partly a consequence of a low level of SHBG since SHBG binds testosterone with high affinity, and plasma SHBG and total testosterone levels are strongly positively correlated in men with a functional hypothalamic-pituitary-testicular unit [5]. Low SHBG is partly due to hyperinsulinemia and cytokines from hepatic steatosis with insulin resistance inasmuch as each of these factors suppresses the expression of HNF4α, a transcription factor which activates the SHBG promoter [6]. Mean LH levels are generally within the reference range although values are slightly lower than in normal controls, consistent with mild hypothalamic-pituitary dysfunction. Some LH pulsatility studies have found reduced pulse amplitude with normal pulse frequency [7], although other studies did not confirm this finding. Suppression of GnRH-LH by increased levels of estradiol and cytokines, leptin signaling, hypoxia in OSA, and feedback modification by low SHBG levels have all been proposed to explain these findings. There is also some evidence that obesity impairs Leydig cell function directly.

While a low total testosterone level is often the basis for the diagnosis of testosterone deficiency in AOH, men with low total testosterone due primarily to low SHBG levels may be viewed incorrectly as testosterone deficient. The European Male Ageing Study (EMAS) of 3369 men at eight European sites found that 12% of men age 40–79 years had low serum testosterone and low/normal LH levels and were diagnosed as hypogonadotropic hypogonadism, but the authors did not take into consideration the impact of low SHBG or measure free testosterone [8] which, unlike the total testosterone level, is unaffected by the level of SHBG.

Various methods to determine free testosterone levels are available [9, 10]. Reference laboratories have replaced immunoassays with liquid chromatography-mass spectroscopy (LC-MS) methods which directly or indirectly measure free testosterone in filtrates following equilibrium dialysis. While this method is the current "gold standard," it is technically difficult, not readily automated, and more expensive. I generally reserve the free testosterone assay as a second-line test for adult men in whom the total testosterone level is borderline or men with low/high SHBG levels. The free testosterone level can be readily calculated from the levels of SHBG and total testosterone according to the law of mass action (www.issam.ch/freetesto.htm), as done in this case, but this approach has theoretical limitations because the association constant of SHBG for testosterone can occasionally vary among individuals and is estimated not measured [10]. Direct analog assays are inaccurate and should not be used [11]. In addition to assay nomenclature, "direct" assays can be recognized by the relatively low reference range (e.g., 8.7–25 pg/mL). In spite of the methodological controversies surrounding free testosterone assays, low levels by equilibrium dialysis imply that testosterone production is reduced in men with extreme obesity [12].

While low testosterone levels may be a biomarker for obesity and its metabolic consequences, profound testosterone deficiency *is* a cause as well as a consequence of obesity and metabolic syndrome in men, representing a bidirectional relationship. Froelich's syndrome (adiposogenital dystrophy) is a classical diagnosis that recognized the association between profound male hypogonadism and obesity. DEXA scans revealed that percent body fat was substantially higher in men with congenital hypogonadotropic hypogonadism who are inadequately treated compared to a group of CHH men receiving consistent androgen replacement. Moreover, bilateral orchiectomy as well as testosterone deficiency produced by GnRH analogs in prostate cancer patients leads to an increase in body fat and insulin resistance by HOMA-IR, as well as a decline in muscle mass.

Whatever the mechanisms, the low total testosterone level increased our patient's risk for developing CVD and for increased CVD mortality [13]. Among those with diabetes, the CVD risk with low testosterone is independent of age, BMI, and duration of diabetes and A1C. While low SHBG as a marker for insulin resistance would be expected to increase the CVD risk, and perhaps account for the link between low total testosterone levels and CVD [14], other studies [15] have found no association between low SHBG and incipient CVD events. The associations between free testosterone and CVD are much less consistent, and low testosterone levels could be a consequence rather than a cause of poor health [16]. What is not controversial is that men with AOH should have a lipid panel and be screened for NAFLD and T2DM, and most need lifestyle interventions.

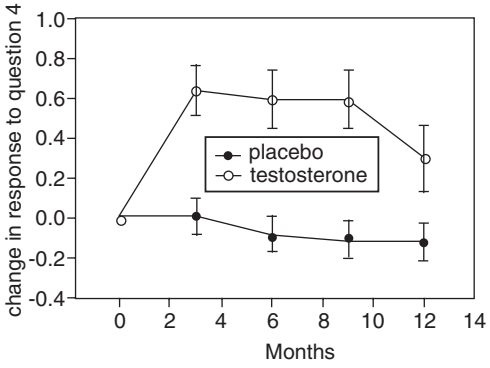
Total testosterone levels are low in men with obstructive sleep apnea although much of the effect may be explained by coexistent obesity and insulin resistance [17]. Some studies have shown that continuous positive airway pressure (CPAP) treatment increases testosterone levels, but this is an inconstant finding and might relate to changes in body weight and composition since SHBG may increase.

There is some evidence that obesity disrupts spermatogenesis and predisposes to infertility although the data are not compelling [18, 19]. A meta-analysis failed to detect a relationship between BMI and sperm count [19], while a second study, which also found no linear relationship between BMI and sperm concentration, noted a 1.28 increased risk for oligo-azoospermia among men with obesity and a 2.04-fold increase with extreme obesity [18]. In a survey of 501 couples hoping to conceive with no prior diagnosis of infertility, the time to conception, however, was unaffected by male (or female) BMI [20]. Hormone changes, insulin resistance, and scrotal temperature have been proposed to affect sperm production in obese men. One provocative idea is that lower inhibin-B levels among obese adult men and pubertal but not prepubertal boys reflect reduced proliferation of Sertoli cells during puberty with obesity [6], and consequently there are fewer germ cells.

Much of the disturbance in pituitary-testicular function in obese males is reversible. Weight loss, especially following bariatric surgery [21, 22], results in a substantial rise in SHBG and total testosterone levels. Free testosterone, calculated from total testosterone and SHBG, also increases. Estradiol levels tend to decrease, and LH levels tend to rise, but the mechanism for the increase in testosterone when obese men lose weight, like the cause of the low levels in obesity, is incompletely understood. There appears to be no increase in sperm concentration, motility, or morphology following bariatric surgery, however [23]. Case reports and small series suggest that extreme low calorie diets and rapid profound weight loss may lower testosterone levels and reduce sperm production.

Treatment Strategies

Testosterone treatment is often prescribed for men with symptomatic AOH, with mostly positive outcomes reported in observational studies, but there are some conflicting results with variable patient populations, age, T formulations, and dosing. The "T trials" were a series of carefully coordinated double-blind placebo-controlled trials conducted during the past decade at 12 US sites in 788 men age 65 and older with a total testosterone level of <275 ng/dL [24]. Men were randomized to receive a daily testosterone gel, with dose adjustments to maintain a level within the normal range for young men (free testosterone ~150 pg/mL by two-step equilibrium dialysis) or placebo gel, for 12 mo. The major positive finding was a statistically significant increase in sexual functioning (Fig. 30.2). Closer analysis of the data, however, reveals that the improvement was quite modest. The outcome was based on the results of a Psycho-Sexual Daily Questionnaire with 12 questions, each scoring 1 point for a "yes" answer. While a young man might score 10–12, the score in T-treated men rose from 1.4 to 2.0 compared to a decline from 1.4 to 1.3 in men randomized to placebo ($p < 0.001$ for the difference). The hematocrit and bone mineral density also rose slightly. There was no increase in the distance walked in 6 minutes, in energy, or in cognitive function. Coronary artery calcified plaque volume increased although there was no increase in clinical cardiovascular or prostate



YES or NO

Sexual daydreams
Anticipation of sex
Sexual interactions
Flirting (by you)
Flirting towards you
Orgasm
Ejaculation
Intercourse
Masturbation
Night spontaneous erection
Day spontaneous erection
Erection with sexual activity

	Baseline	12 months
Testosterone	1.4±1.3	2.0±1.5
Placebo	1.4±1.3	1.3±1.2

Fig. 30.2 Effects of testosterone treatment on sexual function in hypogonadal older men. From Snyder et al. [24]. In the "T trial," 790 men older than age 65 yrs. with an AM total testosterone level <275 ngdL at baseline were randomized to treatment with a transdermal testosterone preparation or placebo daily for 12 months. They completed a sexual activity questionnaire in which 1 point was scored for each of the yes/no questions listed over the preceding week. There was a significant difference between the two groups, but the improvement must be viewed as small insofar as the score for a healthy young man might be 10–12, and the final score for the men treated with testosterone was 2.0 ± 1.5

events. Many subsequent reviews conclude that "T treatment is associated with multiple benefits including amelioration of sexual dysfunction" which I believe overstates the results of the T trials. Moreover, whether these results are applicable to obese middle-aged men with the MetS, such as our patient, is unknown.

Other Effects of Testosterone Treatment

Among other effects of testosterone treatment, the most clearly established is suppression of gonadotropin secretion and thereby spermatogenesis, such that testosterone treatment is fundamental to ongoing efforts to develop a hormonal male contraceptive [25]. Consequently, the US Endocrine Society "recommends against starting T therapy in patients who are planning fertility in the near term" [26]. While receiving T treatment for AOH, our patient experienced infertility and was found to be azoospermic. When treatment was stopped, his wife conceived although a repeat semen analysis was not performed. Based on contraceptive trials, recovery to pretreatment values generally occurs in 90% of men by 12 months [25], but in clinical practice recovery will be affected by the dose and duration of treatment and the

androgens used. Therefore, some men treated with testosterone also take hCG in an effort to preserve spermatogenesis [27].

Specific estrogen receptor response modifiers (SERMs) such as clomiphene that function as an estrogen receptor-α antagonist in the hypothalamic-pituitary unit, or aromatase inhibitors (AI) that reduce estrogen production, increase LH and testosterone levels in AOH as in normal men because they interrupt estrogen negative feedback regulation of GnRH and LH secretion. These drugs represent an alternate treatment approach for AOH since they increase testosterone levels without suppressing gonadotropins and spermatogenesis [28, 29]. Headache, dizziness, gynecomastia, and vision disturbance have occasionally been reported with clomiphene, and there is concern that prolonged use of an aromatase inhibitor will predispose to low bone mass and fractures, as in women. The long-term safety of these products has not been adequately established, and neither clomiphene nor AIs are US FDA-approved for use in men.

The major concern in the treatment of AOH with testosterone relates to its potential impact on incident cardiovascular disease. While the inverse association between endogenous testosterone levels and CVD risk suggests that testosterone may be cardio-protective, several retrospective studies published in 2013–2014 and one clinical trial in 2010 found that testosterone treatment instead increased the risk for cardiovascular disease and that large doses of testosterone given to elderly men may cause edema and contribute to congestive heart failure [30]. Because of these concerns, the FDA product-labeling states that the safety and efficacy for men with age-related hypogonadism have not been established.

Consequently, the cardiovascular effects of testosterone treatment have been the subject of substantial reexamination and ongoing debate. There are many observational studies of cardiovascular outcomes in which the subjects had a variety of causes for low testosterone levels. This is both a strength and a weakness. Several placebo-controlled studies have examined the metabolic effects and surrogate CVD outcomes of testosterone treatment in men with T2DM, a high-risk group for AOH and CAD, as briefly summarized in Table 30.1. Treatment was for 3 months or more, age and body composition at baseline varied, and various testosterone preparations and doses were used. The most consistent findings were a reduction in fat mass and no effect on HbA1C; other results varied. It is intriguing to consider that a decrease in fat mass and improvement in insulin sensitivity with T treatment could lead to a reduction in CVD risk, rather than an increased risk as initially proposed. Hopefully, answers to these questions will be forthcoming.

Because prostate is an androgen target tissue, testosterone treatment has been considered to contribute to BPH and has historically been contraindicated in men with prostate cancer.

Most guidelines recommend against T treatment if there is a palpable prostate nodule, a PSA level >4 ng/mL, or >3 ng/mL in high-risk populations. Prostate volume and PSA levels will increase in proportion to the testosterone treatment dose, and testosterone-treated men require careful follow-up. The increase in PSA averages 0.3 ng/ml and usually stabilizes over time. It is uncommon for the PSA level to exceed 4.0 ng/ml, but if so, or if the increase above baseline exceeds 1.4 ng/mL,

Table 30.1 Effects of testosterone treatment on metabolic outcomes in men with T2DM

	Favored testosterone	No difference from placebo
Adipose tissue	Decr sc not visceral fat-Ginetti 2017 Decr waist circumference-Hackett 2014 Decr sc fat-Dhindsa 2016 Decr total and truncal fat-Magnussen 2016	Gopal 2010 Jones 2011
A1C		Ghopal 2010, Jones 2011, Hackett 2013, Ginetti 2014, Dhindsa 2016, Magnussen 2017
Insulin resistance by HE clamp	Dhindsa 2016	Magnussen 2017
HOMA	Jones 2011, Dhindsa 2016	Gopal 2010, Gianetti 2016, Magnussen 2016

Dhindsa et al. [31]; Gianatti et al. [32]; Gopal et al. [33]; Hackett et al. [34]; Jones et al. [35]; Magnussen et al. [36]

referral to a urologist is recommended. Most studies suggest that testosterone treatment does not increase the risk for developing prostate cancer or the likelihood of aggressive disease, but these were observational studies not randomized prospective trials. Nowadays, testosterone treatment is not recommended for men with locally advanced or metastatic prostate cancer, or with breast cancer, whereas recommendations vary for those with a history of prostate cancer that has been definitively treated, and the PSA level is low. Most studies using replacement doses of testosterone show no adverse effect on lower urinary tract symptoms, or increased risk for urinary retention, and some studies have shown unexpected improvement.

In summary, testosterone treatment for men with AOH often improves mood and sexual behavior, and body composition, but changes on average are modest. Gonadotropins and spermatogenesis are suppressed by testosterone, and treatment should not be offered to men seeking fertility. Finally, the long-term risks for prostate disease and CVD among men with AOH remain unknown. The FDA is requiring manufacturers of approved testosterone products to conduct a clinical trial to determine whether there is an increased risk of heart attack or stroke among users of their products.

Multiple-Choice Questions

1. A 42-year-old man presents with erectile dysfunction. He was married for 11 years and had 2 children, but divorced 2 yrs. ago. He is otherwise healthy and takes no medications. His libido is strong. His maternal and paternal grandmothers each had type 2 diabetes. On physical examination, he is healthy and well-appearing. His height is 6′ and his weight is 190 pounds (BMI 26 kg/m^2). There is no goiter or gynecomastia. Both testes are 4.6 × 2.8 cm and 20–25 ml in volume. His total testosterone level was 236 ng/dl. Each of the following tests is useful at this time, except:

   A. Lipid profile
   B. Fasting blood sugar

C. Free testosterone
D. PRL
E. TSH

Answer D. The likely diagnosis is metabolic syndrome with low SHBG to explain the low total testosterone level. Free testosterone should be measured. ED is a predictor of cardiovascular disease such that guidelines suggest screening for diabetes and dyslipidemia. Hypothyroidism results in a low SHBG level and may reduce sexual function. Hyperprolactinemia is a rare occurrence in men with ED whose libido is preserved, but should be measured if free testosterone proves to be low.

2. A 30-year-old man presents with bilateral breast enlargement. He was previously healthy and is the father of two children. Hypertension was diagnosed 2 years ago, and he is treated with lisinopril. He lost 10 pounds in weight during the past year. On physical examination, the pulse is 100. There is a small goiter. He has prominent breasts that are tender to palpation. The testes are each 4.8 × 2.7 cm. The serum testosterone level is 988 ng/dl. Each of the following tests is useful at this time except:

A. TSH
B. hCG
C. Mammogram
D. SHBG
E. LH/FSH

Answer C. Gynecomastia is common in men with hyperthyroidism and may be the presenting complaint. One hypothesis is that the primary event is the potent increase in SHBG. LH/FSH is helpful in excluding primary gonadal insufficiency. hCG-producing tumors, while very rare, should always be excluded with tender gynecomastia which is hormonally stimulated, A mammogram is uninformative with bilateral tender breasts.

3. A 60-year-old African American man with a non-functional pituitary tumor is referred to you for treatment including testosterone replacement. His free T4 level is low at 0.7 ng/dL (normal 0.8–1.7) as was his total testosterone of 60 ng/dL. PRL is normal at 8.6 ng/ml, and he responds normally to cortrosyn with a rise in cortisol from 8 to 21 μg/dL. He is a nonsmoker but the screening PSA is 3.8 ng/ml (normal <4). At this point which of the following would you recommend:

A. Insulin tolerance testing
B. Referral to a urologist
C. Repeat PRL
D. hCG stimulation test
E. Treatment with clomiphene

Answer B. PSA levels are generally very low in men with hypopituitarism. Moreover, current guidelines recommend a urological consultation when the

verified serum PSA concentration exceeds 3.0 ng/ml in men with increased risk for prostate cancer, e.g., Blacks.

4. A 20-year-old man with cystic fibrosis is taking megestrol 400 mg daily to increase his appetite. Which of the following complications of therapy are likely to occur?
   A. Hyperprolactinemia
   B. Hypothyroidism
   C. Hypogonadism
   D. Osteoporosis
   E. C and D

   Answer E. Megestrol is a progestin and glucocorticoid. It suppresses LH and thereby testosterone levels, and its glucocorticoid action adds to its effect to decrease bone mass. There are no effects on PRL or thyroid function.

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Chapter 31
Congenital Hypogonadotropic Hypogonadism

Stephen J. Winters

Objectives

1. Learn the variable clinical presentations of CHH in males.
2. Summarize what is known about the genetic mechanisms for CHH.
3. Be aware of approaches to distinguish CHH from constitutional delay of puberty.
4. Understand treatment options for gonadotropin-deficient men.

Case Presentation

A 19-year-old college student was referred because of gynecomastia. He was otherwise healthy, with a normal sense of smell. His childhood growth and development were normal, but he failed to develop body hair with his peers and so far has not shaved his beard. His breast enlarged at about age 13. There was no family history of hypogonadism or consanguinity. He was healthy and well appearing. His height was 71 inches, and his arm span was 72 inches. His blood pressure was 120/76. He looked hypogonadal and much younger than his stated age, with reduced muscle mass and little body hair. There was Tanner 3 gynecomastia. The testes were each quite small, measuring about 1.5 cm in length (3 ml in volume), and the phallus was 5 cm in length and normal in anatomy.

Laboratory data: Serum testosterone 15 ng/dL, LH 0.5 IU/L, FSH 1.1 IU/L, free T4 1.3 ng/dl, PRL 5 ng/ml, estradiol 24 pg/ml, IGF 1 254 ng/ml (normal 114–492), and AM cortisol 12 μg/dL. DEXA scan: BMD of the lumbar spine T score was −2.4 and hip −1.5 S.D. Pituitary MRI was normal.

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He was treated with increasing doses of testosterone enanthate subcutaneously (sc) and subsequently with transdermal testosterone. He masculinized normally and married at age 29. Two years later, he and his wife wished to conceive. Genetic testing revealed compound heterozygous mutations of the GnRH receptor gene [1] (GnRHR, gln106 to arg (Q106R; 138850.0001) and arg262 to gln (R262Q; 138850.0002)).

Treatment was changed to hCG 750 U sc three times a week. His testes increased slightly in size over 6 months, and the total testosterone level was 350 ng/dL. He remained azoospermic, however, and 75 IU recombinant human follicle stimualting hormone (rhFSH) sc three times a week was added. Six months later, his sperm count rose to 18 million/ml with normal sperm motility and morphology. Four months later, his wife became pregnant and subsequently delivered a healthy full-term female infant. He chose to continue hCG injections since they were planning for a second child.

Review of How the Diagnosis Was Made

Endocrinologists are often asked to evaluate young adult men who present with absent or incomplete puberty [2]. This young man was otherwise healthy and was of normal height and weight. There was no clinical or biochemical evidence for hypothyroidism or cortisol deficiency, and the PRL level was not increased. In spite of gynecomastia, the estradiol level was normal. The testosterone level was consistent with his phenotype and was typical for a prepubertal boy, and the serum levels of LH and FSH were in the low-normal range. Pronounced hypogonadism at age 19 excluded constitutional delay of puberty. There was no clinical evidence for a tumor or other pathological condition affecting the pituitary or suprasellar region, and an unexpected mass lesion was excluded by the normal MRI. His overall good health excluded infiltrative disorders such as hemochromatosis and histiocytosis. Thus, the presumptive diagnosis was congenital isolated hypogonadotropic hypogonadism (CHH). The patient was not anosmic, and no congenital abnormalities were found. The family history was negative for hypogonadism and developmental defects.

Patients with CHH are classically divided into those with anosmia or hyposmia (Kallmann syndrome) or those with normal olfaction [3]. He is in the latter subgroup. A sporadic case with no family history suggested an autosomal recessive disorder, most often of the GnRH-R, or a spontaneous mutation. An algorithm for the evaluation of males with pubertal delay is shown in Fig. 31.1.

Lessons Learned

Hypogonadotropic hypogonadism (HH) results from inadequate secretion of the gonadotropic hormones from the pituitary with resultant sex hormone deficiency and infertility. It can be acquired, e.g., pituitary tumor, or congenital. Mutation of many transcription factors involved in the complex process of pituitary

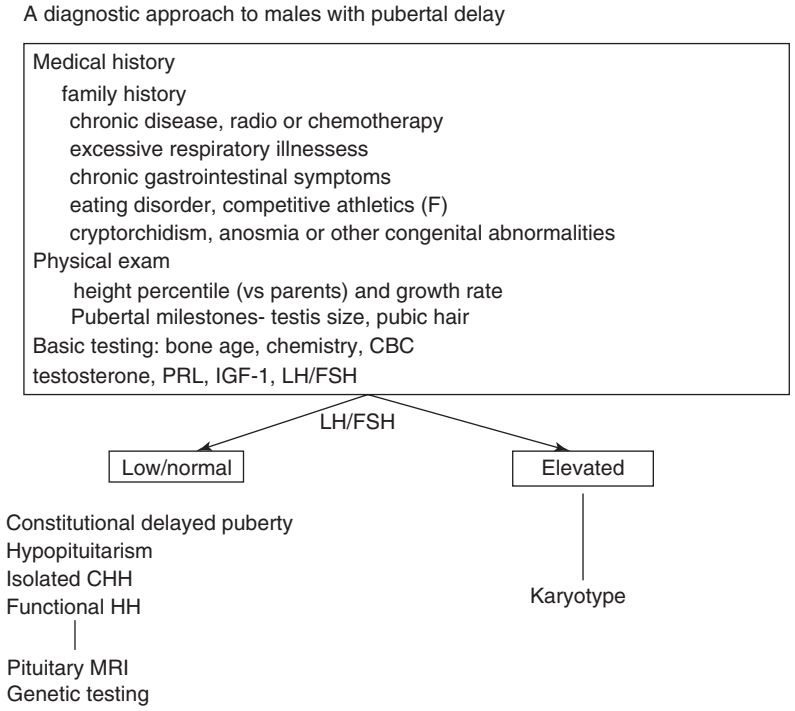

Fig. 31.1 An algorithm for the evaluation of a male with pubertal delay. (Modified from Howard and Dunkel [2])

development has been linked to combined pituitary hormone deficiencies, most notably GH deficiency, which occur in the absence or presence of malformations of the brain and other organs [4]. HH may also be selective, however, as in this case. It is now understood that congenital isolated hypogonadotropic hypogonadism (CHH) has many causes and a variable clinical presentation [5, 6]. The prevalence of CHH is estimated at 1:10,000 in males and 1:50,000 in females. Patients of either sex present because of failure to enter puberty, although newborn males may be diagnosed with cryptorchidism or a microphallus, or as adults with infertility or osteoporosis and nearly normal sexually maturity. The testes are often similar in size to those of a prepubertal child (<3 ml in volume) but are sometimes of nearly normal adult size even with clinical hypogonadism. The latter patients were historically termed "Fertile Eunuchs" because they were clinically hypogonadal with soft smooth skin and reduced body hair, but the testes were not small. In addition to hypogonadism, some subjects have developmental defects most notably anosmia but also cleft lip and palate, short metacarpals, renal agenesis, sensorineural hearing loss, eye defects, and poor balance. While the hypogonadism of CHH is generally lifelong, some cases appear to recover (sometimes briefly) following treatment [7]. Most often, these are males with an X-linked inheritance pattern, but autosomal

recessive and autosomal dominant kindreds are also common, and many kindreds do not adhere to classic Mendelian transmission.

The endocrine findings in patients with CHH are also variable [6]. The circulating testosterone level can range from <30 to 200–300 ng/dL. In some cases, the level may be in the normal adult male range in the morning but very low in the evening. LH levels may be undetectable, or LH pulse amplitude or frequency may be reduced. This clinical, laboratory, and genetic variability implied that CHH is a syndrome with multiple etiologies.

Understanding of CHH has advanced dramatically in the past 20 years [8, 9]. It is now known that CHH results from inactivating mutations of multiple genes that result in deficient GnRH secretion or function. Moreover, there is overlap with common reproductive disorders such as constitutional delay of puberty and hypothalamic amenorrhea [2, 10, 11]. CHH is now known to result from at least 40 separate gene mutations [8, 9] (Table 31.1), and while CHH is a rare disorder, discovery of these genes has provided major insight into the pathways that are essential for hypothalamic-pituitary control of reproduction. Disease-causing mutations have been divided into genes involved in neuron development and migration which are often associated with somatic defects and those which disturb GnRH synthesis,

Table 31.1 Selected gene mutations associated with congenital hypogonadotropic hypogonadism

Gene	Inheritance	Phenotype	% of patients
With development defects			
KAL-1	X-linked recessive	Anosmia, ichthyosis, synkinesis, renal agenesis	8–15%
FGFR1	Autosomal dominant	Anosmia craniofacial abnormalities severe to mild hypogonadism	10%
FGF8	Autosomal dominant	Anosmia craniofacial abnormalities	1%
PROK2	Oligogenic, recessive, autosomal dominant	Anosmia	2–3%
PROKR2	Oligogenic, recessive, autosomal dominant	Anosmia, normosmic CHH, septo-optic dysplasia	8–10%
SEMA3A	Oligogenic	KS	6%
CHD7	Autosomal dominant	CHARGE syndrome, variable penetrance	
SOX10	Autosomal dominant	KS, sensorineural deafness, variable penetrance	
FEZF1	Autosomal recessive	Anosmia	
Without developmental defects			
GnRH	Recessive	HH	
GnRH-R	Recessive	HH, partial or complete	2–15%
Kisspeptin-R	Recessive	HH	
Kisspeptin		HH	
Tach3	Recessive	Microphallus HH with reversal in adults	
TAC3R3	Recessive	HH	5%

secretion, and action on gonadotrophs with no associated somatic abnormalities. Recognition that at least 7% of patients have oligogenic inheritance (more than one disease-causing gene is mutated and interacts to produce the phenotype) helps explain the variable reproductive and extra-gonadal phenotypic features within families and non-Mendelian inheritance patterns [12]. Commercial tests to detect these mutations, often in panels, can be found at the NIH-supported website (ncbi.nim.nih.gov). Mutations are identified in only 50% of patients, however, indicating that other disease-causing genes remain to be discovered.

Neurodevelopmental Genes

In 1944, Kallmann et al. reported several families in which men had CHH and anosmia, suggesting an X-linked trait. The discovery of mutations in KAL-1 (now ANOS1) gene and its localization to the short arm of the X chromosome provided an explanation for the male predominance of this disorder and the link between GnRH secretion and olfaction, a critical sense for reproductive success among lower animals. Midline defects, including anosmia, are found in nearly 50% of CHH patients, and CHH with anosmia is known as Kallmann syndrome.

KAL-1/ANOS1 encodes a protein, anosmin, which shares homology with other proteins involved in axon pathfinding and neuron migration. It is now known that GnRH neurons, uniquely among hypophysiotropic neurons, originate with olfactory epithelium outside of the brain and migrate to arrive to their hypothalamic location during fetal development and that this process fails to occur normally in Kallmann syndrome patients [13]. Anosmin is thought to play a role in this neuronal migration and in the development of the olfactory structures, hence the connection between anosmia and CHH. More than 60 mutations of KAL-1 have been identified, with most mutations representing deletions or insertions leading to frameshifts or stop codons in exons 5–14 which encode four fibronectin III domains. These regions of the molecule have heparin sulfate (HS) binding affinity and are present in a number of adhesion proteins that are involved in cell-cell or cell-matrix interaction. KAL-1 transcripts are found not only in the developing olfactory bulb together with GnRH mRNA but also in the retina, spinal column, and developing kidney. The latter location may explain the renal agenesis and horseshoe kidney that sometimes occur in affected patients, while involuntary movements, known as mirror movements, are thought to result from disorganization of the pyramidal tracts of the spinal column. Men with KAL-1 mutation present with the most severe form of CHH with lack of LH pulsatile secretion, prepubertal testosterone levels, and sometimes microphallus and/or cryptorchidism. Heterozygous females are asymptomatic carriers.

Fibroblast growth factor receptor 1 (FGFR1) was first gene associated with autosomal dominant CHH [13]. More than 140 different mutations have been reported accounting for about 10% of patients with CHH. In addition to hypogonadism in affected males and females, some patients have cleft lip, cleft palate, dental

agenesis, and other skeletal anomalies, as well as anosmia, and the disorder is therefore designated KAL-2. Some affected individuals have pubertal delay only, whereas others have hyposmia with normal sexual function. The hypogonadism is also variable and less severe than with KAL-1 mutation. There are four functional FGF receptors and more than 20 FGFs that are paracrine stimulators of these receptors. FGF signaling is involved in the development and growth of a variety of tissues, and deletion of FGFR1 in mice causes early embryonic death. KAL-2 and KAL-1 may be functionally interrelated in that there is evidence that anosmin interacts with and may function as a co-receptor for FGF signaling.

Mutations in the genes *PROK2* and *PKR2* which encode prokineticin and its G-protein-coupled receptor-2 have been found in approximately 10% of Kallmann syndrome patients as well as in patients without anosmia, with PKR2 much more common than PROK2 [14]. There is evidence that the anosmin protein interacts with PLR2. Prokineticins are widely expressed and have diverse biological functions [15]. The name "prokineticin" derives from their effect to stimulate gastrointestinal motility. They also function in the ovary, testis, uterus, and placenta. PKR1 plays a role in food intake and adipocyte biology. PKR2 is expressed in the olfactory bulb, and mice deficient in PKR2 have hypoplasia of the olfactory bulbs and hypogonadotropic hypogonadism. Most CHH patients with mutations in these genes are heterozygotes, but the same mutations have been found in apparently unaffected individuals. Among those heterozygotes with hypogonadism, a digenic disorder has been found in a few patients with mutations in other genes implicated in KS (KAL01, FGFR1 *PROKR2*, or *PROK2*) or in genes causing CHH without developmental defects (see below). The absence of mutations in other genes known to cause CHH implies that hypogonadotropic patients with heterozygous mutation solely of *PROK2* or *PKR2* harbor mutations in other disease-causing genes that remain to be identified.

Semaphorins are proteins secreted by target tissues that repel or attract a wide range of neuronal and non-neuronal cells depending on the cellular targets and the expression of different subunits of its receptor complexes [16]. Mice with SEMA3A deletion have altered olfactory bulb development, and the migration of GnRH neurons into the brain is disrupted. In one series, 6% of KS patients were positive for SEMA3A heterozygous mutation, in some cases together with mutations in other candidate genes.

Less common mutations linked to CHH with developmental defects are mutations in CHD7, FGF8, NELF, *WDR11, HS6S*, and *SOX10.* CHARGE syndrome, with ocular *coloboma*, congenital *heart* defects, choanal *atresia*, *retardation* of *growth* and development, *genital* hypoplasia, and *ear* anomalies and deafness, results from mutation of CHD7 on chromosome 8q. Male and female patients with this mutation may present with Kallmann syndrome, normosmic HH, or anosmia alone. De novo mutations are common. WDR11 interacts with EMX1, a homeodomain transcription factor involved in the development of olfactory neurons. Like Kal-1, HS6ST, FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are genes involved in FGF receptor signaling and have been found to be mutated in a few CHH patients.

CHH Without Developmental Defects

Normosmic CHH patients have mutations in genes involved in GnRH secretion and action including GnRH-R, KISS-1R, and TACR3, as well as their ligands, GnRH1, Kiss, and TAC3. Compound heterozygous mutation of GnRH-R, as in our case, is responsible for nearly 50% of normosmic CHH, but homozygosity for inactivating mutations is common in isolated populations [1]. The most common mutations are Gln^{106} to Arg^{106} and Arg^{262} to Gln^{26} which result in loss of ligand binding or defective intracellular signaling, respectively, and thereby loss of receptor function. The GnRH-R is encoded on chromosome 4, so males and females are equally affected, and affected patients predictably have no midline defects. Heterozygote carriers appear to be disease-free. There is wide phenotypic variation even in the same family with the same mutation. Most often, LH secretion responds poorly or not at all to exogenous GnRH stimulation.

Perhaps the most significant advance in the neuroendocrinology of reproduction in the past two decades was the identification of kisspeptin as the key upstream regulator of GnRH secretion for the onset of sexual maturation, seasonal breeding, and feedback control by gonadal hormones and metabolic and environmental factors [17] (currently 2471 Medline citations). This major breakthrough began with the identification of a few patients with normosmic CHH who were found to have loss-of-function mutations of a G-protein-coupled receptor, encoded by a gene on chromosome 19p13 (formerly called GPR54 but now termed the kisspeptin receptor KISS-1R). The disorder accounts for approximately 2% of normosmic CHH, with concentrations in Brazil and the Middle East, with a variety of homozygous or compound heterozygous mutations. The hypogonadism phenotype is variable but is often severe with microphallus and/or cryptorchidism. Female siblings present with primary amenorrhea. A large consanguineous family with four female siblings with CHH (and two unaffected males) associated with a loss-of-function mutation of the ligand *KISS1* has also been described. In addition, activating mutations of Kiss1 and Kiss-1R have been found in patients with central precocious puberty.

Most neurons in the arcuate nucleus of the hypothalamus that express kisspeptin co-express the neuropeptides neurokinin B (NKB) and dynorphin, and mutations in the genes encoding neurokinin B and its receptor NK3R (*TAC3* and *TACR3*, respectively) were shown to account for about 5% of CHH cases [18]. Hypothalamic expression of tachykinins increases prior to sexual maturation in rodents, and experiments in monkeys revealed that NKB stimulates kisspeptin to control GnRH pulsatility. The clinical hypogonadism observed with TAC3 and TACR3 mutations is variable, and several subjects with established CHH and TACR3 mutations showed evidence of endogenous GnRH-LH secretion in adulthood following testosterone treatment [19], suggesting complex TACR3 function that is sex steroid regulated. Activating mutations of TAC3 and TACR3 have also been identified in patients with central precocious puberty, further establishing the connection of tachykinins to GnRH secretion.

While mutation of the GnRH gene was an obvious candidate for CHH, and a mouse with a large deletion within the GNRH1 gene (hpg) causing autosomal recessive hypogonadism in both sexes was discovered in 1977, it was not until 2009 that homozygous inactivating mutations in the GNRH1 gene were reported, and only a few affected subjects have been identified [20]. Some patients with recessive or dominant inheritance patterns also have mutations in other CHH genes. Nevertheless, these patients provide definitive proof for the pivotal role of GnRH in human pubertal development and reproduction.

Several patients with inactivating mutations of the LH-β gene have been reported [21] with a variety of genotypic abnormalities. They have presented as phenotypic males with absent or impaired pubertal development, low testosterone level, small testes, and hypospermatogenesis. Treatment with hCG markedly increased testosterone levels and produced virilization. Mutations have resulted in LH deficiency due to abnormal LH-β processing, inability to bind to the α-subunit, and failure to traffic intracellularly. One man was reported with a high LH level due to a point mutation producing an immunoreactive LH molecule that was unable to activate the LH receptor. FSH levels are normal or elevated. Affected men have a masculine phenotype because fetal testosterone production is governed by hCG, and only the postnatal production of testosterone under LH control is disrupted.

Mutations of the FSH-β gene causing FSH deficiency result in lack of sexual development and elevated serum LH levels in women. Affected male relatives were discovered to have small testes and azoospermia with variable but impaired Leydig cell function causing LH levels to increase. The abnormal FSH-β protein is unable to associate with the common α-subunit to form the active dimer. A polymorphism in the FSH-β gene promoter is also associated with lower levels of FSH and lower sperm counts in otherwise normal men.

Adrenal hypoplasia congenita (AHC) is a disorder characterized by primary adrenal failure in infancy/childhood and CHH [22]. *DAX1* gene (dosage-sensitive sex reversal-adrenal hypoplasia congenita (AHC) critical region on the X chromosome gene) mutations cause X-linked AHC. Thus, the disorder affects males, and females are almost always disease-free. The gene is expressed in the hypothalamus and pituitary, as well as in the gonads and adrenal cortex. More than 60 frameshift or missense mutations produce a truncated protein with limited function. Boys present with salt-losing adrenal crisis as newborns or with more subtle presentations later in childhood with absent or partial pubertal development. DAX1 is an orphan nuclear receptor that interacts with steroidogenic factor 1 (SF1) – a transcription factor that regulates the α-subunit, LH-β, and GnRH receptor genes accounting for CHH although the biological functions of DAX1 remain incompletely understood. Testicular expression in Sertoli cells is associated with unresponsiveness to gonadotropin stimulation.

The most common cause of pubertal delay, and therefore an important diagnostic consideration for our patient, was constitutional delay of puberty (CDP), which can be difficult to distinguish from CHH. In CDP patients (boys > girls), the physiological GnRH deficiency of childhood is prolonged but is followed by normal adult gonadal function [2]. In a recent study from Denmark, based on interviews and a

comparison with drawings, nearly 100% of normal boys had testis growth by age 14 and pubic hair development by age 15 [23]; our patient was far beyond these milestones. Also, CDP unlike CHH is often associated with short stature. CDP like CHH is familial with more than 80% of cases having a first-degree relative with pubertal delay [24]. When developmental defects such as anosmia, cryptorchidism, or micropenis are present, the diagnosis is presumably CHH, but in normosmic subjects, CHH remains a consideration until there is spontaneous and complete pubertal development, and reversal of HH in patients with established CHH mutations [7] further blurs the distinction between these conditions. In spite of extensive study, there are no endocrine tests to otherwise reliably distinguish CDP from CHH; however, a level of inhibin-B of <35 pg/ml and a peak LH level of <4.0 mIU/ml following GnRH stimulation favors CHH. Genetic testing can be performed for CHH genes, but CDP is believed to be polygenic and not amenable to genetic testing at this time [24].

Treatment Strategies

All forms of testosterone treatment (e.g., parenteral injection or transdermal application) will effectively stimulate secondary sex characteristics and increase male sexual behaviors in males with CHH [9]. Parental and topical testosterone are used to treat micropenis, while hCG or LH/FSH may be an alternative to surgery for cryptorchidism [25]. In CHH teenagers, low doses of testosterone are used initially due to concerns for acne and emotional lability, especially if the diagnosis of constitutional delay of puberty remains tenable, with gradual dose escalation over ~3 years. Testosterone replacement increases bone density in young, previously untreated men with CHH but is less effective in older men in whom bisphosphonates are also generally recommended [26]. Testosterone will not appreciably activate spermatogenesis, however, and testis growth during testosterone treatment suggests reversal of CHH or CDP. If so, treatment should be stopped and the patient retested. Likewise, a rising level of insulin-like factor 3 suggests endogenous Leydig cell function.

The testes of men with CHH are variably immature and lacking in LH/FSH activation, but most men with CHH can produce sperm with diligent treatment although a history of cryptorchidism portends a poorer prognosis [27, 28]. To stimulate spermatogenesis, our patient was first treated with human chorionic gonadotropin (hCG). hCG purified from the urine of pregnant women and a recombinant product from Chinese hamster ovary cells are therapeutic analogs of LH which stimulate Leydig cell function. Recombinant hCG, while purer and with little batch-to-batch variation, is marketed as a 0.5 ml vial containing 250 μg hCG (equivalent to about 10,000 IU) for use in ovulation induction and is costly with the regimen for CHH males. Purified hCG is available in 10,000 IU vials as brand name and generic products that can be reconstituted in 10 ml of normal saline to deliver 1000 IU/ml. A dose of 750–1000 IU intramuscularly or subcutaneously three times weekly is

generally sufficient; larger doses may increase estradiol production and produce gynecomastia. All products occasionally produce a rash and rarely a more serious allergic reaction.

hCG alone usually stimulates spermatogenesis in men with acquired HH due to pituitary tumor and is sometimes effective as a sole agent in CHH, especially in men with partial gonadotropin deficiency (testes ≥5 ml prior to treatment) [29]. In our case, the testes were smaller in size, and although hCG treatment normalized the testosterone level and increased the size of the testes, he remained azoospermic after 6 months of treatment. Therefore, FSH was added. Recombinant hFSH is available in vials containing 75 IU, and the usual dose is 75–150 IU three times weekly. Most men with partial CHH and more than 50% of men with more severe CHH will produce sperm with this regimen. Pregnancy may take several years of treatment, however, and the total sperm count rarely reaches the level of normal men [30]. Recombinant hFSH is costly and can be discontinued after the pregnancy since hCG alone can maintain spermatogenesis even for extended periods of time although sperm counts gradually decrease.

Alternatively, GnRH can be administered using a pulsatile infusion pump to stimulate spermatogenesis in men with GnRH deficiency. GnRH administered continuously, however, will downregulate testicular function because GnRH receptors are depleted and GnRH receptor signaling is disrupted. The dose of GnRH that effectively increases adult testosterone levels and stimulates spermatogenesis has ranged from 5 to 20 μg/pulse. This approach is more cumbersome and more costly.

Since most men require both hCG and FSH, treatment can alternatively be combined at the outset. In fact, some have proposed that treatment should begin with FSH with the idea that Sertoli cell proliferation will be greater without previous exposure to testosterone [31]. In one study, 7/7 CHH men treated with hFSH for 4 months followed by pulsatile GnRH were sperm positive at 24 months compared to 4/6 men treated with pulsatile GnRH alone. The groups were too small to permit a definite conclusion. Regardless of the treatment regimen, in vitro fertilization is sometimes performed for oligospermia, and there are case reports of successful pregnancies using testicular sperm extraction (TESE) in CHH men who remained azoospermic.

Finally, stimulated spermatogenesis and IVF may transmit genetic disorders to the offspring, so testing and counselling for the patient and partner are essential for informed decision-making. The spectrum of clinical features found in patients with Kallmann syndrome and related disorders has been published [32]. In this case, with an autosomal recessive mutation of the GnRH-R, the disorder is limited to CHH, and the risk of disease transmission to his offspring was very low [33] although consanguinity and endogamy (in-marriage: parents are both from a local community, clan, or tribe) would increase the risk substantially.

Multiple Choice Questions

1. A 22-year-old man presents with minimum beard and boy hair growth when compared to his father and brother. He is otherwise healthy with normal childhood growth. He denies headache. The family history is negative. He has a normal sense of smell. He looks younger than his stated age with sparse beard

and body hair and lack of musculature. His height is 65 inches, and his arm span is 68 inches. His testes are each 4.0 × 2 cm. There are no other positive findings. Which of the following mutations is the likely cause of his condition?

A. ANOS1
B. FGFR1
C. GnRH-R
D. IGF-1
E. Prop-1

Answer: C. Missense mutations in the GnRH receptor gene explain about 50% of cases of normosmic CHH. They result in a variable defect in GnRH signaling and a range of reproductive phenotypes. IGF-1 and Prop-1 mutations would result in short stature. There is no abnormality of neuronal migration or associated abnormalities as occurs with mutations of ANOS1 or FGFR1 (Kallmann syndrome).

2. Your clinical diagnosis of congenital hypogonadotropic hypogonadism is confirmed with a testosterone level of 35 ng/dl, LH 1.2, and FSH 2.5 U/L. Each of the following should be assessed at this time, except:

A. PRL level
B. MRI pituitary
C. Iron and iron-binding capacity
D. Peripheral blood karyotype
E. Free thyroxine

Answer: D. The karyotype is invariably 46,XY in men with CHH. While hemochromatosis is a very rare cause of hypogonadism in adolescents, it can be fatal and screening is advised.

3. Other than hypogonadotropic hypogonadism, his endocrine function is normal, the percent iron saturation is 35%, and there is no mass on the MRI. Which additional tests are needed at this time?

A. DEXA scan
B. Inhibin-B
C. GnRH stimulation test
D. Estradiol
E. hCG stimulation test

Answer: A. Men with congenital hypogonadotropic hypogonadism are deficient in testosterone and estradiol, have reduced peak bone mass in early adulthood, and are at increased risk for osteoporosis. Inhibin-B levels tend to be lower and the LH response to GnRH less robust but are not diagnostic of CHH. Similarly, testosterone response to hCG will not appreciably affect diagnosis or management. Activating mutations of the aromatase gene will cause HH with an elevated level of estradiol, but there is pre- or peri-pubertal onset of gynecomastia.

4. The patient and his wife would like to have children. After obtaining a baseline semen analysis, you recommend which of the following treatments:

   A. hFSH
   B. Testosterone gel
   C. hCG
   D. hGH
   E. Clomiphene

   Answer: C. While parenteral testosterone will produce virilization in men with CHH, it has little effect on spermatogenesis. Some men with CHH will produce sperm with hCG alone, especially those with a partial defect as suggested by his testicular exam. Although co-administration of hFSH may ultimately be needed, the drug is very costly, and in these cases, treatment is generally begun after 6 months of hCG if the patient remains azoospermic. Clomiphene is ineffective in CHH, and hFSH is ineffective without co-treatment with hCG.

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Chapter 32
Klinefelter Syndrome

Stephen J. Winters

Objectives

1. Recognize the clinical presentations of Klinefelter syndrome.
2. Review the pathophysiology and genetics of Klinefelter syndrome.
3. Be aware of less common causes of primary gonadal failure.
4. Learn the clinical consequences of undiagnosed primary testicular failure.
5. Review management options for men with Klinefelter syndrome.

Case Presentation

A 20-year-old man was referred by his pediatrician because of small testes. He had a patent ductus arteriosus that was repaired at age 9 months and is followed with yearly echocardiograms for partial anomalous pulmonary venous return. He is otherwise healthy. He began shaving his beard at age 14 and now shaves every 2–3 days. He has some chest hair but less than his father and brother. He seemed shy and reserved. He is 6′1″ tall and is the tallest member in his family; his father is 5′10″, mother is 5′6″, and brother is 5′9″. He is thin, with an unusually long face. There is no thyromegaly. He has bilateral gynecomastia. The testes were each 2.3 cm in length (3 ml L, 4 ml R). The phallus was 6 cm long and had 2 meatal openings: the dorsal opening was a shallow blind pit, and an opening on the ventral surface of the glans was the urinary channel. The testosterone level was 316 ng/dL, LH 36.9, and FSH 66.3 U/L. The Sex hormone-binding globulin (SHBG) was 45 nmol/L, and the non-SHBG testosterone was 81.6 ng/dL (normal >110). The peripheral blood karyotype was 47,XXY.

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Review of How the Diagnosis Was Made

The clinical appearance of moderate androgen deficiency with gynecomastia and very small testes suggested primary testicular failure [1]. There was no history of head trauma or headaches, no evidence for dysfunction of other endocrine systems, and no visual disturbance to suggest hypogonadotropic hypogonadism. Elevated LH and FSH levels confirmed primary testicular failure. The total testosterone level was within the reference range, as is often the case in young adults [2], but the calculated non-SHBG testosterone level was low. Many of the causes of primary testicular failure (Table 32.1) were readily excluded by the medical history and physical examination, and the most frequent cause of primary testicular failure, Klinefelter syndrome (KS), was confirmed by the 47,XXY karyotype. Fifty leukocytes were analyzed to exclude a mosaic karyotype because of the hypospadias and congenital heart disease. Transdermal testosterone treatment produced an increase in muscle mass and strength and an increase in self-esteem.

Lessons Learned

In 1942, Klinefelter et al. [3] described nine unrelated adult men with gynecomastia, small firm testes, scant body hair, and elevated FSH levels (a bioassay for FSH in urine based on stimulating the development of the reproductive tract in female mice was performed). While the authors wrote that "nothing has been found in these patients to explain the testicular lesion," the inactivated X chromosome was identified in normal women (Barr body) in 1949, and the 47,XXY chromosomal basis of KS was described in 1959. It is now known that KS is the most common form of congenital male hypogonadism and X and Y chromosome variation, affecting 1 in 500–600 male births, and accounts for approximately 3–4% of infertile men and 10–12% of men with azoospermia. Intrauterine mortality does not appear to be increased. The diagnosis is most often made in teenagers with delayed or

Table 32.1 Causes of primary testicular failure

Congenital	Acquired
Klinefelter syndrome	Trauma
Cryptorchidism	Orchitis
Congenital anorchia	Spinal cord injury
Noonan syndrome	Immune polyglandular failure
Sickle cell disease	Testicular torsion
Laurence-Moon-Bardet-Biedl syndrome	Medications: ketoconazole, cancer chemotherapy
Myotonic dystrophy	
LH-R mutation (Leydig cell hypoplasia)	X-irradiation
XX male	Retroperitoneal fibrosis
Adrenomyeloneuropathy	Amyloidosis
	AIDS
	Alcoholic liver disease
	Chronic kidney disease

incomplete pubertal development or gynecomastia or in adults with hypogonadism or infertility [4]. KS is also diagnosed with prenatal screening, in newborns with cryptorchidism or microphallus, and in prepubertal boys with language delay, learning disabilities, or behavioral problems. Bojesen et al. [5] estimated that 75% of adult men with KS in Denmark remain undiagnosed. See Gravholt et al. [6] for a recent comprehensive review.

Genetics/Etiology

In individuals with more than one X chromosome, all in excess of one condense to form Barr bodies, a darkly staining mass of chromatin most often at the cell's nuclear rim that is detected by nuclear stains such as Feulgen. Nowadays, a karyotype is performed instead using rapidly dividing T lymphocytes in peripheral blood that are chemically arrested in metaphase and stained, and chromosomes are counted to establish the diagnosis [7]. The extra X chromosome in KS results from nondisjunction during meiotic division in germ cell development or in less than 5% of cases, during early embryonic mitotic division. Roughly half of the cases are paternally derived and result from the formation of an XY sperm in meiosis I, whereas maternal XX oocytes can result from errors in either meiosis I or meiosis II. The risk of KS appears to increase when mothers are older than age 40.

About 10% of men with Klinefelter syndrome have a mosaic karyotype, usually 47,XXY/46,XY, and have a milder phenotype. The leukocyte karyotype may occasionally be 46,XY, especially if only 5–20 cells are counted, and if counting more cells remains uninformative, a karyotype of skin fibroblasts or a testicular biopsy specimen may occasionally be needed to confirm the mosaic diagnosis. Higher-grade chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY) also produce the Klinefelter phenotype but are rare and cause psychomotor retardation.

When two X chromosomes are present, most genes on one X are silenced as a result of the X chromosome inactivation. Some genes escape X-inactivation, however, and are expressed from both the active and inactive X chromosome. About 15% of X chromosome genes, especially genes in the pseudoautosomal region, escape X-inactivation in KS and thus have a higher level of tissue expression than in normal men. The uneven overexpression of these genes in various tissues of the body, together with the hypogonadism, explains the variable Klinefelter phenotype.

Rarely, phenotypic males with primary testicular failure have a 46,XX karyotype. This condition generally results from the translocation during paternal meiosis of the distal end of the short arm of the Y chromosome, containing the testis-determining gene (SRY), to the X chromosome or sometimes to an autosome. The Y chromosome material can be detected by fluorescence in situ hybridization (FISH) analysis although a few cases are SRY-negative. Most cases go undetected until puberty when the extra X results in seminiferous tubule degeneration, and elevated levels of LH/FSH are found. XX males are shorter than XY controls, presumably because of loss of growth genes on the Y chromosome. As in KS, high levels of LH can stimulate estradiol production and result in gynecomastia.

Phenotypic Manifestations

The phenotypic features of KS are quite variable, and their frequencies are listed in Table 32.2. Adults with classical 47,XXY KS can be readily identified, however, because they have small firm testes. Most cases are identified as teenagers with gynecomastia and/or delayed puberty or as infertile adults. Newborns with KS generally have a normal male phenotype although cryptorchidism and hypospadias may occur [8].

KS patients are often tall, but rather than classic eunuchoidal skeletal proportions (arm span at least 6 cm >height), they have exaggerated pubis-floor growth. Even prepubertal boys with KS may have long legs, implying that this abnormality may not be from a sex hormone disturbance. Long legs are instead thought to be due to overexpression of short stature homeobox (SHOX) gene on pseudoautosomal region 1 of the X chromosome, a gene that plays a major role in growth [10].

Gynecomastia While breast enlargement was the essential finding in the initial description by Klinefelter et al., many men with KS do not have gynecomastia. Early studies found elevated circulating estradiol levels, whereas more recent studies report normal estradiol levels in KS men [11]. All cases have low testosterone relative to estradiol levels, however. Because of insulin resistance [12], SHBG levels may be low, and it may be more informative to measure free estradiol (<1 pg/mL), which is currently not realistic. It is also possible that gynecomastia is due in part to effects of X-linked genes that escape silencing. Breast pain may occur, and gynecomastia can be psychologically disturbing, especially to adolescents. Long-standing gynecomastia generally contains extensive fibrous stroma as well as glandular tissue and may be irreversible, and claims that antiestrogens or aromatase inhibitors substantially decrease breast tissue mass have come from open-labeled uncontrolled trials with self-reported outcomes. These drugs are unapproved for this

Table 32.2 Clinical features of Klinefelter syndrome

Feature	Frequency %	Feature	Frequency %
Infertility	91–99	Cryptorchidism	27–37
Small testes (bi-testicular size <6 ml)	>95	Hypospadias	3–5
Increased gonadotropins	>95	Learning disabilities (children)	>75
Azoospermia	>95	Delay of speech development (children)	40
Decreased testosterone	63–85	Psychiatric disturbances	25
Decreased facial hair	60–80	Tall stature	30
Decreased pubic hair	30–60	Abdominal adiposity (adults)	~50
Gynecomastia	38–75	Metabolic syndrome (adults)	46
Breast cancer	50× incr	Osteopenia (adults)	5–40
Mediastinal cancers	500× incr	Type 2 diabetes (adults)	10–39

Adapted from Groth et al. [9]

purpose and cannot be recommended at this time. Plastic surgery techniques restore the breast contour with minimal scarring and protect areolar anatomy and sensation. Corrective surgery will often favorably impact the emotional disturbance and academic difficulties that these teenagers endure.

Primary Hypogonadism Serum LH and FSH levels are almost always elevated in adults with KS and indicate lack of negative feedback signals due to Leydig cell and seminiferous tubule dysfunction. Rare exceptions are men with coexistent gonadotropin deficiency due to pituitary tumor, acute or chronic illnesses, or morbid obesity. Mean total testosterone levels are lower than those of normal men but may overlap the low normal range [2], while free testosterone levels are most often subnormal. Hormone values in prepubertal boys with KS are generally within the normal range although the neonatal increase in FSH (minipuberty) may be slightly greater and the rise in testosterone slightly less than in normal boys [8]. Inhibin B levels decline to barely detectable values during mid-late puberty rather than increase as in normal adolescents because germ cells and Sertoli cells die and are replaced by fibrosis. Insulin-like factor 3, a peptide produced by Leydig cells, is also low.

Histopathology of the Testis Nearly all (95%) of men with KS are azoospermic, and KS accounts for 3–4% of male infertility cases and 10–12% of men with azoospermia. Microscopic examination of testicular tissue generally reveals absent spermatogenesis with hyalinizing fibrosis of the seminiferous tubules (Fig. 32.1). In some individuals, however, there are tubules with Sertoli cells but no germ cells, and there may be focal areas of spermatogenesis [13]. Although the peripheral blood cells in these men may be 47,XXY, there may be undiscovered 46,XY cell lines in the testis. In spite of defective testosterone production, the number of Leydig cells is maintained or surprisingly increased producing the histological picture of Leydig cell hyperplasia which may occur through disrupted intratesticular inhibin-activin signaling and increased LH drive [14].

The degenerative process may start during fetal life, as testicular tissue from XXY fetuses has fewer germ cells although tubules are non-sclerotic and Sertoli cells appear normal. In the first few years of life, the number of spermatogonia decreases. Germ cell differentiation is arrested at the spermatogonia or early primary spermatocyte stage, and rather than meiosis, there is germ cell apoptosis. The testis of affected early teenage boys reveals hyalinization and hyperplastic Leydig cells. Ten percent of the 1000+ genes on the X chromosome are expressed in the testis, and the overexpression of these gene products is the presumed proximate cause of seminiferous tubular degeneration and fibrosis.

Comorbid Conditions

KS is associated with many comorbidities due to hypogonadism and the genes expressed by the extra X chromosome [15]. KS is associated with a loss of 2.1 years in lifespan, and there is increased risk for hospitalization (about 70%) from

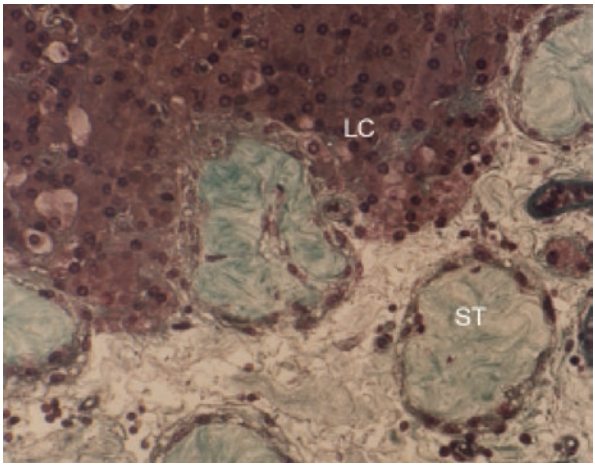

Fig. 32.1 Testicular biopsy from a man with Klinefelter syndrome. Note the hyalinized seminiferous tubules (ST) that are devoid of germ cells and Sertoli cells and the hyperplastic Leydig cells (LC). (Photograph was provided by Dr. C. Alvin Paulsen)

Table 32.3 Comorbid conditions associated with Klinefelter syndrome

Osteopenia	Learning disability
Glucose intolerance	Depression
Dyslipidemia	Breast carcinoma
Chronic leg ulcerations	Germ cell cancers
Deep vein thrombosis and pulmonary embolism	Taurodontism

infection; endocrine disorders; neurological and psychiatric conditions; and circulatory, pulmonary, and gastrointestinal disorders. Some conditions associated with KS are listed in Table 32.3**.**

Bone mineral density is reduced, and osteoporosis occurs more often in men with KS than in normal men. Moreover, their age-related decrease in bone mass is more pronounced [16]. Free testosterone levels are inversely correlated with bone mineral density in some studies; however, testosterone deficiency alone does not appear to explain the low bone mass in KS. BMD may increase with testosterone replacement, especially in younger men.

Our patient was shy and had few close friends and was an average student. He had not dated in high school nor so far in college. Language-based learning disabilities, reading disorders, speech and language abnormalities, and social dysfunction are common in KS [17]. They have lower verbal IQ than performance IQ, with normal full-scale IQ, whereas patients with higher-grade aneuploidies tend to be mentally retarded. Babies with KS tend to have expressive language delay, while school-age boys demonstrate a verbal cognitive deficit with significant

underachievement in reading, spelling, and writing. Some also have reduced mathematical ability. These learning disabilities lead to poor school performance and to less-skilled occupations in adulthood. Behavioral problems and difficulty with social relationships may accompany academic underachievement. Many patients are quiet, sensitive, and insecure, with lack of insight and poor judgment. The risk for anxiety and depression is increased [18]. On the other hand, some men with KS are intelligent and professionally and financially successful. Between-subject variability in the overexpression of X chromosome genes and variable CAG repeat length in the androgen receptor promoter have been proposed to account for the range of symptoms. It is often written that quality of life would be considerably more favorable if the KS diagnosis was made in childhood and information, counseling, support, and hormone treatment were given beginning at an early age, but this is unproven.

Metabolic syndrome (MetS) is common in KS men [19]. Low testosterone, high FSH, and genes expressed by the extra X chromosome have all been proposed to play a role in the MetS in KS. The percent body fat by bioelectrical impedance is increased [20], and MetS components are evident even before puberty [21]. In one study, nearly 50% of KS men ages 19–66 met the criteria for MetS compared to 10% of controls. LDL and triglyceride levels are increased, and HDL cholesterol is reduced, and the risk for nonalcoholic fatty liver disease is increased, but blood pressure seems to be unaffected. When compared to men with obstructive azoospermia, fasting and glucose-stimulated insulin secretion were increased, and the prevalence of Type 2 diabetes mellitus (T2DM) has ranged from 10% to 39% [22]. Consequent to these risk factors, the cardiovascular disease mortality is 40% higher in KS men (Table 32.4).

Varicose veins, venous insufficiency, and leg ulcers are far more common than in normal men and are thought to result from venous thrombosis. The risk for pulmonary embolism is also increased. Platelet hyper-aggregation, factor V Leiden mutation, deficient fibrinolysis, and increased activity of factor VIII coagulant as well as an increase in the estrogen/testosterone ratio have all been proposed to explain the risk for thromboembolic events.

Our patient had partial anomalous pulmonary venous return, and a variety of cardiovascular abnormalities including aortic and mitral valve disease, atrial septal defect, pulmonary stenosis, Ebstein anomaly, and tetralogy of Fallot have been reported as case reports, especially in those with higher-grade chromosome

Table 32.4 Increased cardiovascular disease risk in KS

Risk for metabolic syndrome is increased fourfold
Total and visceral adipose tissue are increased
KS men are more insulin-resistant
Increased HOMA-IR
Hyperinsulinemic on GTT
IR by hyperinsulinemic clamp
Increased risk for T2DM that develops earlier in life
High triglyceride and low HDLc levels

aneuploidies. In one series using echocardiography, 55% of patients had mitral valve prolapse. Pulmonary diseases such as chronic bronchitis, bronchiectasis, and emphysema are also more common in KS, and pneumonia was noted to occur more often than expected in the Danish registry study [6].

Men with KS are at increased risk for certain malignancies, including breast cancer; germ cell tumors, particularly extragonadal germ cell tumors involving the mediastinum; nonlymphocytic leukemia, non-Hodgkin lymphoma, and marrow dysplastic syndrome, while their risk for prostate cancer is reduced [15]. For breast cancer, the data support a 20- to 30-fold higher risk than expected, although it is important to recognize that <1% of KS patients will develop breast cancer. The risk for mediastinal germ cell tumors is 20–50-fold increase, and 3–8% of patients with these tumors have KS such that a chest X-ray should be performed when KS men have progressive dyspnea [23]. Occasionally, mediastinal germ cell tumors produce hCG and may cause precocious puberty. Testicular failure predisposes to gonadotroph hyperplasia, but unlike severe primary hypothyroidism, pituitary tumor is very rare [24] although PRL levels may be slightly elevated.

Sex hormones and gender are important determinants of many autoimmune diseases which occur more often than expected in KS including hypothyroidism, adrenal failure, Type 1 diabetes mellitus (T1DM), rheumatoid arthritis, Sjögren syndrome, scleroderma, and systemic lupus [25]. One study of 174 KS men found that 7% had Hashimoto thyroiditis [26]. The prevalence of systemic lupus is 14-fold higher in KS than in 46, XY males and is similar to that of women [27]. There are case reports of KS patients with lupus treated with testosterone whose hematologic and serologic abnormalities, including elevated levels of anti-DNA antibodies and depressed complement levels, returned to normal.

Treatment Strategies

Testosterone replacement in KS patients most often corrects the classic features of hypogonadism including sexual infantilism, reduced muscle size and strength, osteopenia, anemia, and fatigue, and sexual interest and function improve [28]. When to begin treatment is controversial, however, although most authors agree that androgen replacement should be begun by mid-puberty [29]. Some have suggested a low total testosterone level as the criteria for starting treatment, while others advocate elevated LH levels as a marker for testosterone deficiency in the CNS even if circulating testosterone levels are within the reference range. Testosterone treatment is advocated in KS newborns with micropenis, and studies to examine other potential benefits of T treatment beginning in childhood are underway [30]. Cross-sectional studies found that T-treated KS men have less body fat and are less insulin-resistant than are untreated KS men, but two prospective studies failed to show improvement. Similarly, the benefits of testosterone substitution on cognitive and behavioral endpoints are uncertain.

To avert mood changes, priapism, and acne, a tempered dose escalation is suggested. This can be accomplished using intramuscular/subcutaneous testosterone injections or with metered pumps that deliver testosterone in a gel as in our case. High levels of circulating testosterone are needed to suppress LH into the normal range in men with testicular failure perhaps because of increased GnRH receptor expression due to inhibin deficiency. Therefore, the level of testosterone, rather than LH, should be used to guide the treatment dose, and treatment should normalize but not exceed physiological levels.

Men with 47,XXY KS are usually (95%) azoospermic, whereas those with mosaic 46,XY/47,XXY karyotypes occasionally produce sperm and can be fertile, especially early in adulthood. Reports of paternity and sperm in the ejaculates of 47,XXY men lead to the use of testicular sperm extraction (TESE) coupled with intracytoplasmic sperm injection as a method to help KS men become biological fathers. At surgery, the testis is widely opened and microdissected with examination of the morphology of seminiferous tubules using an operating microscope. Enlarged seminiferous tubules are removed, and the sperm are harvested in the operating room by an embryologist for subsequent ICSI. A meta-analysis by Corona et al. [31] of 37 published studies of azoospermic KS men revealed that the chance of finding sperm was 44%, and 29 trials reported a live birth rate of 43% for these men per ICSI cycle. Thus, the overall success rate approximates 20%. So far, there are no useful preoperative predictors of successful sperm recovery, however (e.g., age, testis size, LH/FSH, testosterone, or inhibin-B). While there is concern for increased risk for producing sex chromosome or other aneuploidy in KS ICSI offspring, this concern seems to be unfounded. Nevertheless, preimplantation genetic diagnosis is generally offered in which one or two blastomeres are biopsied from embryos at the eight-cell stage.

Some data support the idea that advancing age into adulthood reduces the fertility potential, and some authors recommend evaluating KS teenagers with sperm banking or TESE if no sperm are found, with cryopreservation of sperm for future ICSI. Others recommend sperm banking later in puberty or in adulthood as the relative success rates of these different approaches remain to be clearly demonstrated [32]. Some have suggested that lowering LH and FSH with androgen replacement may reduce the likelihood that sperm will be found by TESE, and propose that androgen treatment should be replaced by hCG, clomiphene, or an aromatase inhibitor. While intriguing ideas, they remain unproven, and need to be weighed against the consequences of withholding treatment or of less effective therapies than testosterone replacement as well as the potential adverse effects of blocking estrogen production or action on developing bones.

Multiple Choice Questions

1. You are asked to evaluate a 15-year-old boy who has no palpable testes. He is otherwise healthy and has a male phenotype. He is 69″ tall. He has soft smooth skin and little body hair. The phallus is 5 cm stretched and normally formed. Which of the following diagnostic tests should be performed at this time?

(a) Pituitary MRI
(b) Peripheral blood karyotype
(c) LH/FSH
(d) Free testosterone
(e) Inhibin B

Answer: (c) From an endocrine perspective, the first step to establish a diagnosis in this patient is to determine if he has hypogonadotropic hypogonadism or primary testicular failure. The other tests may be indicted depending on these results.

2. A 25-year-old man presents with gynecomastia and small testes but a normal phallus and pubic hair. The LH is 35 IU/L and the FSH is 46 U/L. Which of the following is not in the differential diagnosis?

(a) XX male
(b) Klinefelter syndrome
(c) 5-Alpha reductase deficiency
(d) Mumps orchitis
(e) Congenital androgen insensitivity

Answer: (c) 5-Alpha reductase deficiency leads to ambiguous genitalia and low body hair, but LH levels are only slightly elevated, and gynecomastia does not occur. Each of the other disorders leads to primary testicular failure.

3. Plasma levels of inhibin B can be used to determine which men with Klinefelter syndrome will have testicular sperm for use with in vitro fertilization.

(a) True
(b) False

Answer: (b) So far, there is no reliable marker for sperm-positive Klinefelter syndrome patients.

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Part IX
Endocrine Disorders in Pregnancy

Chapter 33
Introduction to Endocrine Disorders in Pregnancy

Elizabeth N. Pearce

Pregnancy has wide-ranging effects on the endocrine system. The synthesis, metabolism, and binding of many hormones are altered in pregnancy. Immune tolerance induced by pregnancy can alter the course of autoimmune endocrine disorders such as Graves' disease. The placenta secretes multiple hormones including human chorionic gonadotropin (hCG), human placental lactogen, growth hormone, estrogen and progesterone, all of which have downstream effects on other hormonal axes [1]. It is important to consider pregnancy-specific hormonal alterations in the diagnosis and treatment of women with endocrine disorders during gestation and to consider both the maternal and fetal impacts of any diagnostic or therapeutic interventions. While most women with appropriately treated endocrine disorders will have uneventful pregnancies, undiagnosed or untreated endocrine disease can have devastating consequences.

The diagnosis of endocrine disorders in pregnant women may present specific challenges. Symptoms of normal pregnancy, such as fatigue, tachycardia, increased urination, constipation, and weight change, overlap with symptoms of endocrine disorders such as thyroid dysfunction, adrenal insufficiency, diabetes insipidus, and uncontrolled diabetes mellitus. Reference ranges for many hormonal assays change during gestation. For example, because hCG is a weak stimulator of the thyroidal TSH receptor, thyroid hormone levels typically increase, and serum TSH level decreases in early gestation when serum hCG levels are highest. Non-pregnancy-specific laboratory reference ranges should not be used for the interpretation of serum thyroid function tests in pregnant women. High estrogen levels in pregnancy will substantially increase levels of thyroxine and cortisol-binding globulins, which will increase total, but not free, serum hormone concentrations. Some serum hormone levels, including those for prolactin, LH, and FSH, are so profoundly altered

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by normal pregnancy that measurement is unhelpful in the diagnosis of endocrine disorders. Growth hormone is secreted both by the placenta and by the maternal pituitary, and assays cannot distinguish between the two forms. However, other hormonal assays and reference ranges, such as those for plasma metanephrines, are not affected by gestation. Because it is important to limit radiation exposure to the fetus, imaging modalities such as radionucleotide imaging and CT scan are contraindicated in pregnancy with rare exceptions.

In treating pregnant women with endocrine disease, it is important to understand which hormones and medications do and do not cross the placenta to the fetus. Teratogenicity of medications needs to be considered both in women who are in the first trimester of pregnancy, during the period of organogenesis, and in women of reproductive age who might become pregnant. In the postpartum period, it is important to consider the safety of medications in lactation. Targets of therapy may be altered in gestation. Given the importance of maternal thyroid hormone for fetal brain development, it is recommended to target levothyroxine dosing to a serum TSH <2.5 mIU/L in treating pregnant women with hypothyroidism [2]. Guidelines recommend aiming for much tighter glycemic control in treating women with type 1 and type 2 diabetes during gestation than outside the pregnancy setting in order to reduce risk for obstetric complications [3].

When needed for endocrine disorders, surgery is generally safest in the second trimester of pregnancy, due to concerns about the teratogenicity of anesthetic agents and increasing the risk for miscarriage in the first trimester and concern about introducing premature delivery in the third trimester. In addition, some surgical approaches may have to be adjusted in pregnant women to avoid prone positioning.

For some endocrine disorders, full guidelines are dedicated to guiding management decisions in pregnancy [2–5]. For other endocrine conditions, more general guidelines include sections on management during gestation [6–10]. However, for rare disorders, such as pheochromocytoma, where no formal clinical practice guidelines exist for pregnancy, management strategies must be based on limited data and expert opinion. Even where there are formal guidelines, randomized controlled trial data in pregnancy tend to be scarce, and recommendations are most frequently based on lower-quality evidence and expert opinion.

In this section, four cases of endocrine disorders in pregnancy are presented. A case of a patient with a prolactin-secreting macroadenoma in pregnancy illustrates the need for ongoing surveillance for compressive symptoms caused by prolactinoma growth during gestation and decision-making around whether to continue dopamine agonists when pregnancy occurs. A case of papillary thyroid cancer demonstrates clinical considerations related to the timing of fine-needle aspiration biopsy and surgery for pregnant women with suspected thyroid cancer and highlights similarities and differences in cancer treatment and tumor surveillance for pregnant women compared to non-pregnant adults. A rare case of pheochromocytoma in pregnancy sheds light on considerations regarding diagnosis, medical and surgical management, and options for delivery. Finally, the case of a patient with newly diagnosed autoimmune adrenal insufficiency during gestation demonstrates the challenges in diagnosing and treating this condition in pregnant women.

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Chapter 34
Prolactinoma in Pregnancy

Danica M. Vodopivec and Sonia Ananthakrishnan

Objectives

1. Review normal pregnancy physiology as it relates to the pituitary and prolactin production.
2. Discuss the approach to managing patients with prolactinomas during pregnancy.
3. Identify risks and benefits of therapy, particularly dopamine agonists, for patients with prolactinomas in pregnancy and the postpartum period.

Case Description

A 39-year-old woman presented to the endocrine clinic having being referred by her PCP for the workup of an elevated prolactin level. The patient reported bilateral galactorrhea and no menstrual periods for the past 2 years. She noted being sexually active for the past year without being able to conceive and had recently developed frequent frontal headaches. A pregnancy test was negative. Serum prolactin was elevated at 1890 ng/ml, a result which was verified by dilution (n, 5.2–26.5 ng/ml), while LH, FSH, and estradiol were low. TSH was normal at 1.15 uIU/ml (n, 0.35–4.9 uIU/ml) with a normal free T4 of 1.2 ng/dl (n, 0.6–1.8 ng/dl). IGF-1 was normal at 156 ng/ml (n, 52–328 ng/ml). ACTH was normal at 22 pg/ml (n, 6–50 pg/ml) with an AM cortisol of 18 μg/dl. Serum sodium was normal at 140 mEq/L. A pituitary MRI showed a 3.2 cm mass extending from the sella into the right sphenoid sinus and clivus as well as the inferior portion of the right cavernous sinus without narrowing the right internal carotid artery. The sellar mass had minimal superior extension with no mass effect on the optic chiasm (Fig. 34.1a, b). The patient was

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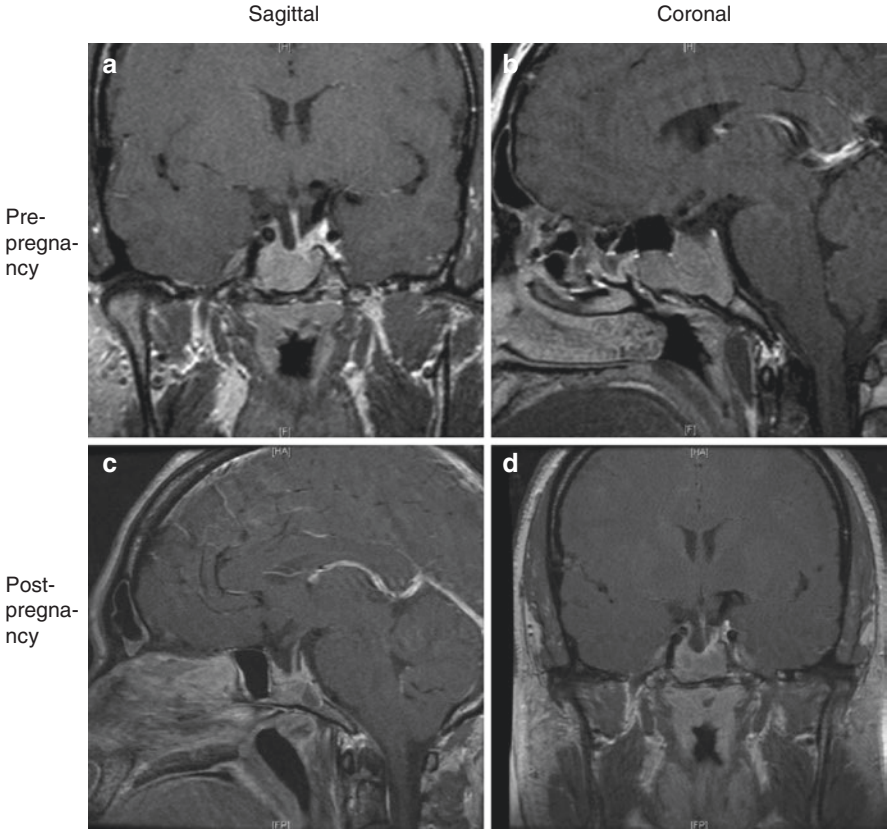

Fig. 34.1 (**a**, **b**) are T1 sagittal and coronal post-gadolinium MRI images from the case patient prior to pregnancy. These images show a mass lesion extending from the sella to the sphenoid sinus with anterior extension into the right posterior ethmoid. The tumor measures 2.4 cm × 2.2 cm × 3.2 cm (TRV × CC × AP). It surrounds the cavernous segment of the right internal carotid artery without causing narrowing. Normal pituitary tissue and stalk are seen displaced to the left. Given the lack of significant superior extension, there is no mass effect on the optic chiasm. (**c**, **d**) are sagittal and coronal post-gadolinium MRI images from the case patient following delivery and lactation. At this later time point, there is demonstration that the tumor has decreased in size to 2.5 cm × 1.4 cm × 1.8 cm in size (TRV × AP × CC), due to dopamine agonist therapy

diagnosed with macroprolactinoma and started on cabergoline 0.25 mg twice a week. Her dose was later increased to 0.5 mg twice a week. Eight months later, the prolactin had decreased to 5.7 ng/ml with resolution of her galactorrhea and headaches. In addition, her menstrual periods returned to normal. Around this time, the patient became pregnant. Because her macroadenoma was invasive beyond the limits of the sella, it was recommended that she continue to take cabergoline to prevent compression from tumor growth. However, she declined in an effort to preserve lactation ability. During pregnancy, she was followed-up every 2–3 months in the

endocrine clinic and by ophthalmology to monitor for new onset of compressive symptoms (headache and visual field defects). She did not develop any complications from her prolactinoma during pregnancy. Fortunately, she was able to breastfeed for 6 months after which cabergoline was resumed. A follow-up MRI demonstrated that the tumor had decreased to 2.5 cm in size (Fig. 34.1c, d).

Introduction

Prolactinomas are the most common type of functioning pituitary tumor. Patients can present with galactorrhea and hypogonadism with subsequent oligo/amenorrhea, infertility, and decrease in bone mass. Compressive symptoms related to mass effect such as headache, visual field defects, and ophthalmoplegia may also be present in cases of macroadenomas. Dopamine agonists (cabergoline and bromocriptine) are the first line of treatment, while surgery and radiotherapy are considered for refractory and medication-intolerant patients [1].

Many of these same considerations for prolactinomas are important to take into account in a patient who becomes pregnant. This chapter focuses on the evaluation and management of patients with prolactinoma immediately prior to, during, and immediately following pregnancy.

Physiology: Prolactin and Lactation

During pregnancy, both anatomic and physiologic changes occur in the breast to prepare for lactation. The increase of progesterone promotes lobular branching and enlargement in the breast, while the elevated estrogen levels induce ductal proliferation and elongation [2]. The high estrogen levels also cause lactotroph cell hyperplasia which translates into increased synthesis and secretion of prolactin from the anterior pituitary gland. Autopsy studies of pregnant women have demonstrated a 30–100% increase in the weight of the pituitary gland [3]. In addition, in vivo MRI studies by Gonzalez et al. showed a pituitary gland increase of 2.6 mm in longitudinal, anteroposterior, and transverse dimensions at the end of pregnancy which translated into an overall increase in volume of 136% when compared to age-matched healthy nulliparous women. The pituitary growth in all the 32 normal primigravid patients did not produce cavernous sinus or chiasm compression, and the pituitary stalk remained in the midline [4].

During pregnancy, high levels of progesterone and estrogen inhibit the stimulatory effect of prolactin on milk production. Lactation starts at the end of pregnancy with the rapid decrease in progesterone levels and a suckling stimulus. The suctioning of the nipple stimulates the 4th intercostal nerve, causing the hypothalamus to release oxytocin. This mechanism is known as the let-down reflex (neuroendocrine reflex). Prolactin causes milk production at the level of the alveolar cells of lobules,

while oxytocin contracts myoepithelial cells around the alveoli to squeeze the milk down the ducts and out of the nipple [5]. Upon termination of breastfeeding, prolactin levels fall, with a subsequent cessation of milk production. Cell apoptosis occurs and the tissue in the breast is remodeled [6].

The Role of Prolactin in Hypogonadism and Fertility

Kisspeptin is a protein produced by neurons in the periventricular and arcuate nuclei of the hypothalamus and is responsible for the release of gonadotropin-releasing hormone (GnRH). Elevated prolactin from any cause, including prolactinomas, suppresses kisspeptin which, in turn, decreases GnRH with a subsequent reduction in luteinizing hormone (LH) pulse amplitude and frequency [7]. The mid-cycle positive estrogen feedback on gonadotropin secretion is blunted by hyperprolactinemia, which suppresses ovarian production of estrogen and progesterone [8, 9]. In the event of a macroprolactinoma, gonadotropin secretion can also be directly inhibited via mass effect causing hypopituitarism.

The overall result is oligo/amenorrhea and infertility from anovulation, part of the classic clinical presentation of a prolactinoma [10]. The use of dopamine agonists, which suppress prolactin secretion, can enable resumption of ovulation and decrease prolactin levels in over 90% of woman with amenorrhea and anovulation [11].

Counseling Women with Prolactinoma

In women of childbearing age with prolactinomas who aim to conceive, two important aspects should be discussed before starting dopamine agonists: (1) the risk of compression to adjacent structures from prolactinoma growth during pregnancy and (2) the potential teratogenic effects of dopamine agonists [12].

Prolactinomas can increase in size during pregnancy for a variety of reasons. Hyperplasia of lactotroph cells caused by the physiologic increases in estrogen levels during pregnancy can cause prolactinoma enlargement. In addition, the common practice of discontinuation of dopamine agonist treatment once pregnancy is achieved can also contribute to prolactinoma enlargement. Tumor growth is more relevant in women with macroprolactinomas where there is a higher risk of clinically significant enlargement and mass effect, manifested by headaches, visual field defects, and/or ophthalmoplegia. For this reason, a decrease in the tumor size should be prioritized before attempting to conceive. Once the macroadenoma shrinks to within the confines of the sella, it is safer to attempt pregnancy [12–14].

If tumor reduction is not achieved in patients with macroprolactinomas prior to pregnancy, for instance, due to resistance or intolerance to cabergoline or bromocriptine, these dopamine agonists may not be effective in preventing clinically

significant and symptomatic expansion of tumor size during pregnancy. Under these circumstances, prepregnancy transsphenoidal surgery to decrease macroadenoma size and prevent complications from pregnancy-related mass expansion can be considered, even if the macroadenoma is not immediately compressing or elevating the optic chiasm [1]. The benefits of debulking surgery need to be weighed against the risk of infertility as a result of the surgery.

For patients on medical therapy, safety of dopamine agonist therapy during pregnancy is important to review. Bromocriptine has been shown to cross the placenta in both animals and humans. Cabergoline has only been shown to cross the placenta in animals, with no studies performed in humans [15]. Most of the existing data on dopamine agonist exposure is in the first 8 weeks of gestation (before pregnancy is confirmed), and there is less information about exposure throughout pregnancy. A long-term follow-up study of 64 children who were exposed to bromocriptine in the first 6 weeks of pregnancy showed no developmental defects at up to 9 years of age [16]. When used in over 100 women throughout gestation, bromocriptine was not associated with congenital anomalies except for two infants, one infant with talipes deformity and another with an undescended testicle [17–20].

There are three different studies which have examined the use of cabergoline within the first few weeks of gestation: (1) Ono et al. showed no physical or mental development abnormalities in the long-term follow-up studies of 83 children of up to 12 years old [21], (2) Lebbe et al. described mildly decreased verbal fluency in two children and difficulty in achieving complete continence in one child at age 4 from a total of 88 children [22], and (3) Stalldecker et al. found seizures in two children and an autism spectrum disorder in two others from a total of 61 children [23]. There are only 15 reported cases of women receiving cabergoline throughout pregnancy, with all infants being healthy at birth except for one intrauterine death at 34 weeks in a patient with severe maternal preeclampsia [24].

In summary, the use of bromocriptine and cabergoline (both FDA pregnancy category B) is not associated with greater deleterious effects on pregnancy outcomes or the fetus when compared to the general population. Bromocriptine has a larger safety database than cabergoline, but experts agree that both are safe to use leading up to and in the early months of pregnancy [1, 12].

Management of Prolactinoma in Pregnancy

Most women with prolactinomas can be advised to discontinue dopamine agonist treatment upon confirming pregnancy. Exceptions to this are patients with macroprolactinomas that are invasive, abutting the optic chiasm, or actively causing compressive symptoms. In these three circumstances, cabergoline or bromocriptine may be continued throughout pregnancy, but the patient should be informed that lactation may be difficult [1].

Women with microadenomas should be followed-up in clinic every 3 months (once in each trimester of pregnancy), with clinical assessments for headaches,

visual changes, and ophthalmoplegia. For patients with macroprolactinomas, women should be seen at a minimum of every 3 months. The higher risk of compression and invasion can prompt more frequent monitoring [1].

Serum prolactin levels are not routinely measured or monitored during pregnancy. They are difficult to interpret for two reasons: (1) the expected physiologic increase of prolactin levels during pregnancy (as high as 400 ng/ml) and (2) the predicted increase in prolactin with cessation of dopamine agonists at the beginning of pregnancy. As a result, it is difficult to differentiate between a rise of prolactin from tumor growth and the expected changes during pregnancy [1].

Pituitary MRI without gadolinium is only indicated when there is clinical tumor enlargement, manifested as new or worsening headaches, changes in vision, and/or ophthalmoplegia. A review of the literature concluded that the risk of symptomatic tumor enlargement for microadenomas was 2.4% (18/764), for macroadenomas with prior surgery/radiation was 4.7% (7/148), and for macroadenomas without prior surgery/radiation was 21.0% (50/238) [12]. However, because for most patients the physiologic tumor growth during pregnancy causes pituitary gland enlargement without symptomatic clinical significance, routine MRI is not indicated [1, 3, 4].

Routine visual field testing is also not indicated during pregnancy for most patients with prolactinomas. However, women who develop compressive symptoms during pregnancy should have urgent visual field testing. For patients with a known macroadenoma that extends above the sella, visual field testing can be performed prepregnancy and then serially every 3 months during gestation, even if no visual symptoms are reported [1].

In the event of compressive symptoms from an enlarging adenoma, patients should undergo urgent MRI without gadolinium, complete visual field testing, and resumption of cabergoline or bromocriptine for the remainder of pregnancy. Under these circumstances, the patient should be clinically monitored more frequently, at least once a month, to assess for headaches and alterations of visual fields. If the adenoma does not respond to medical treatment with persistence of compressive symptoms, transsphenoidal surgery can be considered in the second trimester or deferred until after delivery. If near term, inducing delivery may be reasonable to facilitate a neurosurgical procedure immediately postpartum [1].

Breastfeeding for Patients with a Prolactinoma

Breastfeeding does elevate serum prolactin levels. Therefore, lactation is a viable option postpartum for women with stable micro- or macroadenomas. This requires holding of dopamine agonist therapy until breastfeeding is completed to avoid inhibition of lactation caused by the dopamine agonist-induced lowering of prolactin levels. Lactation has not been shown to increase the risk of tumor growth. On the other hand, women with compressive symptoms in the postpartum period should be

immediately started on dopamine agonist therapy, and lactation should be considered contraindicated in these patients [25, 26].

Serum prolactin levels will return to basal values within 6–12 weeks postpartum. Domingue et al. reported that 41% (30/73) of women with prolactinomas (54 microprolactinomas and 19 macroprolactinomas) treated with dopamine agonists that were stopped in early pregnancy had a normal serum prolactin after a median follow-up of 22 months after delivery or stopping breastfeeding. The likelihood of remission was associated with a smaller adenoma size at diagnosis (5 vs 8 mm) and a normalization of the pituitary MRI after pregnancy [27]. Auriemma et al. described 91 patients with hyperprolactinemia (76 microadenomas, 10 macroadenomas, and 5 nontumoral hyperprolactinemia) treated with cabergoline up to the first 6 weeks of gestation. Normalization of serum prolactin without the need to resume medical therapy for up to 60 months was found in 68% of the patients [28]. It is important to highlight that the duration of breastfeeding did not influence the recurrence rate of hyperprolactinemia in either of these studies [27, 28].

To conclude, in order to evaluate the need for continued dopamine agonist treatment after pregnancy, consider obtaining serum prolactin levels approximately 3 months postpartum in women who avoid breastfeeding or 3 months after stopping lactation.

Lessons Learned

1. Pregnancy is safe for most patients with prolactinoma.
2. Most women with prolactinomas do not require medical treatment with dopamine agonists during pregnancy. However, those with large tumors who are at risk for compression may benefit from continued therapy during pregnancy.
3. Although both dopamine agonists, bromocriptine and cabergoline, are FDA pregnancy category B, multiple case series suggest no increased risk for pregnancy outcomes or for the fetus in treated women when compared to the general population.
4. Women should be monitored clinically at a minimum once a trimester for compressive symptoms. Closer monitoring, including formal visual field testing, may be indicated for patients with more invasive tumors.
5. Routine use of serum prolactin monitoring and/or serial pituitary MRI during pregnancy is not warranted unless clinical compressive symptoms occur.
6. Lactation is safe for most patients with prolactinoma.

Questions

1. For most women with microprolactinomas in pregnancy:

   A. They should be continued on dopamine agonist therapy throughout pregnancy.
   B. They should be routinely monitored with MRI and formal visual field testing every trimester throughout pregnancy.
   C. They should be monitored clinically for headaches and visual field changes every trimester throughout pregnancy.
   D. They should have routine serum prolactin measurements every trimester throughout pregnancy.

2. All the following are reasons to consider continuation of medical therapy with dopamine agonists during pregnancy in a patient with a 3 cm macroprolactinoma except:

   A. Tumor invasion of local structures.
   B. Serum prolactin level >5000.
   C. Tumor abutting the optic chiasm.
   D. Tumor causing compressive symptoms.

3. Dopamine agonist therapy, including bromocriptine and cabergoline, use in pregnancy is considered:

   A. Pregnancy risk factor class A, where controlled human studies show no risk.
   B. Pregnancy risk factor class B, where no evidence of fetal risk has been shown in studies, and there is a lack of controlled studies.
   C. Pregnancy risk factor class C, where risk to the fetus cannot be ruled out, and there is a lack of controlled studies.
   D. Pregnancy risk factor class D, where there is positive evidence of risk, but the benefits of use in pregnant women are acceptable despite this risk.

Answers to Questions

1. C. They should be monitored clinically for headaches and visual field changes every trimester throughout pregnancy.
2. B. Serum prolactin level >5000.
3. B. Pregnancy risk factor class B, where no evidence of fetal risk has been shown in studies, and there is a lack of controlled studies in women.

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Chapter 35
Adrenal Insufficiency in Pregnancy

Meenu Jain, Sarah Knapp, and Florence M. Brown

Objectives

1. To understand how to diagnose and manage adrenal insufficiency in pregnancy
2. To differentiate between different types of adrenal insufficiency in pregnancy and their main etiologies
3. To understand the prevention and treatment of adrenal crisis by using appropriate doses of stress dose steroids

Case Presentation

A 31-year-old G1P0 at 7 6/7 weeks' gestation with well-controlled type 1 diabetes mellitus (DM) for 22 years and no known diabetic complications presented to the endocrinology clinic with complaints of severe nausea and vomiting of 4 days duration, which she attributed to normal symptoms of pregnancy. She reported progressive inability to hold down food and worsening fatigue despite her efforts to self-hydrate with energy drinks and water. She denied salt craving but reported the development of a food aversion to the pickles and pickle juice that had been a part of her normal diet for the last few years. She had undergone an uncomplicated appendectomy a month earlier when there was no confirmation of pregnancy yet. Multiple first- degree relatives had type 1 diabetes, but there was no family history

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of thyroid disease or other endocrinopathies. Lab work in the clinic showed sodium of 118 mEq/L, so she was sent to the emergency department for further management. On exam, she was alert, oriented, with blood pressure of 92/57 mm Hg, heart rate of 93 bpm, and with diffuse skin darkening and gingival hyperpigmentation but no evidence of hyperpigmentation of any scars or creases. Her thyroid was not enlarged and was nontender. Labs were consistent with severe hypotonic hyponatremia, with serum sodium 118 mEq/L, osmolality 250 mOsm/kg H_2O, K 4.6 mEq/L, normal blood counts, thyroid-stimulating hormone (TSH) 5.4 mIU/L, free T4 1.2 ng/dL, urine Na 123 mEq/L, and initial urine osmolality 688 mOsm/kg H_2O. Serum Na initially improved to 124 mEq/L with intravenous infusion of normal saline but then decreased back to 121 mEq/L, and urine osmolality decreased at 364 mEq/L. Given her history of autoimmune endocrinopathy, adrenal insufficiency was considered, and a random cortisol on admission labs was found to be 3.6 μg/dL. Cosyntropin (250 μg) stimulation demonstrated cortisol levels of 3.6, 3.9, and 3.9 μg/dL at 0 min, 30 min, and 60 min, respectively. Aldosterone levels were < 1 ng/dl at all three intervals. Adrenocorticotropic hormone (ACTH) was 1380 pg/ml (reference range 6–50). The low cortisol and aldosterone levels at baseline and failure of cortisol to stimulate and the very high ACTH levels confirmed the diagnosis of primary adrenal insufficiency. Adrenal cortex antibodies were later found to be positive with a titer of 1:10. A diagnosis of Addison's disease in this patient with type 1 diabetes mellitus met criteria for autoimmune polyglandular syndrome type 2 (APS-2). She was tested for autoimmune thyroid disease, but anti-thyroid peroxidase (TPO) antibodies were negative. She was started on oral hydrocortisone 15 mg q AM and 5 mg q PM. Her serum sodium normalized and nausea improved over the next 24 hours. She was discharged to home and was closely followed by her endocrinologist throughout the pregnancy. She was maintained on hydrocortisone 15/5 mg the remainder of her pregnancy. Fludrocortisone was deferred as she was normotensive and did not have symptoms of orthostasis due to the intrinsic mineralocorticoid effect of hydrocortisone. A repeat TSH, days after initiation of maintenance glucocorticoids, normalized to 1.04 mIU/L. She continued to have good control of her diabetes with the expected uptitration of both basal and bolus insulins. Second and third trimester hemoglobin A1c levels were 6.2% and 5.9%, respectively. She underwent a primary cesarean section at 38 3/7 weeks' gestation for suspected macrosomia with a fetal abdominal circumference >99th percentile. Birth weight was 4150 grams. She received 50 mg IV hydrocortisone 1 hour prior to cesarean delivery and 10 mg orally postdelivery as a part of a plan for sick day dosing of steroids. She received oral hydrocortisone 30 mg AM and 10 mg PM for the next 2 days and then returned to her usual maintenance dose of 15 mg q AM and 5 mg q PM. Her diabetes was managed with an insulin drip for 16 hours peripartum, and she was transitioned to subcutaneous multiple daily injections with the usual postpartum dose reduction at the time of her first meal. The baby did well postpartum. There was no neonatal hypoglycemia, jaundice, or need for neonatal intensive care unit monitoring.

The patient was followed up at 2 and 6 weeks postpartum. She was exclusively breastfeeding her baby, and both were doing well.

Introduction

Adrenal insufficiency is a potentially life-threatening condition, predominantly affecting women of reproductive age. Although the incidence of adrenal insufficiency is very low in pregnancy, serious maternal and fetal adverse effects can result if the diagnosis is missed [1].

Types of Adrenal Insufficiency

Adrenal insufficiency (AI) results from failure of the adrenal cortex to produce cortisol. In primary AI, destruction of the adrenal cortex leads to the cortisol deficiency and the appropriately increased pituitary ACTH production. Autoimmune adrenalitis (Addison's disease) is the most common cause of primary adrenal insufficiency in developed countries, and tuberculosis is the most common cause in the developing world. Addison's disease may occur in isolation (30–40%) or as a part of an autoimmune polyglandular syndrome (APS). APS type 2 is the most common form, presenting as a combination of Addison's disease, thyroid autoimmune disease, type 1 diabetes, and/or premature ovarian failure [2]. The complete triad is present only in a minority of patients. Type 1 diabetes, when present, usually develops before Addison's disease, whereas thyroid autoimmunity can develop before, concurrent with, or after the appearance of adrenal insufficiency. In secondary or tertiary AI, the decreased production of corticotropin-releasing hormone (CRH) or ACTH from the hypothalamus and pituitary, respectively, leads to decreased secretion of cortisol and adrenal androgens with typically preserved mineralocorticoid function due to the separate feedback systems. Mineralocorticoid levels are regulated by the renin–angiotensin system, independent of hypothalamic or pituitary signals [3]. Prolonged exogenous suppression of the hypothalamic pituitary adrenal axis due to chronic usage of exogenous steroids for various conditions such as asthma, rheumatological disorders, or inflammatory bowel disease is the most common cause of secondary AI. Sheehan's syndrome and lymphocytic hypophysitis may be pregnancy-related causes of secondary AI, whereas hypothalamic/pituitary tumors most frequently will have been diagnosed and treated before conception. Our patient likely had APS type 2 with type 1 diabetes preceding the diagnosis of Addison's disease.

Normal Fetoplacental Steroidogenesis

The fetoplacental unit has marked steroidogenic capacity and is responsible for various changes in the maternal hypothalamic–pituitary–adrenal (HPA) axis leading to a state of physiological hypercortisolism in pregnancy. In healthy pregnant women, total and free plasma cortisol, ACTH, CRH, and cortisol-binding globulin

(CBG) levels increase multifold. There is a threefold increase in maternal cortisol concentrations, usually seen as early as 11 weeks [4], primarily due to the estrogen-stimulated increase in cortisol-binding globulin (CBG) production and decreased hepatic clearance of this bound hormone. From the 22nd gestational week onward, increased production of biologically active CRH and ACTH from the placenta and displacement of maternal cortisol from CBG by rising progesterone result in increases of free cortisol levels accompanied by hypertrophy of the adrenal glands [5]. However, despite this state of hyperactivation of the HPA axis and physiological hypercortisolism, the normal diurnal variation of plasma cortisol is maintained throughout the pregnancy, possibly due to an altered set point of the HPA axis and relative tissue refractoriness to the effects of cortisol in pregnancy [6]. These increased cortisol levels may have diagnostic and therapeutic implications in pregnant women with AI.

Pregnancy is also characterized by activation of the renin–angiotensin–aldosterone system (RAAS); however, progesterone exerts anti-mineralocorticoid effect and results in reduced sodium reabsorption, reduced vascular resistance, and a net volume expansion during pregnancy [7].

Challenges in Diagnosing Adrenal Insufficiency in Pregnancy

The clinical and biochemical diagnosis of new-onset AI in pregnancy is challenging due to the overlap with normal symptoms of pregnancy as well as pregnancy-induced changes in cortisol values. Patients with undiagnosed AI usually present to their obstetrician with complaints of nausea, vomiting, weakness, light-headedness, fatigue, abdominal pain, and electrolyte disturbances. Chloasma of pregnancy may mimic the hyperpigmentation associated with Addison's disease; however, the latter typically affects nonexposed areas of increased mechanical friction such as scars, nipples, knuckles, and oral mucosa. Persistent unexplained orthostasis, hypotension, and hyponatremia with a >5 mEq/L decrease in plasma sodium, particularly associated with hyperemesis gravidarum [8], infection, delivery, or obstetric hemorrhage, can point toward underlying undiagnosed adrenal insufficiency.

Diagnosing AI involves three stages: demonstrating inappropriately low serum cortisol levels, determining whether the cortisol deficiency is dependent or independent of ACTH, and ascertaining the etiology of this deficiency. However, if clinical suspicion of adrenal crisis is high, confirmation of a biochemical diagnosis should not delay empiric treatment with high-dose IV glucocorticoids. Patients with suspected adrenal insufficiency should be screened by drawing paired samples of plasma cortisol and ACTH levels. Unlike nonpregnant individuals in whom an early morning plasma cortisol <5 μg/dL in the setting of typical clinical features is considered highly suggestive of adrenal insufficiency, interpretation of cortisol levels during pregnancy becomes challenging, as both serum cortisol and ACTH levels increase due to steroidogenesis by fetoplacental unit. Though using higher cutoffs for random morning serum levels of cortisol <11, 16.3, and 22 μg/dL during the 1st,

2nd, and 3rd trimesters has been suggested [9], an inappropriately normal cortisol level for the stage of gestation should raise a red flag for the diagnosis of AI. It is also important to note that ACTH may not be low with secondary adrenal insufficiency in pregnancy because of the placental production of this hormone, further posing a diagnostic challenge. According to Endocrine Society guidelines [10], the 250 μg cosyntropin stimulation test remains the test of choice in pregnant women if adrenal insufficiency is suspected, although studies suggest using higher trimester-specific cutoff values for stimulated cortisol values due to enhanced maternal adrenal responsiveness to ACTH stimulation. The recommended diagnostic cutoffs are 25 μg/dL for the first trimester, 29 μg/dL for the second trimester, and 32 μg/dL for the third trimester [11]. In case of adrenal crisis, a cortisol level should be drawn with baseline labs, and life-saving treatment with intravenous fluids and hydrocortisone should not be delayed for diagnostic workup. Antibody assays in pregnancy remain helpful to confirm the autoimmune nature of AI (Addison's disease), as approximately 90% of patients with Addison's disease have 21-hydroxylase antibodies.

Our patient initially dismissed her symptoms as normal for pregnancy, but as she developed an aversion to salty food and hyperemesis in the first trimester, her features of AI were unmasked. Her severe hyponatremia on presentation seemed to be multifactorial in etiology: hypovolemic (due to multiple episodes of vomiting), a component of SIADH due to severe nausea, and glucocorticoid deficiency from AI. A positive cosyntropin test with ACTH 1380 pg/ml (normal 6–50) and the presence of 21-alpha hydroxylase antibodies clinched the diagnosis of primary AI due to Addison's disease as well as the additional diagnosis of autoimmune polyglandular syndrome type 2 (APS type 2), given her history of type 1 diabetes. She did not have autoimmune thyroid disease as her anti-TPO antibodies were negative and the TSH decreased from 5.4 to 1.04 mIU/L after the replacement of cortisol [12].

Treatment of Adrenal Insufficiency in Pregnancy

Pregnant patients with AI should be managed by a multidisciplinary team that includes an endocrinologist and an obstetrician. The primary aim of glucocorticoid therapy in pregnancy is to achieve optimal replacement to enhance maternal and fetal outcomes. Hydrocortisone is the preferred glucocorticoid as it is degraded by the placental enzyme 11-beta hydroxysteroid dehydrogenase type 2 (HSD2) and does not cross the placenta [5].The original recommended dose of hydrocortisone, based on estimated daily production of 12–15 mg/m^2/day, was very high and resulted in overtreatment. Current recommendation, based on more accurate estimates of cortisol production (6–11 mg/m^2/day), usually results in a lower total daily dose [13]. Most patients do not require more than 20 mg/day, usually divided into a 2–3 times daily dosing schedule, due to the short half-life of the drug and to mimic physiological conditions. To mimic the physiological increase in the last trimester, a 20–40% increase in the dosage of hydrocortisone is sometimes recommended,

although this may not be always clinically indicated [9]. Higher doses are needed at times of stress (hyperemesis gravidarum or infection) and during the active stage of labor to prevent adrenal crisis. A hydrocortisone dose equivalent to that used for major surgical stress should be initiated at the onset of active labor (cervix dilation 4 cm and/or contractions every 5 min for the last hour) with an intravenous bolus injection of 50–100 mg hydrocortisone followed by continuous infusion of 200 mg hydrocortisone/24 hours [9]. After delivery, hydrocortisone can be quickly tapered back to prepregnancy doses and should be continued during breastfeeding [12] and beyond. However, there is no universal agreement regarding the timing and dosage adaptation of glucocorticoid substitution peripartum.

Fludrocortisone is the most commonly used mineralocorticoid in pregnancy, but there are no studies of mineralocorticoid replacement for primary adrenal insufficiency (PAI) in pregnancy as yet. Oral fludrocortisone is usually given in doses of 0.05–2 mg daily. Hydrocortisone has intrinsic mineralocorticoid activity, with 40 mg of hydrocortisone equivalent to 100 μg of fludrocortisone [14]. Thus, changes in the hydrocortisone dose can affect fludrocortisone dose requirements. Also, due to the anti-mineralocorticoid effect of progesterone, the fludrocortisone dose may need to be increased [15]. Dose adjustment should be based on clinical parameters including the presence of orthostatic hypotension or edema and levels of serum and urine sodium and potassium rather than on plasma renin levels.

Our patient had an uneventful pregnancy on oral hydrocortisone 15 mg q AM and 5 mg q PM, without requiring any further increase in her dosage except for receiving 50 mg intravenous dose an hour prior to elective caesarean section, 10 mg orally postdelivery, and double the dose of her routine dose orally for next 48 hours, with a return to her baseline dosage on postpartum day 3. This implies that every case should be individualized and clinical features including general well-being, appropriate weight gain, blood pressure, and potassium levels rather than serum cortisol, ACTH, plasma Na, and renin levels should be used to titrate the doses of glucocorticoid and mineralocorticoids during pregnancy. Clinicians should avoid overtreatment which can result in hyperglycemia, excessive weight gain, and hypertension and should avoid undertreatment, which can result in adrenal crisis and electrolyte imbalance.

Patients should be followed by an endocrinologist at least once every trimester. Proper counselling about adherence to medication and education about sick day rules is of paramount importance to achieve good maternal and fetal outcomes.

Lessons Learned

1. Although mild hyponatremia can be physiologic in pregnancy, severe hyponatremia in association with hypotension or excessive fatigue, especially in the presence of other autoimmune diseases like type 1 DM or a family history of endocrine autoimmune disease, should alert physicians to the possibility of Addison's disease.

2. Consideration of a new diagnosis of PAI during pregnancy poses a significant diagnostic challenge. If clinical suspicion is high, paired serum samples of cortisol and ACTH, and if possible, a cosyntropin stimulation test should be performed prior to empiric initiation of hydrocortisone replacement for adrenal insufficiency.
3. Peripartum management includes the intravenous administration of hydrocortisone in doses recommended for major surgical stress (50–100 mg every 6–8 hours) and should be initiated at the onset of active phase of labor or prior to a planned caesarean section.

Questions

1. All of the following are the causes of primary adrenal insufficiency except:

   (a) Bilateral adrenal hemorrhage
   (b) Addison's disease
   (c) Tuberculosis of adrenal glands
   (d) Lymphocytic hypophysitis

2. All of the following lead to increased total serum cortisol levels in pregnancy except:

   (a) Increased estrogen levels in pregnancy
   (b) Decreased cortisol-binding globulin (CBG) levels
   (c) Increased production of cortisol from placental ACTH and CRH
   (d) Increased displacement of cortisol levels from CBG by increased progesterone

3. Which of the following is true in diagnosing AI in pregnancy:

   (a) AI is commonly diagnosed in pregnancy
   (b) Clinical features of AI may mimic symptoms of early pregnancy
   (c) Therapy for suspected adrenal crisis must be delayed until diagnosis is confirmed
   (d) An AM cortisol level of >3 μg/dL rules out AI

4. Which is the recommended glucocorticoid for management of AI in pregnancy:

   (a) Betamethasone
   (b) Hydrocortisone
   (c) Dexamethasone
   (d) Deoxycorticosterone

Answers

1. d
2. b
3. b
4. b

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Chapter 36
Pheochromocytoma in Pregnancy

Danica M. Vodopivec and Anand Vaidya

Objectives

1. Review normal pregnancy physiology as it relates to the catecholamine physiology.
2. Discuss the appropriate approach to managing patients with pheochromocytoma during pregnancy.
3. Identify benefits and risks of medical therapy in patients with pheochromocytomas, particularly adrenergic receptor blockers and calcium channel blockers.
4. Discuss surgical planning including the timing of surgery and recommended surgical approaches in pregnant patients with pheochromocytoma.
5. Discuss delivery options in pregnant patients with pheochromocytoma.

Case Description

A 24-year-old woman presented to her primary care doctor with several weeks of worsening palpitations, headache, nausea, and pleuritic chest pain. She reported amenorrhea for approximately 3 months. She had a known history of neurofibromatosis type 1 diagnosed 10 years earlier. She was initially followed with spinal MRIs every 2 years but had not had recent follow-up in 5 years. Her only clinical manifestations were cutaneous neurofibromas.

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Pregnancy testing revealed that she was pregnant with an approximate gestational age of 12 weeks. Her blood pressure was 170/90 mmHg, and she was sent to the emergency room where her blood pressure was 200/95 mmHg with a heart rate of 104 beats per minute. She was treated with intravenous labetalol to control her blood pressure and heart rate and admitted to the hospital. Testing revealed markedly elevated plasma metanephrines (normetanephrine 25 nmol/L (<0.9), metanephrine 4.0 nmol/L (<0.5)), markedly elevated 24-hour urinary metanephrines (24-hour metanephrine 4360 mcg (<400), 24-hour normetanephrine 14,000 mcg (<900)), and markedly elevated 24-hour urinary fractionated catecholamines (24-hour dopamine 1748 mcg (<400), 24-hour epinephrine 566 mcg (<21), 24-hour norepinephrine 1424 mcg (<80)). An abdominal MRI without contrast revealed a 5.5 × 5.6 × 5.3 cm heterogeneous left adrenal mass with T2 hyperintensity that was highly suspicious for a pheochromocytoma. There were no other abdominal masses or tumors.

After detailed counseling regarding medical therapy with adrenergic antagonists, surgical adrenalectomy, and/or pregnancy termination, the patient chose to undergo adrenalectomy. After optimizing her blood pressure and symptoms with preoperative adrenergic blockade, she underwent a successful laparoscopic right adrenalectomy at 18 weeks. Her blood pressure and symptoms resolved postoperatively, and the remainder of the pregnancy was uncomplicated. She delivered a healthy baby at 39 weeks.

Introduction

Pheochromocytoma is a rare catecholamine-secreting tumor that originates from the chromaffin cells of the adrenal medulla. It has a reported incidence of 0.05% in the general population and 0.007% in pregnancy [1, 2]. Antepartum diagnosis is only made in 73–75% of patients; underdiagnosis is explained by several factors such as scarcity of disease and nonspecific and varied symptoms that can be erroneously attributed to other common disorders of pregnancy (gestational hypertension or preeclampsia). If undiagnosed before delivery, maternal and fetal death rates can be as high as 48% and 54%, respectively. On the other hand, antepartum diagnosis with proper treatment is associated with a reduced mortality rate of 0–2% in the mother and 9–15% in the fetus [3–6]. Even though pheochromocytoma in pregnancy can be life-threatening to the mother and fetus, no consensus or guidelines exist for optimal management, and most available recommendations stem from anecdotal case reports and case series.

Physiology and Pathophysiology of Catecholamines in Pregnancy

Norepinephrine is the main neurotransmitter of the sympathetic nervous system and is also produced in the adrenal medulla. In contrast, epinephrine is exclusively produced in the adrenal medulla. Both catecholamines play a

physiological role in the adjustment to stressful stimuli, including pregnancy and delivery [5]. These catecholamines are metabolized to inactive and stable metabolites that are useful for diagnostic purposes. Norepinephrine is metabolized to normetanephrine, and epinephrine is metabolized to metanephrine. Pheochromocytomas can secrete either or both catecholamines resulting in stimulation of α and β receptors in target organs. The stimulation of α1 receptors at the level of the blood vessels causes vasoconstriction, in contrast to β2 receptors which results in vasodilation and bronchodilation. Activation of cardiac β1 receptors increases heart rate and contractility [8].

During normal pregnancy, catecholamine levels are relatively similar to those in nonpregnant healthy women except from labor to postpartum day 2, when they are higher [9]. Moreover, women with gestational hypertension and preeclampsia, which are the most common causes of hypertension in pregnancy, have relatively normal levels of plasma and 24-hour urinary fractionated metanephrines [8]. However, 24-hour urinary catecholamines (epinephrine and norepinephrine) have been found to be elevated in hospitalized patients with preeclampsia; therefore, catecholamines lack specificity for the diagnosis of pheochromocytoma [9, 10].

Maternal catecholamines do not enter the fetal circulation due to the presence of monoamine-oxidase and catechol-O-methyltransferase in the placenta which metabolize catecholamines into inactive compounds [7, 11].

The uteroplacental circulation expresses α1 receptors that can induce vasoconstriction when stimulated. As a result, high concentration of catecholamines can cause uteroplacental insufficiency which may lead to spontaneous abortion, fetal growth restriction, fetal hypoxia, and intrauterine fetal death. Furthermore, paroxysmal increases in blood pressure may lead to placental abruption, severe intrauterine hypoxia, and adverse fetal outcomes [11].

Different mechanisms during pregnancy can exacerbate a hypertensive crisis, turn asymptomatic pheochromocytomas into an overt presentation, and/or worsen symptomatology as pregnancy progresses. These mechanisms include mechanical pressure on the tumor caused by increased intra-abdominal distention, an enlarging uterus, uterine contractions, fetal movements, spontaneous hemorrhage into the tumor, abdominal palpation, and/or surgery. Other mechanisms known to cause a catecholamine surge include stress associated with labor, foods containing tyramine, and/or drugs commonly used in pregnancy. Among these medications are metoclopramide, methyldopa (most frequently prescribed to treat hypertension during pregnancy), glucocorticoids (commonly used to stimulate fetal lung maturation in threatening preterm labor), morphine, anesthetics (thiopental for induction and maintenance of general anesthesia), halothane, desflurane anesthetic gases, mivacurium as neuromuscular blocking agent, and atropine for reversal of neuromuscular blockade [4, 6, 8, 11]. In addition, elevated circulating levels of estrogen may induce tumor growth [12, 13].

Diagnosis of Pheochromocytoma in Pregnancy

Clinical Presentation: Signs and Symptoms

Pheochromocytoma in pregnancy has a similar clinical presentation to that of non-pregnant women. Symptoms are varied and range from the typical presentation of paroxysmal hypertension associated with palpitations, headache, diaphoresis, and pallor; to subtle symptoms that progress through gestation; to a normotensive asymptomatic gravida with an incidentally found pheochromocytoma.

Hypertension may be labile, paroxysmal, or constant, but periods of hypotension may also develop in about 50% of the patients [8]. Other nonspecific associated symptoms include dizziness; nausea; vomiting; nervousness; chest pain; gestational diabetes; and, in the event of malignancy, signs and symptoms from local invasion and metastasis. Catecholamines promote hyperglycemia through gluconeogenesis and glycogenolysis, inhibition of insulin secretion, and peripheral resistance to insulin [6, 8]; thus, many pregnant women with pheochromocytoma may fail standard glucose tolerance testing.

Cardiovascular manifestations may include arrhythmias, angina pectoris, acute coronary syndrome, dilated cardiomyopathy, acute heart failure with pulmonary edema, and/or cardiogenic shock. Pheochromocytoma-induced cardiomyopathy can present with ballooning of the left ventricle apex (Takatsubo's cardiomyopathy) that mimics a myocardial infarction but lacks angiographic evidence of obstructive coronary artery disease. Removal of the pheochromocytoma and catecholamine excess usually reverses the cardiomyopathy. Other life-threatening conditions caused by acute release of catecholamines include aortic dissection and stroke [6, 8].

Resistant hypertension, peripartum cardiomyopathy, and/or orthostatic hypotension should prompt a high clinical suspicious of pheochromocytoma during pregnancy. Orthostatic hypotension is explained by baroreflex impairment from desensitization and the relative hypovolemia from prolonged vasoconstriction induced by high catecholamine exposure [7, 8].

On physical exam, specific phenotypical features such as cutaneous lichen amyloidosis (multiple endocrine neoplasia type 2A – MEN 2A), marfanoid habitus (multiple endocrine neoplasia type 2B – MEN 2B), café-au-lait spots, freckles, and neurofibromas (neurofibromatosis type 1 – NF-1) suggest a hereditary syndrome-based pheochromocytoma. Paradoxical supine hypertension due to the gravid uterus compressing large tumors in the supine position may be seen with normal blood pressure in the sitting or erect position. Taking a detailed family history is also helpful as it may uncover an inherited pheochromocytoma syndrome (discussed further below) [6, 8].

Differential Diagnosis

The prevalence of hypertension in pregnancy is approximately 3–5% [14]. Because gestational hypertension and preeclampsia are more common during pregnancy, pheochromocytoma can be easily missed. Elevated blood pressure from gestational

hypertension or preeclampsia appears after gestational week 20, and it is usually moderate and sustained, while hypertension in pheochromocytoma can be present at any time during pregnancy (even before week 20), and it is usually severe, labile, and paroxysmal. Preeclampsia is associated with proteinuria (≥300 mg in a 24-hour urine specimen), weight gain, and edema, which are usually absent in pheochromocytoma. Although nausea and vomiting can be present in preeclampsia and pheochromocytoma, left upper quadrant pain and/or epigastric pain is characteristic of preeclampsia [6]. Elevated uric acid levels or clinical features of the HELLP syndrome (microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets) indicate toward pregnancy-related hypertension and are not compatible with pheochromocytoma [7, 8].

It is useful to obtain a detailed hypertension history. A personal or family history of hypertension during pregnancy makes gestational hypertension more likely [15]. Finally, resistant hypertension in a young patient is suspicious not only for pheochromocytoma but also for other causes of secondary hypertension that are beyond the scope of this chapter.

Biochemical Studies

The biochemical diagnosis of pheochromocytoma in pregnancy is based on the results of 24-hour urinary fractionated metanephrines (metanephrine and normetanephrine), fractionated catecholamines (epinephrine, norepinephrine, and dopamine), and/or plasma-free fractionated metanephrines with the same reference values as those used for nonpregnant women. Measurement of circulating plasma catecholamines is less sensitive, but values >2 times the upper limit of normal range can be strongly suggestive of the diagnosis [7, 16–18].

Catecholamine O-methylation is the dominant pathway of the tumor which results in the continuous increased secretion of metanephrines into the circulation. As a result, measurement of metanephrines has a higher sensitivity when compared to the parent catecholamines (epinephrine, norepinephrine) that are released from the tumor in an episodic and variable fashion [12].

Inappropriate sampling conditions, medications, and significant illness requiring hospitalization are potential confounders that can contribute to false-positive results. When measuring the 24-hour urinary collection, urinary creatinine should be measured to verify completeness of the urine collection. Plasma metanephrines are best measured in the supine position to prevent a false-positive increase in the seated position. Metanephrine assays should be based on high-performance liquid chromatography with tandem mass spectroscopy (LC-MS/MS) methodology to ensure reliable interpretations. Medications that cause a false-positive result regardless of the type of laboratory technique include drugs that block the reuptake of catecholamines, including tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, cyclobenzaprine, some nasal decongestants, prochlorperazine, levodopa, and amphetamines [5, 8, 9].

Patients with symptomatic pheochromocytoma typically have marked elevations of metanephrines above the upper limit of the reference range, usually fourfold or greater. It is uncommon for elevations less than fourfold above the reference range to represent a symptomatic pheochromocytoma. In contrast, false-positive elevations due to sympathoadrenergic excess (anxiety, stress, illness, pain, or reuptake inhibition) typically present with more modest elevations (two- to fourfold above the upper limit of the reference range).

Imaging Studies

Once a biochemical diagnosis is confirmed, imaging studies can be performed to localize the tumor. Pheochromocytoma is usually the most common culprit; however, paragangliomas arising from the ganglia of the sympathetic nervous system are also possible and can occur anywhere from the base of the skull to the pelvis. Abdominal imaging is the preferred option since most tumors will be pheochromocytomas or abdominal paragangliomas. The available options during pregnancy are abdominal ultrasound and MRI without gadolinium, with the latter being the modality of choice. Gadolinium contrast crosses the placenta, and its use is controversial in pregnancy. The disadvantage of abdominal ultrasound is that small tumors can be easily missed, especially when the enlarged gravid uterus interferes with retroperitoneal visibility [4, 7–9]. Metaiodobenzylguanidine (MIBG) scintigraphy, FDG-PET, ^{68}Ga-Dotatate PET, and CT imaging should only be used postpartum to detect lesions that may have been missed by MRI. The use of these imaging studies becomes more relevant in inherited syndromes because MRI is less accurate for detecting extra-adrenal lesions or tumors <1.5 cm in size [9, 19]. Finally, tumor biopsy is contraindicated for making the diagnosis of pheochromocytoma because of the risk of inducing a hypertensive crisis [5].

Genetic Screening

Approximately 40% of patients with pheochromocytoma harbor a germline mutation, but this proportion is higher at 66% in the pregnant population [3, 17]. Genetic mutations may predispose not only to pheochromocytoma and paraganglioma but also in some syndromes to other tumors as well. Genetic testing should be considered in all pregnant women because germline mutations tend to be present in younger individuals. In this setting, pheochromocytomas tend to be bilateral, recurrent, and/or metastatic with a positive family history and suggestive clinical findings of a syndromic disorder such as MEN 2, NF-1, von-Hippel Lindau (VHL), or the familial paraganglioma syndromes (succinate dehydrogenase subunits A, B, C, D, AF2). Detection of a germline mutation allows for early detection and intervention in other affected family members [8, 12].

Treatment

The treatment of pheochromocytoma in pregnancy starts by preventing hypertensive crisis with the use of α and β blockers and calcium channel blockers. Intensification of α-blockade 1 week before surgery or delivery should be conducted [3]. The definitive treatment is surgical adrenalectomy, but optimal timing remains controversial, depending on the age of gestation, maternal response to medical treatment, tumor accessibility, fetal condition, and access to a multidisciplinary team [20]. Typically, when surgical adrenalectomy is necessary, the second trimester is the optimal time to conduct the operation in terms of minimizing risk to the mother and fetus. In the largest study of pheochromocytoma in pregnancy to date, medical therapy with α-blockade was observed to also result in favorable outcomes for the mother and fetus; thus, when the resources or ability to conduct a safe adrenalectomy are not available, medical therapy can be considered [3].

Preoperative Medical Management

Patients must undergo appropriate preoperative medical management to block the deleterious cardiovascular effects of catecholamines, with emphasis on the time of surgery where manipulation of tumor may cause massive catecholamine release. Blood pressure, heart rate, and volume depletion should be restored as far as possible. In nonpregnant patients with pheochromocytoma, the target blood pressure is <130/80 mmHg while in seated position and systolic blood pressure >90 mmHg while in a standing position. Since the published literature on pheochromocytoma in pregnancy largely involves case reports, the blood pressure target in pregnancy is not well established. In general, the blood pressure goal in pregnant women with chronic hypertension is <140/90 mmHg with a diastolic blood pressure >80 mmHg. The blood pressure goal in women with preeclampsia is 130–150/80–100 mmHg [7, 16]. The most important factor is to avoid hypotension to preserve uteroplacental circulation [7, 12, 16].

The foundation of pre-surgical preparation is α-blockade with phenoxybenzamine or doxazosin for at least 10–14 days before surgery. Both are considered fetal risk category C [8]. Doxazosin and other selective α1-antagonists are most frequently used given that they are easily available, relatively inexpensive, and effective. Satisfactory α-blockade reduces fetal mortality from 55% to 6% and maternal mortality from 9.5% to 0% [12]. Notably, pregnant women with normal blood pressure should be treated with a low-dose α-antagonist to prevent paroxysmal peaks in blood pressure [7]. Phenoxybenzamine is an irreversible, noncompetitive α1- and α2-adrenoreceptor antagonist with a prolonged half-life [8]. Its side effects include orthostatic hypotension, tachycardia, and nasal congestion. The disadvantage of phenoxybenzamine is that it predisposes to postoperative hypotension from its prolonged action after tumor removal. It also crosses the placenta with the risk of perinatal hypotension and respiratory depression [21]. Neonates should

be monitored for 3 days after delivery [5]. The availability and cost of phenoxybenzamine can be prohibitive. Doxazosin is a competitive, reversible, selective α1-adrenoreceptor blocker. The advantages of doxazosin over phenoxybenzamine include (1) a lower incidence of reflex tachycardia, (2) less risk of postoperative hypotension due to its shorter half-life and reversibility of effect, and (3) easy availability and lower cost. Doxazosin crosses the placenta, but it does not cause known adverse effects in the neonate [7, 8, 11].

In addition to α-blockade, β-blockade is often necessary to counteract catecholamine-induced tachycardia and α-blockade-induced reflex tachycardia. A β-blocker should be started several days after initiation of α-blocking agents. This time lag is necessary to prevent a hypertensive crisis from unopposed α-adrenoreceptor-mediated vasoconstriction by catecholamines. The most common β-blockers used in pregnancy are propranolol and atenolol. β-Blockers are considered fetal risk category C, except for atenolol, which is category D. They should not be used for an extended period of time because of associated intrauterine growth retardation. However, fetal growth restriction is more likely due to the pheochromocytoma itself rather than being medication-induced. Importantly, the combined α- and β-adrenoreceptor blocker labetalol has a relatively weak α-adrenergic blocking activity which may lead to paradoxical hypertensive crisis if used as a single agent [8, 11, 12].

Calcium channel blockers (nifedipine or nicardipine) can be considered when hypertension is not fully controlled with an α-adrenergic blocker and no tachycardia is present (the presence of tachycardia will make a β-blocker a better second option). They are considered fetal risk category C. There are reports of nicardipine causing neonatal hypotension and acidosis. The use of calcium channel blocker in the third trimester is linked with increased risk of neonatal seizures, jaundice, and hematologic conditions [7, 11].

Patients with pheochromocytoma are volume contracted and may develop orthostatic hypotension, which may worsen with α-blockade. It is usually advisable to increase dietary sodium intake and to administer hydration with saline to restore the intravascular volume a few days before surgery. This may further help to minimize the risk of large fluctuations in blood pressure during surgery and the risk of postoperative hypotension. Furthermore, appropriate intravascular volume sustains uteroplacental circulation [7–9].

Management of Hypertensive Crisis

Parenteral antihypertensive medications are available in case of hypertensive crisis. Phenoxybenzamine is not widely available for intravenous use. For this purpose, phentolamine, a competitive α1- and α2-antagonist, is more accessible. Its presynaptic α2-blockade can originate reflex tachycardia. There are two β-blockers available for intravenous formulation: (1) esmolol is a selective β1-blocker ideal for controlling both hypertensive crisis and tachyarrhythmias and (2) labetalol with more β- than α-blockade properties. Both should only be administered after proper

α-blockade is achieved. Nicardipine is a short-acting calcium channel blocker available as another parenteral option [8]. Intravenous magnesium sulfate is well known in obstetrics for the treatment of eclampsia. It causes direct vasodilation, prevents catecholamine release, and increases peripheral resistance of α-adrenoreceptors to catecholamines. It requires monitoring of serum magnesium levels. Magnesium sulfate was recently changed from fetal risk category A to category D due to concerns of fetal and neonatal bone mineralization and fractures associated with long-term in utero exposure. These concerns about bone effects are based on retrospective studies, with the long-term clinical significance being uncertain. However, pheochromocytoma during pregnancy can be life-threatening with the benefits of using magnesium sulfate outweighing its risks [7, 11]. Other direct vasodilators like hydralazine, nitroglycerin, and sodium nitroprusside are also therapeutic options. Nitroprusside can cause fetal cyanide toxicity at infusion rates ≥1 μg/kg/min [5, 8].

Surgery

Timing of Surgical Intervention

According to expert recommendations, pheochromocytomas diagnosed early in pregnancy should be excised in the second trimester, before the 24 weeks of gestation. Organogenesis and vulnerability to spontaneous abortion make surgical intervention during the first trimester inappropriate. After 24 weeks of gestation, the goal is to treat the patient medically and await fetal maturity at 38 weeks of gestation. The enlarged uterine fundus restricts surgical access, and adrenalectomy should be postponed until the time of C-section delivery or 2–6 weeks postpartum [7, 9, 19, 20]. Concomitant tumor resection with C-section exposes the patient to a one-time intervention. However, deferred adrenalectomy offers three advantages: (1) complete α-blockade if time since diagnosis has been short, (2) a strict α-blockade can be achieved without worrying about hypoperfusion at the level of the fetoplacental unit, and (3) the use of CT scan and radioisotope images like MIBG or ^{68}Ga-Dotatate PET when multiple or metastatic pheochromocytoma is suspected. Laparoscopic adrenalectomy is the treatment of choice; hence, some authors believe there is no need for an elective cesarian delivery and open adrenalectomy in a combined surgical intervention [2, 7, 8]. Interestingly, Bancos et al. showed that adrenalectomy during pregnancy was not associated with improved outcomes but lack of α-blockade was associated with adverse outcomes [3].

Surgical Approach

As in the general population, if the pheochromocytoma is suspected to be benign and less than 7 cm in size, laparoscopic adrenalectomy is preferred when compared to a conventional open laparotomy [6, 8]. Laparoscopic surgery entails a shorter

duration of hospitalization and less morbidity, including decreased risk of catecholamine release and hemodynamic instability, resulting in greater safety for the mother and the fetus [2, 8, 19].

During pregnancy, a lateral laparoscopic transperitoneal/transabdominal approach should be used. An extraperitoneal approach is contraindicated during pregnancy because it requires prone positioning of the patient. It is important to take into consideration that both right and left lateral positioning of the patient have been used successfully, although a left lateral position for right adrenal resection is easier for the anesthesiologist to handle due to positional decompression of the inferior vena cava from the enlarged uterus. On the other hand, a right lateral position for left adrenal resection increases the risk for inferior vena cava compression with subsequent uteroplacental hypoperfusion during surgery. After birth, both the transabdominal and retroperitoneal approaches are considered appropriate [19].

Donati et al. reported two patients with bilateral pheochromocytoma who underwent laparoscopic adrenalectomy in the second trimester with subsequent C-section at week 38 and removal of the remaining tumor postpartum. The reason behind the delayed second surgery was to prevent adrenal insufficiency during pregnancy [19]. An initial bilateral adrenalectomy or cortical-sparing adrenalectomy has also been reported as safe [8].

Postsurgical Acute Catecholamine Deficiency

After tumor removal, there is risk for hypotension and hypoglycemia. Hypotension is due to acute catecholamine deficiency with possible α-adrenoreceptor downregulation, residual α-blockade (especially with the long-acting phenoxybenzamine), and relative decreased intravascular volume from catecholamine-sustained vasoconstrictive effect. Hypoglycemia can occur due to insulin resistance associated with reduction of lipolysis and glycogenolysis after surgery [8].

According to Konno et al., risk factors for developing postsurgical hypotension are the size of the tumor and elevated preoperative noradrenaline levels [22]. Treatment of postoperative hypotension consists of volume repletion and, if needed, norepinephrine as the pressor of choice followed by vasopressin [8].

Evaluating the Appropriate Timing and Route of Delivery

The timing of delivery is determined by the well-being of the fetus and adequate blood pressure control in the mother. Indications for early delivery are fetal distress indicators (intrauterine growth retardation, decreased fetal movements, and decelerations on fetal cardiac monitoring), poorly controlled maternal blood pressure, or high suspicion for malignant pheochromocytoma [2, 9, 11].

Bancos et al. reported the largest cohort of pregnant patients with pheochromocytoma (232 patients and 249 pregnancies), collected from 1980 to 2019. The study

showed that adverse outcomes were not associated with any specific form of delivery (C-section vs. vaginal delivery). C-section was two times more common than vaginal delivery and preferentially done in patients with higher catecholamine levels. The authors concluded that the mode of delivery was not a major determinant of adverse outcomes [3].

Vaginal delivery can be elected when adequate α-blockade is achieved, under epidural anesthesia to prevent the stress from pain, and in multiparous women with a likely short second stage of labor (period of active pushing and stress). However, oxytocin should be used with caution as it may elicit tachycardia and hypotension. On the other hand, C-section allows a more controlled environment, but as for any other surgery, blood loss and manipulation of the peritoneum can trigger catecholamine release. A dedicated multidisciplinary team should be involved to determine the optimal timing and route of delivery taking into consideration the obstetric history (parity and route of previous deliveries), maternal and fetal conditions, response to medical treatment, and the patient's preference [7, 11].

When adrenalectomy has been performed successfully before delivery (second trimester), timing and route of delivery depend solely on obstetric indications [10].

Follow-Up

Lifelong follow-up in patients with surgically resected pheochromocytoma is suggested to detect recurrent or metastatic disease, particularly when there is a known pathogenic genetic mutation. Annual biochemical testing, followed by imaging in case of positive results, is suggested [8, 16].

Effects of Preoperative Medication on Neonates During Lactation

When pheochromocytoma excision is planned for after delivery, breastfeeding can occur while taking preoperative medications. Less than 1% of phenoxybenzamine is present in maternal milk, and the potential effects on the neonate are unknown [8, 12]. A single case report indicates <0.1% of doxazosin in the breast milk without evident effects in the neonate [23]. Propranolol is considered safe during lactation by the American Academy of Pediatrics [24].

Lessons Learned

1. Although pheochromocytoma in pregnancy is rare, it should be considered in women with severe, labile, and paroxysmal hypertension (especially if present before gestational week 20). Other suspicious factors during pregnancy are resistant hypertension, peripartum cardiomyopathy, and/or orthostatic hypotension (not clinically explained by volume depletion).

2. Prepartum detection of pheochromocytoma significantly reduces maternal and fetal mortality due to the institution of adequate treatment before delivery.
3. Preeclampsia is associated with proteinuria (≥300 mg in a 24-hour urine specimen), weight gain, and edema, which are usually absent in pheochromocytoma.
4. Biochemical diagnosis is based on plasma metanephrines, 24-hour urinary fractionated metanephrines, and catecholamines with the same reference values as nonpregnant women.
5. MRI without gadolinium is the imaging study of choice during pregnancy to localize the tumor.
6. Genetic testing should be considered for all pregnant women with pheochromocytoma.
7. As in the general population, treatment of pheochromocytoma in pregnancy is based on adrenergic receptor blockade and volume repletion followed by surgical excision of pheochromocytoma, which is the definitive treatment.
8. The foundation of pre-surgical preparation is α-blockade with phenoxybenzamine or doxazosin for at least 10–14 days before surgery. Both are considered fetal risk category C, but only phenoxybenzamine is known to cause hypotension and respiratory depression in the neonate.
9. If tachycardia develops, a β-blocker should be started several days after initiation of α-blocking agents. The most common β-blockers used in pregnancy are propranolol and atenolol. β-Blockers are considered fetal risk category C, except for atenolol being category D. They should not be used for an extended period of time because of associated intrauterine growth retardation.
10. Calcium channel blockers (nifedipine or nicardipine) can be considered when hypertension is not fully controlled with an α-adrenergic blocker and no tachycardia is present. They are considered fetal risk category C.
11. When surgical adrenalectomy is necessary, the second trimester is the optimal time to conduct the operation via a lateral laparoscopic transperitoneal/transabdominal approach. When the resources or ability to conduct a safe adrenalectomy are not available, medical therapy with adrenergic receptor blockade can be considered throughout pregnancy with the aim of tumor removal concomitantly with C-section or 2–6 weeks postpartum.
12. Both C-section and vaginal delivery are considered safe in pregnant women with pheochromocytoma, and the delivery method should be tailored to each individual case.
13. As in the general population, pregnant women with a removed pheochromocytoma require lifelong follow-up with annual biochemical testing, followed by imaging in case of positive laboratory results, especially if they are known to have an inheritable genetic syndrome predisposing them to pheochromocytoma.
14. Phenoxybenzamine, doxazosin, and propranolol are considered safe during breastfeeding in the event a surgical excision of pheochromocytoma is planned for after delivery.

Questions

1. Which of the following is false regarding the biochemical diagnosis of pheochromocytoma:

   A. The biochemical diagnosis of pheochromocytoma in pregnancy is based on the results of plasma-free fractionated metanephrines and 24-hour urinary fractionated metanephrines and catecholamines, with the same reference values as nonpregnant women.
   B. Metanephrines are more sensitive when compared to the parent catecholamines (epinephrine, norepinephrine).
   C. Metanephrine assays should be based on high-performance liquid chromatography with tandem mass spectroscopy (LC-MS/MS) methodology to ensure reliable interpretations.
   D. Gestational hypertension and preeclampsia, which are the most common causes of hypertension in pregnancy, have high levels of plasma and 24-hour urinary fractionated metanephrines.

2. Which of the following is false about the pre-surgical medical management in pregnant patients with pheochromocytoma:

   A. The foundation of pre-surgical preparation is α-blockade for at least 10–14 days before surgery.
   B. Phenoxybenzamine and doxazosin are both considered fetal risk category C.
   C. Satisfactory α-blockade reduces fetal and maternal mortality.
   D. A β-blocker should be started before initiation of α-blocking agents.

3. Select the false statement regarding surgical removal of pheochromocytoma in pregnancy:

   A. When surgical adrenalectomy is necessary, the second trimester is the optimal time to conduct the operation.
   B. During pregnancy, a lateral laparoscopic transperitoneal/transabdominal approach is contraindicated.
   C. A left lateral position for right adrenal extirpation is easier for the anesthesiologist to handle due to positional decompression of the inferior vena cava from the enlarged uterus.
   D. After tumor removal, there is risk to develop hypotension and hypoglycemia.

Answers to Questions

1. D. Gestational hypertension and preeclampsia, which are the most common causes of hypertension in pregnancy, have high levels of plasma and 24-hour urinary fractionated metanephrines.
2. D. A β-blocker should be started several days before initiation of α-blocking agents.
3. B. During pregnancy, a lateral laparoscopic transperitoneal/transabdominal approach is contraindicated.

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Chapter 37
Diagnosis and Management of Thyroid Cancer in Pregnant Women

Sun Y. Lee and Elizabeth N. Pearce

Objectives

1. Review the evaluation of thyroid nodules found in pregnant women.
2. Identify treatment and management options for differentiated thyroid cancer when newly diagnosed during pregnancy.
3. Discuss considerations around timing of radioactive iodine treatment in the postpartum period.
4. Describe tumor surveillance and management strategies in pregnant women who are thyroid cancer survivors.

Case Presentation

A 30-year-old woman with no significant past medical history was referred to endocrine clinic for evaluation of a newly diagnosed thyroid nodule. She was 15 weeks pregnant and had noticed nontender anterior right neck enlargement over the prior 2–3 months. Her only medication was a prenatal vitamin. She denied any dysphagia, orthopnea, or voice changes. She had no symptoms suggestive of thyroid dysfunction, such as palpitations, hand tremor, heat or cold intolerance, or menstrual irregularity prior to conception. She had no personal history of radiation treatment or any family history of thyroid cancer or thyroid disease. On physical exam, her vital signs were normal, and the only significant finding was a palpable firm 2 cm nodule in the right thyroid lobe.

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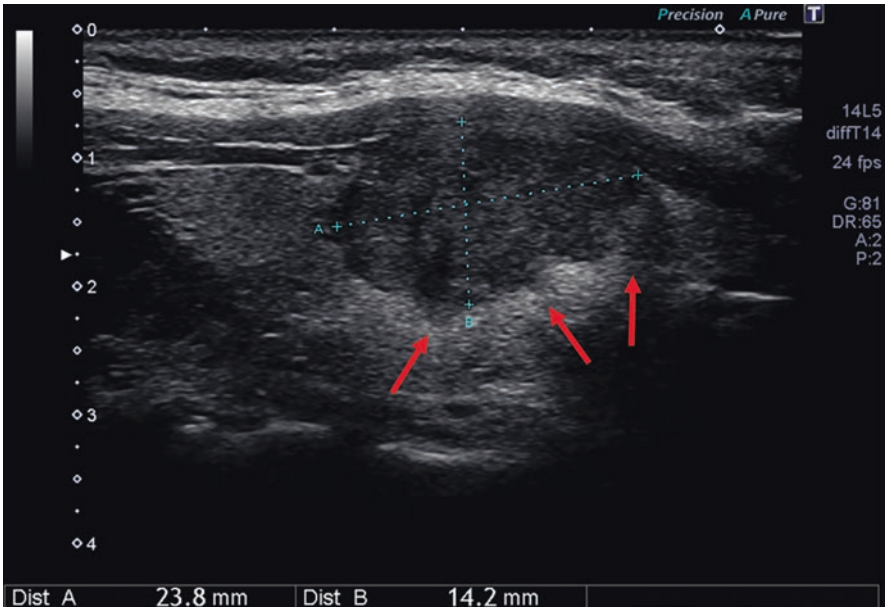

Fig. 37.1 Ultrasound image of the thyroid nodule. A sagittal image of the thyroid nodule shows a hypoechoic solid nodule measuring 2.4 cm, which has irregular borders (arrows)

Her serum TSH level was normal at 0.84 mIU/L. Thyroid ultrasound showed a diffusely enlarged thyroid gland with a single 2.4 cm hypoechoic solid nodule in the right mid lobe (Fig. 37.1). This nodule had irregular borders with possible extrathyroidal extension. There were no microcalcifications or intranodular vascularity. No significant adenopathy was noted in the bilateral cervical neck. Given the ultrasound findings of a nodule with a high suspicion for malignancy, her endocrinologist discussed options for the timing of fine-needle aspiration (FNA) biopsy and, if needed, thyroid surgery. The patient chose to undergo FNA biopsy of the 2.4 cm thyroid nodule 2 weeks later. This was read as Bethesda VI (papillary thyroid cancer) with a positive BRAF V600E mutation.

After further discussion, the decision was made to postpone thyroidectomy until after delivery. Repeat thyroid ultrasound done 1 month after delivery showed a 2.5 cm hypoechoic nodule in the right mid lobe that was invading adjacent strap muscle. There were two small reactive lymph nodes in bilateral level VI, but no likely malignant nodes were noted. The patient underwent total thyroidectomy with central neck dissection 2 months after delivery. Surgical pathology confirmed a 2.4 cm classical-type papillary thyroid cancer without margin involvement, but with focal angioinvasion, lymphatic invasion, and extrathyroidal extension to the strap muscles. Four out of six level VI lymph nodes removed were positive for papillary thyroid cancer. She was staged as American Joint Committee on Cancer (AJCC) 8th stage 1 (age < 55 and pT3bpN1aMx) [1]. The American Thyroid Association (ATA) initial risk for recurrence for this patient was intermediate [2]. She weaned her

infant, who had been breastfeeding, to allow for radioactive iodine (RAI) adjuvant therapy with 100 mCi I-131 following recombinant human thyrotropin (rhTSH) injection 3 months after the thyroid surgery.

Thyroid Nodules and Thyroid Cancer in Pregnant Women

Human chorionic gonadotropin (hCG) has a weakly thyrotrophic effect on the thyroid gland. This can lead to a slight increase in the size of the thyroid gland and in the size of preexisting thyroid nodules during gestation. Thyroid nodules have been reported in up to one-third of pregnant women, depending on regional dietary iodine intakes [3, 4]. Higher age and parity are associated with a higher incidence of thyroid nodules in pregnancy. The prevalence of thyroid cancer in pregnant women is unclear, as most previous studies have been done at tertiary referral centers where the prevalence is likely higher than that in the general population. However, there has been an overall increase in diagnoses of differentiated thyroid cancer, including in women of reproductive age, over the last three decades [5].

Workup of Thyroid Nodules in Pregnant Women

When a palpable thyroid nodule is found during physical exam, thyroid ultrasound should be performed to assess nodular characteristics. Criteria for determining whether a thyroid nodule should be biopsied in pregnancy are the same as in non-pregnant adults, taking into account features including nodule size and shape, echogenicity, evidence of extranodular or extrathyroidal invasion, and the presence of microcalcifications [2]. TSH levels usually decrease in early pregnancy, as stimulation from hCG increases thyroid hormone production, which, in turn, feeds back and causes decreased TSH secretion by the pituitary gland. Therefore, the ATA recommends using a serum TSH reference range of 0.1–4 mIU/L in pregnancy when pregnancy- and assay-specific reference ranges are not available [3]. Autonomous nodules are unlikely to be malignant. Nucleotide thyroid scans are contraindicated during gestation and thus cannot be used to assess for nodular autonomy in pregnancy. If the serum TSH remains suppressed beyond 16 weeks of gestation without evidence of Graves' disease, suggesting a toxic nodule, FNA biopsy can be deferred until after pregnancy.

FNA biopsy is generally low risk and is safe during pregnancy. However, given the anxiety that can be engendered by the procedure or by learning of a new malignancy, some women prefer to defer FNA biopsy until after delivery. Based on retrospective studies, this appears safe in most cases. In a retrospective cohort which included 61 women with thyroid cancer diagnosed during pregnancy, outcomes (including the proportion treated with RAI postoperatively, cancer recurrence, and distant metastases) over a mean 22.5 years of follow-up did not differ between the

14 women who opted for thyroid surgery during pregnancy, the 47 who deferred surgery until after delivery, and 528 age-matched controls who were not pregnant at the time of cancer diagnosis [6]. A Korean study of 19 women who were diagnosed with micropapillary thyroid cancer just before or during the first trimester of pregnancy showed no significant increase in tumor volume or development of malignant lymph nodes during pregnancy [7]. Among 50 Japanese women undergoing active surveillance for low-risk papillary cancer, pregnancy was associated with an increase in tumor size in only 8%, and no patients developed nodal metastases [8]. Thus, timing of FNA should be determined based on the clinical assessment and patient preference.

If cytopathology is benign, thyroid nodules in pregnant women can be managed the same way as in nonpregnant adults with benign results. If cytology is read as atypia of undetermined significance (AUS) or a follicular lesion of undetermined significance (FLUS), repeat FNA biopsy is typically recommended. Molecular testing for cytologically indeterminate nodules has not been adequately studied in pregnant women and is currently not recommended because of possible alteration in nodule RNA expression from gestational thyroid stimulation. Repeat FNA can be deferred until after delivery unless there is sonographic evidence suggestive of an aggressive cancer, in which case surgery during pregnancy can be considered [3].

Management of Thyroid Cancer in Pregnancy

Given the lack of evidence of cancer progression in most women, patients with newly diagnosed differentiated thyroid cancer in early pregnancy can be followed with serial thyroid ultrasound. If cancer grows substantially before 24–26 weeks of gestation or if there is evidence of metastatic disease such as cytologically malignant cervical lymph nodes, surgery should be considered during pregnancy [3]. However, if the tumor remains stable until the second half of pregnancy, surgery may be deferred until after delivery. When surgery is needed during pregnancy, it is best performed during the second trimester to avoid potential teratogenic effects of anesthesia during the first trimester and potential risk of inducing preterm labor in the third trimester. If surgery is deferred, there is no clear evidence that thyroid suppressive therapy with levothyroxine is effective in decreasing thyroid nodule or tumor size or improves the prognosis of differentiated thyroid cancer.

Pregnancy may increase tumor aggressiveness by hCG stimulation of TSH receptor and by stimulation of estrogen receptor, which is expressed in some differentiated thyroid cancers [9]. Two retrospective Italian studies have examined whether the diagnosis of differentiated thyroid cancer during or around the time of gestation alters outcomes. One study of 123 women reported that diagnosis during or within 1 year after pregnancy was associated with a much higher risk for persistent or recurrent disease (60%) than diagnosis more than a year postpartum (4%) or diagnosis in women who had never been pregnant (13%) [9]. However, disease persistence/recurrence was defined by elevated serum

thyroglobulin levels, and if pregnancy had influenced the completeness of the initial thyroid surgery, this may have confounded study results. The other study, which included 340 women, also reported a higher risk for persistent or recurrent disease when women were diagnosed during or within 2 years after pregnancy (10.5%) compared to women who were diagnosed at least 2 years after delivery (1.3%) or women without a history of pregnancy (4.7%) [10]. Tumor persistence/recurrence was not clearly defined, but likely was based on serum thyroglobulin. Delaying surgery until after delivery did not appear to influence risk in either of these cohorts.

The impact of pregnancy on medullary or anaplastic thyroid cancer has not been well studied. However, given the more aggressive disease course of these tumor types, surgery should be strongly considered when medullary or anaplastic thyroid cancer is newly diagnosed during pregnancy.

Postpartum Considerations

RAI is concentrated in breast tissue via the sodium-iodine symporter, which is expressed in the lactating mammary gland. Therefore, ensuring cessation of breastfeeding prior to RAI treatment will protect maternal breast tissue from adverse radiation effects and the infant from ingesting I-131 through breast milk. If RAI treatment is indicated after thyroidectomy, it is recommended to completely stop breastfeeding 6 weeks to 3 months prior in order to allow regression of lactation-induced sodium-iodide symporter expression [11].

Management Considerations in Pregnant Thyroid Cancer Survivors

Having a history of treated thyroid cancer is not a reason to forgo pregnancy. During pregnancy, tumor surveillance strategies should be informed by the ATA disease response category [2]. In a single-center retrospective study which included 235 women with differentiated thyroid cancer who had a term pregnancy following initial cancer treatment, evaluation at 3–12 months postpartum demonstrated that none of the 197 women who had an ATA excellent, indeterminate, or biochemical incomplete response to therapy before pregnancy had developed structural disease [12]. However, 11 of the 38 women with a prepregnancy structural incomplete response to therapy had at least a 3 mm increase in tumor size or new metastases after delivery, with three of these women having disease progression which required additional treatment. Women with an ATA excellent or indeterminate response to therapy do not need additional ultrasound and thyroglobulin monitoring during gestation, but closer surveillance in pregnancy is reasonable in women with a known incomplete therapeutic response.

Mild hyperthyroidism in pregnancy is not associated with adverse obstetric outcomes [13], and it is, therefore, safe to maintain TSH-suppressive levothyroxine dosing during gestation. Serum TSH targets in pregnancy are the same as they are outside the pregnancy setting. Due primarily to the increased levels of circulating thyroxine-binding globulin in pregnancy, most women will need a levothyroxine dose increase to maintain targeted serum TSH values. Levothyroxine doses should be empirically increased by 25–30% as soon as pregnancy is confirmed, and serum TSH should be assessed every 4 weeks through mid-gestation [3].

Lessons Learned

1. Thyroid nodules and differentiated thyroid cancer are common in women of childbearing age.
2. FNA biopsy is safe and can be performed in all trimesters of pregnancy. However, some women prefer to defer biopsy until after delivery, and timing of FNA biopsy of suspicious thyroid nodules should be individualized.
3. Serum TSH levels may be low in early pregnancy. If the TSH remains suppressed after 16 weeks of gestation in the presence of a suspicious nodule, FNA biopsy can be deferred until after delivery when radioactive iodine scanning can be performed to determine whether the nodule is autonomously functioning.
4. Surgery for differentiated thyroid cancer can be deferred until after delivery in most women, particularly if cancer is newly diagnosed in the second half of pregnancy or remains stable through mid-gestation.
5. The second trimester is the safest period if thyroid surgery is needed during pregnancy.
6. RAI treatment, if indicated, is contraindicated in pregnancy and should be deferred until 6 weeks to 3 months after cessation of breastfeeding.
7. Serum TSH targets are the same for pregnant women as they are outside the pregnancy setting.
8. Tumor surveillance strategies are not changed in pregnant women with an excellent or indeterminate response to therapy, but more intensive monitoring with ultrasound and serum thyroglobulin is needed in women with a structural incomplete response to therapy.

Questions

1. What is the best initial step in evaluating a palpable thyroid nodule noted on physical exam in a euthyroid pregnant woman?

   (a) CT scan of the neck
   (b) Thyroid ultrasound
   (c) Nucleotide thyroid scan
   (d) FNA biopsy of the thyroid nodule

2. Which of the following is true regarding evaluation of thyroid nodules in pregnant women?

   (a) FNA biopsy of thyroid nodules is unsafe during gestation
   (b) FNA biopsy of thyroid nodules should only be performed during the second trimester of pregnancy

(c) FNA biopsy of thyroid nodules can be postponed until after delivery if the maternal TSH level is suppressed without evidence of Graves' disease
(d) Molecular marker testing should be used to assess malignancy risk in pregnant women with indeterminate FNA biopsy results

3. In a woman with a history of low-risk papillary thyroid cancer who has achieved an ATA excellent response to therapy, which of the following statements is NOT correct?

(a) Serum TSH should be kept between 0.5 and 2 mIU/L during pregnancy
(b) A serum thyroglobulin level should be checked every 3 months during pregnancy
(c) Surveillance neck ultrasound is not necessary during pregnancy
(d) The risk of thyroid cancer recurrence during pregnancy is low

Answers to Questions

1. B
2. C
3. B

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Part X
Type 2 Diabetes Mellitus

Chapter 38
Introduction to Type 2 Diabetes Mellitus

Hanna J. Lee

Diabetes mellitus is a growing global epidemic with a prevalence of 9.3%, affecting 463 million people worldwide [1]. In the United States, 10.5% of the population is estimated to have diabetes, of which 95% have type 2 diabetes mellitus (T2DM). Of the population, 34.5% is approximated to have prediabetes [2]. In 2018 alone, the incidence of newly diagnosed diabetes rose to 1.5 million. Nationally, diabetes is a major cause of premature morbidity and is the seventh leading cause of death [3]. It imposes a heavy burden on healthcare resources, economic costs, and personal quality of life. Diabetes also accounts for 25% of hospital inpatient days and for one in every four US healthcare dollars spent [4].

The increasing prevalence of T2DM mirrors the growing epidemic of obesity in the modern world. Of the US adults with diabetes, 89% are overweight or obese [2]. The underlying pathophysiology of T2DM is insulin resistance and relative insulin deficiency, precipitated by a complex interplay of genetic and environmental factors. Obesity and sedentary lifestyles are prominent causes of peripheral insulin resistance. The subsequent metabolic abnormalities lead to sustained hyperglycemia and chronic inflammation [5]. T2DM may initially be a silent, asymptomatic disease; in fact, 7.3 million US adults are estimated to be unaware of their diagnosis of diabetes. Over time, especially if left uncontrolled, various vascular complications can occur. Diabetes is the primary cause of end-stage renal disease and new-onset blindness in the United States and increases the risk of cardiovascular disease by at least twofold [6].

The prevention and early diagnosis of T2DM are critical to controlling the diabetes epidemic. Regularly testing for diabetes in all adults and, in particular, high-risk populations is recommended. Effective education that empowers the patient and

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leads to weight loss through dietary modifications and increased physical activity is absolutely an essential component to its successful prevention and treatment [7]. Annual screening for microvascular complications and proactive reduction of atherosclerotic cardiovascular disease (ASCVD) risk factors, such as hypertension and hyperlipidemia, are equally essential. Appropriate and timely initiation of pharmacological medications that are tailored to the patient's individualized glycemic targets and comorbidities must be considered.

The following T2DM patient cases describe clinical scenarios commonly encountered in the outpatient office and in the hospital. The recommendations and evidence behind the diagnostic criteria, risk factor modifications, glycemic targets, and inpatient and outpatient management of T2DM are reviewed. The new pharmacotherapy agents, the data behind their cardiorenal protective effects, and the use of continuous glucose monitoring are also discussed. As new therapeutic agents and technology continue to emerge, diabetes care has shifted from a simple HbA1c-driven approach to a patient-centered approach.

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Chapter 39
Initial Diagnosis and Management of Type 2 Diabetes Mellitus

Nisha Suda and Hanna J. Lee

Objectives

1. To review the risk factors that lead to the development of type 2 diabetes
2. To review the methods of diagnosis for prediabetes and type 2 diabetes
3. To review evidence-based outpatient glycemic goals, time-in-range (TIR) targets, and the available technologies for glucose monitoring
4. To review preventative screening and management of the macro- and microvascular complications associated with type 2 diabetes

Case Description

A 53-year-old man with prediabetes (PreT2DM) and hypertension presents for glucose and weight management after being informed his Hba1c was 6% last year. His past medical history is notable for hypertension, diagnosed 2 years ago, for which he takes amlodipine 5 mg daily. His family history is significant for a mother with type 2 diabetes (T2DM), hypertension, and high cholesterol. His father passed away from a sudden cardiac arrest of unknown cause at the age of 46. His older sister has hepatosteatosis and high cholesterol. He denies any history of tobacco use, alcohol consumption, or illicit substance use. He is married with two healthy children and works as an internet cable installer.

He endorses a 10 lbs. weight gain in the past year which he attributes to eating fast food daily. He states that his wife tells him he snores. He denies polyuria, polydipsia, polyphagia, easy bruising, or purple striae.

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He is 5′11″ tall and weighs 116 kg with a BMI of 35.57 kg/m^2. BP is 156/84 mmHg, HR 86 beats per minute, RR 16, and temperature 98.1 °F. On physical exam, he is well appearing with central obesity but without any cushingoid or acromegalic features. Dark, velvety skin changes are noted under his axillae. Cardiovascular and lung exams are unremarkable. He does not have peripheral edema and has 2+ dorsalis pedis pulses bilaterally as well as normal sensation to 10 g monofilament testing. No skin breakdown is noted on his feet.

Repeat laboratory data reveals an Hba1c of 7%; fasting plasma glucose of 250 mg/dL; and otherwise normal chemistry, liver function tests, and CBC. Urine microalbumin/creatinine ratio is 5 mcg/mg, and fasting lipid panel shows a total cholesterol of 215, triglycerides 336, HDL 36, and LDL 112 mg/dL.

He does not feel comfortable starting any new medications and asks what lifestyle changes he could make. He expresses concerns about his ability to check his finger-stick glucoses while at work. He already has a referral to see an ophthalmologist and a nutritionist, and he was advised to sign up for online diabetes self-management education and support (DSMES) classes.

Who Should Be Screened for T2DM?

T2DM develops when there is increased insulin resistance at the level of the peripheral tissues for which endogenous insulin secretion is unable to adequately compensate. This tissue-level dysfunction is the initial metabolic derangement of glycemic dysregulation, resulting in hyperglycemia and eventual progression to T2DM [2]. The onset and degree of metabolic dysfunction differ across populations due to the variable influence of environmental factors on genetic predispositions. It is therefore important to identify specific factors that contribute to metabolic imbalance and the development of insulin resistance. Commonly implicated modifiable risk factors for developing glycemic dysregulation include obesity, sedentary lifestyle, and a diet high in fat and processed simple sugars. Other risk factors are steatohepatitis, older age, and polycystic ovarian syndrome (PCOS). Specifically, the conglomeration of dyslipidemia, obesity, and high blood pressure, called metabolic syndromesyndrome, infers an increased risk of T2DM, cardiovascular disease and stroke [3].

As a result of progressive metabolic dysfunction, there is a slow and gradual rise in serum blood glucoses during which patients may initially be asymptomatic. This initial impaired glucose tolerance and elevated fasting glucose levels are formally categorized as pre-type 2 diabetes (PreT2DM). Not only does PreT2DM carry an increased risk of cardiovascular disease, if untreated, it portends a 5–10% annual rate of progression to T2DM [4, 5]. In order to make an early diagnosis, patients

should have risk-based screening performed by their clinician as outlined by the American Diabetes Association [6]. Overweight adults with a BMI ≥25 kg/m^2 (or BMI ≥23 kg/m^2 if Asian American) who have metabolic syndrome and any of the other abovementioned risk factors or are in a high-risk ethnic group (Native American, African American, Latino, Asian American, Pacific Islander) are recommended for T2DM screening. Other screening criteria for overweight adults include a personal history of hypertension or cardiovascular disease, a first-degree relative with diabetes, a prior history of gestational diabetes, and overweight women who are planning to conceive. The remainder of adults should be screened starting at age 45 and at 3-year intervals if the initial screening is negative.

How Is T2DM Diagnosed?

A reasonable pretest probability for insulin resistance or T2DM should prompt screening. Specific physical exam findings can provide additional clues to the diagnosis of T2DM. Compared to the autoimmune-mediated type 1 diabetes (T1DM), T2DM patients traditionally have an older age of diabetes onset and have central adiposity, steatohepatitis, and/or acanthosis nigricans. The development of the dark, velvety skin changes of acanthosis nigricans occur due to the dermal fibroblast proliferation that is triggered by hyperinsulinemia and the subsequent activation of keratinocyte insulin-like growth factor receptors [7]. On the other hand, T1DM patients are typically lean and do not have insulin resistance; there are indeed overweight or obese T1DM patients, but the insulin resistance, if present, is not the initial, underlying cause for the diabetes.

Screening for insulin resistance and diabetes includes measuring the glycated hemoglobin (Hba1c), fasting plasma glucose (FPG), or plasma glucose levels 2 hours after a 75 g oral glucose load (oral glucose tolerance test or OGTT). Specifically, an FPG level of ≥126 mg/dL, a 2-hour OGTT ≥200 mg/dL, or an Hba1c of ≥6.5% are the diagnostic cutoffs for T2DM. These criteria, set by the ADA, are derived from the greater risk of microvascular complications, particularly retinopathy, associated with values above these thresholds [8, 9]. In addition, patients who display signs and symptoms of hyperglycemia with a concurrent random plasma glucose of ≥200 mg/dL are also diagnosed with T2DM. As noted above, the progression of glucose dysregulation is on a continuum, and recognizing PreT2DM as a harbinger for T2DM is important for early intervention. PreT2DM is diagnosed with an Hba1c of 5.7–6.4%, an FPG between 100 mg/dL and 125 mg/dL, or a 2-hour 75 g OGTT glucose level between 140 mg/dL and 199 mg/dL. For those who have PreT2DM, repeat screening for progression to diabetes should be done annually (Table 39.1).

Table 39.1 Diagnostic criteria for PreT2DM and T2DM. [a]Fasting = no caloric intake for 8 hours. OGTT oral glucose tolerance test (plasma blood sugar level 2 hours after receiving a glucose load)

	PreT2DM	T2DM
Hba1c	5.7 - 6.4%	≥6.5%
Fasting* plasma glucose	100 - 125 mg/dL	≥126 mg/dL
2-hr 75g OGTT**	Plasma glucose 140 - 199 mg/dL	Plasma glucose ≥200mg/dL
Random plasma glucose		signs and symptoms of hyperglycemia + concurrent plasma glucose ≥200 mg/dL

What Are the Evidence-Based Optimal Glycemic and HbA1c Targets for T2DM?

Several landmark studies have assessed how various degrees of glycemic control impact the short and long-term sequelae of diabetes; the data gathered from these studies lay the foundation from which glycemic targets have been set. The Diabetes Control and Complications Trial (DCCT) [10] assessed the impact of intensive insulin therapy versus standard therapy on the development of microvascular and macrovascular complications among T1DM patients with a mean age of 27 years old. Over the 6.5-year study period, patients in the intensive therapy group were treated with a more aggressive insulin regimen and had close, monthly medical follow-ups. They achieved a mean Hba1c of 7.2% with a mean glucose of 155 mg/dL compared to an Hba1c of 9.1% with mean glucose of 231 mg/dL in the standard care cohort. The intensive insulin therapy group demonstrated a 76% risk reduction in the development of retinopathy, a 54% risk reduction in the progression of retinopathy, a 50% risk reduction in the development of diabetic kidney disease, and a 60% reduction in the development of sensory-motor diabetic nerve disease. There were, however, a statistically significant greater number of hypoglycemia events in the intensive group: 62 versus 19 episodes per 100 patient-years. No significant evidence was found to support a decrease in macrovascular complications, presumed to be due to the short time frame of the study and the young age of the patients. These cohorts were subsequently followed for an additional 11 years in the DCCT posttrial extension study, Epidemiology of Diabetes Interventions and Complications (EDIC), in order to evaluate the long-term macrovascular complications [11]. In the group that continued intensive insulin therapy, there was a 57% risk reduction in cardiovascular (CV) events, including nonfatal myocardial infarction (MI), stroke, and CV death. Toward the end of the EDIC trial, the Hba1c levels between the groups were not statistically different. Nonetheless, it was found that there was still

an ongoing risk reduction in microvascular complications in the cohort that comprised the original DCCT intensive therapy group. This revelation suggested that there was some "metabolic memory" that had developed as a result of initial tight glycemic control.

Many of the findings from these T1DM trials have since been applied to T2DM. In the UK Prospective Diabetes Study (UKPDS 33) [12], 3867 newly diagnosed T2DM patients with a mean age of 53 years underwent 3 months of dietary education prior to randomization to either the intensive therapy arm, treated with insulin or sulfonylureas, or the standard of care arm. After an average follow-up of 10 years, the intensive therapy group achieved a mean Hba1c of 7%, while the standard of care group achieved a mean Hba1c of 7.9%. Although there was a 25% reduction in microvascular complications in the intensively treated cohort, there was also a higher incidence of hypoglycemia events. No significant difference was found with regard to macrovascular complications. The UKPDS 34 trial randomized newly diagnosed, overweight T2DM patients to three different treatment arms: metformin versus dietary intervention versus insulin/sulfonylurea. Over the mean follow-up time of 10.7 years, the metformin group safely achieved a lower Hba1c of 7.4%, unlike the insulin/sulfonylurea group that experienced hypoglycemic events. Compared to the HbA1c of 8.0% achieved by the diet-controlled group, the metformin group also demonstrated a greater reduction in microvascular complications and all-cause mortality, suggesting that metformin is a safer and more effective first-line agent in the treatment of overweight T2DM patients [13].

Subsequent RCTs, including the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), corroborated these previous findings by implementing similar interventions among older T2DM patients who already had a history or a risk factor for vascular disease [14, 15]. After a median follow-up of 5 years, the intensive control cohort, assigned to sulfonylurea therapy, achieved an average HbA1c of 6.3%, whereas the standard control cohort achieved an HbA1c of 7%. Although the intensive cohort experienced a statistically greater number of hypoglycemia events, there was a 22% statistically significant reduction in microvascular complications, particularly nephropathy. No reduction in macrovascular events was found. The VADT enrolled a generally homogenous group of mostly Caucasian male military veterans with T2DM. The average age was 60 years, and the average baseline HbA1c was 9.4%. Patients in the intensive therapy group were treated with rosiglitazone with glimepiride or metformin and were treated additionally with insulin to reach an average HbA1c of 6.9%. The standard care therapy group reached an average HbA1c of 8.4%. Again, no difference in macrovascular complications, the primary outcome, was observed after 6 years of follow-up. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated similar decreases in microvascular complications in T2DM participants with tight glycemic control who achieved an HbA1c of 6.4% versus the participants with standard glycemic control who achieved an HbA1c 7.5%. Unexpectedly, a significant increase in all-cause mortality and CV-related death was notable in the intense

Table 39.2 Treatment goals for T2DM. ASCVD atherosclerotic cardiovascular disease

Glycemic Targets	• HbA1c < 7.0% • Preprandial glucose: 70 –130 mg/dL • Postprandial glucose: <180 mg/dL • Time in Range (TIR): 70%
Weight Loss	• ≥ 5% weight loss
Exercise	• ≥ 150 minutes/week of aerobic exercise
Screening for microvascular complications	• Baseline and annual urine microalbumin:creatinine ratio • Baseline and annual ophthalmologic retinal exam • Baseline and annual podiatry exam
Blood Pressure	• < 140/80 mmHg
10 – year ASCVD risk	*Primary Prevention if age 40-75years:* • If ASCVD risk <7.5%: Moderate intensity statin • If ASCVD risk ≥7.5%: High intensity statin *Primary Prevention if age <40 or >75 years:* • Consider statin therapy *Secondary Prevention if age ≤75 years:* • High intensity statin *Secondary Prevention if age >75 years:* • Moderate intensity statin
Aspirin Use	*Primary Prevention:* • If age ≤70 years with ≥1other major risk factor for CVD + benefit of therapy outweighs bleeding risk: consider low dose aspirin • If age > 70years: avoid aspirin *Secondary Prevention:* • Consider aspirin if benefit of therapy outweighs risk

glycemic control cohort. Due to these findings, the study was prematurely stopped after 3.5 years. Overall, the ACCORD trial suggests that there may be increased mortality associated with overly tight glycemic control [16, 17].

In light of the aforementioned major RCTs, the ADA recommends preprandial glucose targets of 70–130 mg/dL, postprandial glucose targets of <180 mg/dL, and an Hba1c goal of <7% (Table 39.2). These targets aim to safely mitigate the development of microvascular complications while avoiding the harms of hypoglycemia. Exceptions to the recommended glycemic goals may apply to certain populations. Pregnant women require stricter glycemic targets, and frail patients with multiple medical comorbidities may benefit from more lenient targets. For example, an HbA1c target of 8% (average glucose 183 mg/dL) is recommended for those with shorter life expectancy for whom the long-term benefits of tight glycemic control may not be realized [18].

What Is the Time in Range (TIR)?

Although the HbA1c is a useful marker for the average blood glucose over an extended period of time, it is unable to provide detailed information about hourly glycemic variability. Marked hyperglycemia in combination with hypoglycemia can average out to a normal Hba1c value and paint an inaccurate picture of a patient's true glycemic status. By gathering more data points from self-monitored blood glucose (SMBG) readings from a finger prick or glucose readings from a continuous glucose monitor (CGM), a series of data points are available for a more detailed assessment of a patient's glycemic pattern.

The ambulatory glucose profile (AGP) provides detailed minute-to-minute blood glucose data from which a patient's "time in range" (TIR), or actual percentage of time a patient spends within their specified glycemic target range, can be determined [19]. In 2019, an international group of CGM experts reviewed CGM and DCCT data to determine the TIR that corresponds to a safe reduction in microvascular complications. Specifically, a TIR was determined for the glycemic target of 70–180 mg/dL based on DCCT data. Each 10% lower TIR was associated with a 64% increase in progression of retinopathy and 40% increase in development of microalbuminuria [20]. A TIR of 65% and 70% corresponded to an Hba1c of 7% and 6.5%, respectively [21]. It was determined that a 10% change in the TIR corresponds to approximately a 0.5% change in the Hba1c in the same direction [22, 23]. Based on these deductions, the ADA recommends a TIR goal of 70% (Table 39.2).

What Is the Utility of Continuous Glucose Monitoring in T2DM?

CGMs provide rapid and near-continuous glucose readings via a small subcutaneous catheter within the interstitial fluid. Due to the variations in the diffusion rate of glucose from the plasma to the interstitial fluid, the direct capillary-derived SMBG levels are truer to the actual blood glucose levels at any particular moment in time [22]. The currently available FDA-approved CGMs fall into two categories: the real-time CGM (rtCGM) and the intermittently scanned "flash" CGM. Both modes allow for the collection of numerous data points and provide an easier way to determine the TIR. By seeing near real-time glucose readings, T2DM patients can correlate these readings with dietary intake and physical activity to gain insight into their glycemic variability. The use of rtCGM has shown to be an effective technology for improving quality of life with statistically significant reductions in the distress and anxiety patients experience surrounding hypoglycemia [23].

A meta-analysis of 669 T2DM patients evaluated the changes in Hba1c and time spent in hypoglycemia between patients using CGM and SMBG. There was a significant HbA1c reduction of approximately 1% from baseline and a statistically significant reduction in the time spent in hypoglycemia in the patients using CGM

devices [24]. In a large multicenter RCT of T2DM patients using insulin, the use of a flash CGM, compared to SMBG finger pricks, was associated with a 43% reduction in the time spent in hypoglycemia [25]. CGMs have been approved by the FDA for outpatient use and are helpful tools, for both the patient and clinician to efficiently assess glycemic patterns and TIR.

What Are the Benefits of Weight Loss in T2DM?

T2DM treatment must include lifestyle modifications is to improve the modifiable variables that contribute to insulin resistance. Reduced caloric intake to achieve weight loss is the mainstay of dietary intervention. Based on meta-analyses, a minimum weight loss of 5% is recommended for all patients with T2DM to achieve any meaningful improvement in HbA1c, lipids, and blood pressure [26]. The Action for Health in Diabetes trial (Look AHEAD) implemented lifestyle interventions in obese T2DM patients to assess the role of weight loss in CVD risk [27]. An aggressive weight loss goal of 10% body weight and a physical activity goal of 175 minutes/week were set. No reduction in CVD was found, but the intervention group had a mean weight loss of 4.7% at 8 years and a reduction in Hba1c and required less insulin. Follow-up analysis revealed that 11.5% of the intensive intervention group transitioned from T2DM to PreT2DM in the first year, suggesting that early, intensive lifestyle modification can result in regression of T2DM [28, 29].

For many patients, battling weight regain is an ongoing challenge [30]. Meta-analyses have estimated that weight regain typically occurs within 5 years of completing a lifestyle intervention program. This can, however, be mitigated with long-term, structured weight loss programs that include dietary changes, physical activity, behavioral strategies, and access to support [31, 32]. One hundred fifty minutes weekly of brisk aerobic exercise was also found to be beneficial. Diabetes self-management education and support (DSMES) services have been effective in building patient empowerment and engagement with the healthcare team by integrating psychosocial support for both the patient and family. It has been shown that every additional 23.6 hours spent with a DSMES educator corresponds to a 1% decrease in Hba1c [33].

Micro- and Macrovascular Complications of T2DM

Retinopathy can begin as early as 7 years before the diagnosis of T2DM, and neuropathy can be seen in 1% of patients just 1 year after diagnosis [34, 35]. It is therefore essential to conduct comprehensive screening for microvascular complications

at initial evaluation. Initial tests include measurements of blood pressure, liver function tests, fasting cholesterol panel, basic metabolic panel, and the urine microalbumin/creatinine ratio. Through early screening, regular monitoring, and maintenance of appropriate glycemic control, the development of these various complications of T2DM can be slowed and even prevented (Table 39.2).

How Can Microvascular Complications Be Prevented and Managed?

Nephropathy

Uncontrolled hyperglycemia, potentiated by hypertension, can lead to chronic kidney disease (CKD). Not only is diabetic nephropathy the leading cause of end-stage renal failure in the United States, but also microalbuminuria is an independent risk factor for cardiovascular disease. Primary prevention of diabetic CKD relies on appropriate glycemic and blood pressure control and begins with annual screening for microalbuminuria. Once microalbuminuria, defined as a urine albumin/creatinine ratio of >30 mcg/mg, is detected, biannual screening is recommended. Additionally, an ACE inhibitor or an angiotensin II receptor blocker (ARB) can be initiated to slow the progression of glomerular damage. A 2006 Cochrane review found a 55% and 51% reduction in the progression to severely increased microalbuminuria with the use of ACE inhibitors and ARBs, respectively [36]. A newer class of diabetes medications that target the proximal nephron is SGLT2 inhibitors. In RCTs, this class of medications has demonstrated a significant reduction in the progression of renal disease in patients with and without T2DM [37].

Retinopathy

Diabetic retinopathy is a major ophthalmological complication of sustained uncontrolled hyperglycemia, hypertension, and hyperlipidemia. It is the most frequent cause of blindness in adults in the developed world and therefore requires at least annual screening from the time that T2DM is diagnosed [38]. Interestingly, although the phenomenon of "early worsening" of retinopathy can be seen with rapid glycemic improvement, this should not deter the proactive treatment of uncontrolled T2DM. The DCCT clearly demonstrated that most initial worsening of baseline retinopathy, within the first year of improved glycemia, had resolved by 18 months. Furthermore, a subsequent 74% long-term reduction in the progression of retinopathy was even observed in the intensive therapy cohort. Primary prevention of diabetic retinopathy involves effective glucose control.

Peripheral Neuropathy

Glycemic optimization is indispensable in the primary prevention of diabetic neuropathy. Annual assessment of peripheral pulses, pin prick sensation with a 10 g monofilament test, and vibratory sensation are recommended. Patients are encouraged to vigilantly self-monitor for any skin breakdown and foot deformities [39].

How Should CVD Risk Factors Be Managed in T2DM?

T2DM is an independent risk factor for cardiovascular disease and is incorporated into the American Heart Association's atherosclerotic cardiovascular disease (ASCVD) risk calculator which estimates the 10-year risk for MI or stroke [40]. Each 1% increase in Hba1c has been associated with a 1.2 relative risk increase for cardiovascular disease. Meta-analyses have confirmed this association by demonstrating an 18% increase in the risk of CVD events per every 1% increase in Hba1c [41].

Hypertension

Hypertension is a risk factor for developing T2DM and is an independent contributor to worsening nephropathy, retinopathy, autonomic neuropathy, and CV events. The UKPDS 36 trial revealed that the risk of T2DM complications was significantly increased in patients with higher blood pressures [42]. The ACCORD BP trial did not show a significant reduction in composite outcomes for CV death, nonfatal MI, or nonfatal stroke in patients with systolic blood pressures (SBPs) <120 mmHg versus those with SBP <140 mmHg. Meta-analyses, however, found that an SBP of <130 mmHg lowered the risk of stroke, retinopathy, and progression of albuminuria. No RCTs have assessed outcomes in T2DM patients specifically with the targeted BP of <130/80 mmHg, and as such, the current evidence-based BP target is less than 140/90 mmHg.

Hyperlipidemia

LDL cholesterol is an important predictor of ASCVD in T2DM. Initial recommendations for lipid management for all T2DM patients include effective diet and exercise. The ADA recommends fasting lipid panels at initial medical evaluation and, if less than 40 years old, every 5 years thereafter. More frequent assessments are needed for those who are older, are taking lipid-lowering therapy, or require secondary CVD prevention. Initiation and dose intensity of lipid-lowering medications, including statins, are based on an individual's 10-year risk for an ASCVD event. Moderate-intensity statins can

lower the LDL cholesterol by 30–49% and are indicated for the primary prevention of ASCVD in T2DM patients. High-intensity statins can lower the LDL cholesterol by more than 50% and are indicated for secondary prevention or primary prevention in patients with an ASCVD risk ≥7.5%. Statin use in T2DM patients younger than 40 years old or older than 75 years old can be considered on a case-by-case basis given the limited data. The addition of ezetimibe can provide additional LDL reduction especially for high-risk patients with a 10-year ASCVD risk ≥20%. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the addition of ezetimibe to a high-intensity statin in high-risk patients provided further significant reduction in LDL and a significant reduction in major adverse CV events [43]. PCSK9 inhibitor therapy can be used as an adjunct for further LDL reduction. Additionally, recent cardiovascular outcome trials have demonstrated that SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists provide CVD benefits.

Aspirin Use

Aspirin is recommended for secondary prevention in patients with established ASCVD. Its use in primary prevention needs to be individualized based on each patient's risk profile. The ASCEND Trial (A Study of Cardiovascular Events in Diabetes) randomized T2DM patients to either a low-dose aspirin or placebo. It found a 1.1% absolute risk reduction in serious vascular events and a 0.9% absolute increase in major bleeding [44, 45]. A low-dose aspirin is therefore recommended for primary prevention in T2DM patients, typically younger than 50 years of age, who are at increased risk for ASCVD and in whom benefits outweigh the risks of bleeding.

How Was Our Patient Diagnosed with T2DM and What Was the Initial Management?

Our patient had a strong pretest probability for having T2DM based on his numerous risk factors: metabolic syndrome, ongoing weight gain, family history of T2DM, and evidence of insulin resistance in the form of acanthosis on physical examination. Laboratory data revealed an Hba1c of 7%, confirming the diagnosis of T2DM. He had the necessary evaluations completed at the time of diagnosis, including evaluation of renal function (basic metabolic panel and urine microalbumin), fasting lipid panel, liver function, blood pressure, and foot exam for neuropathy. Patient had plans for diabetic retinopathy evaluation with an ophthalmologist and had already enrolled in DSMES classes. He did express concern about not being able to check his blood glucoses in light of his physically active job; therefore, a CGM would be an appropriate consideration. In addition to an ongoing, structured, intensive lifestyle intervention program that targets weight loss, this patient would also benefit from at least a moderate-intensity statin.

Lessons Learned

1. Risk-based screening for T2DM is recommended for all adults.
2. A time in range (TIR) of ~70% can decrease the development of microvascular complications. The use CGM technology allows for a more detailed assessment of glycemic variability and facilitates the achievement of recommended glucose targets.
3. Structured and supportive education programs, promoting lifestyle modifications and patient empowerment, are important to T2DM prevention and treatment.
4. Screening for long-term macro- and microvascular complications should begin at the time of T2DM diagnosis in order to implement appropriate interventions.

Questions

1. Which patient does NOT meet criteria for type 2 diabetes screening?

   A. 36-year-old (yo) South Asian woman with BMI of 23.5 kg/m^2 with a sedentary job
   B. 40 yo Latino man with BMI of 23.5 kg/m^2 with a sedentary job
   C. 39 yo Native American man with known prediabetes who lost 20 lbs. with lifestyle intervention in the past 3 years after his last medical exam
   D. 45 yo Caucasian gym trainer with history of premature ovarian failure
   E. None of the above. All should receive screening.

2. Which of the following patient glucose readings is closest to goal for diabetes management in an otherwise healthy adult?

   A. Hba1c 6.8%
   B. Preprandial SMBG readings 70–180 mg/dL 50% of the time
   C. Preprandial SMBG readings 70–130 mg/dL 70% of the time
   D. Bedtime blood sugars <150 mg/dL every night

3. Upon rapidly achieving significantly tighter glycemic control, which organ system may have acute worsening in function?

   A. Nerves
   B. Retina
   C. Kidney
   D. Heart
   E. Liver

Answers to Questions

1. B
2. C
3. B

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Chapter 40
Outpatient Management of Type 2 Diabetes Mellitus

Donna Lee and Joel Zonszein

Objectives

1. To review goals in the management of individuals with type 2 diabetes mellitus
2. To describe the best use of pharmacologic options and personalize pharmacotherapy according to patients' phenotypes and complications
3. To discuss the evolving focus of diabetes treatment: achieving strict glycemic control vs. preventing cardiovascular and renal complications
4. To discuss treat-to-target therapy, step-up therapy, and criteria for initiation of insulin therapy

Case Description

A 47-year-old man with history of hypertension (HTN) presents to the ED with chest pain after a stressful day at work. He never took any medications and also smokes. He has no family history of diabetes or premature cardiovascular death. He is 5′ 10″ tall and weighs 106.8 kg (BMI 33.7 kg/m^2). BP is 158/97, HR 109, RR 24, and SpO_2 89%. He appears anxious with labored breathing. He has acanthosis nigricans, jugular venous distension, S4 heart sound, inspiratory crackles in the left lower lung, hepatomegaly, and smooth shiny skin along his lower extremities with palpable pedal pulses. Initial workup shows normal electrolytes, creatinine 1.4 mg/dL, glucose 263 mg/dL, troponin 0.16 ng/mL, creatinine kinase 130 U/L, proBNP 1825 pg/mL, HbA1c 9.1%, total cholesterol 216 mg/dL, triglycerides 421 mg/dL, HDL 31 mg/dL, and LDL 119 mg/dL. EKG reveals ST elevations in the precordial

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leads, and chest X-ray shows a left-sided pleural effusion. Echocardiography reveals anterior wall hypokinesis with LVEF of 40%. He undergoes cardiac catheterization and stenting of the left anterior descending artery (LAD), which had 89% stenosis. Following a lengthy recovery, he is discharged on an optimized heart failure regimen that includes an angiotensin receptor blocker, diuretics, and a high-intensity statin. His antidiabetic regimen consists of Basaglar 52 units nightly and Humalog 16 units with each meal. Three months later, he presents for follow-up, feeling better. He is following a healthier diet and taking medications regularly but remains with hyperglycemia. His BP is 124/73, and repeat laboratory studies show an LDL of 58 mg/dL and an HbA1c of 8.8%.

Introduction

The landscape of diabetes care has been undergoing a rapid transformation with the emergence of new treatments and technology that can improve the health and well-being of people with diabetes. In spite of these advances, diabetes remains a major health crisis in terms of prevalence, morbidity, and costs. Changing cultural norms and behaviors pose a daunting challenge to sustaining a healthy lifestyle and preventing diabetes. Additionally, the delayed initiation of pharmacologic agents and clinical inertia contribute to progression of disease. Often, aggressive therapy is prescribed only after complications have already occurred. This "too much, too late" approach incurs a high cost for the treatment of complications rather than disease prevention, as is seen in the clinical case.

Studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT), are all attestations to the fact that intensive glycemic control at late stages of the disease is not effective for cardiovascular complications [1].

Pathophysiology

The pathophysiology of T2DM is complex. Hyperglycemia, the hallmark of diabetes, is a marker of severe metabolic dysfunction. An understanding of the different organs and hormones involved is critical for the proper management of individuals with T2DM. Insufficient insulin production and insulin resistance cause hyperglycemia and dysfunction of other metabolic and hormonal pathways (Fig. 40.1). In addition to pancreatic β-cell dysfunction, α-cells secrete excess amounts of glucagon despite the hyperglycemia and hyperinsulinemia, the two major factors that suppress glucagon secretion. The resulting inappropriate endogenous glucose production contributes to both fasting and postprandial hyperglycemia. Central obesity and adipocyte dysfunction are frequent in T2DM and are associated with abnormal

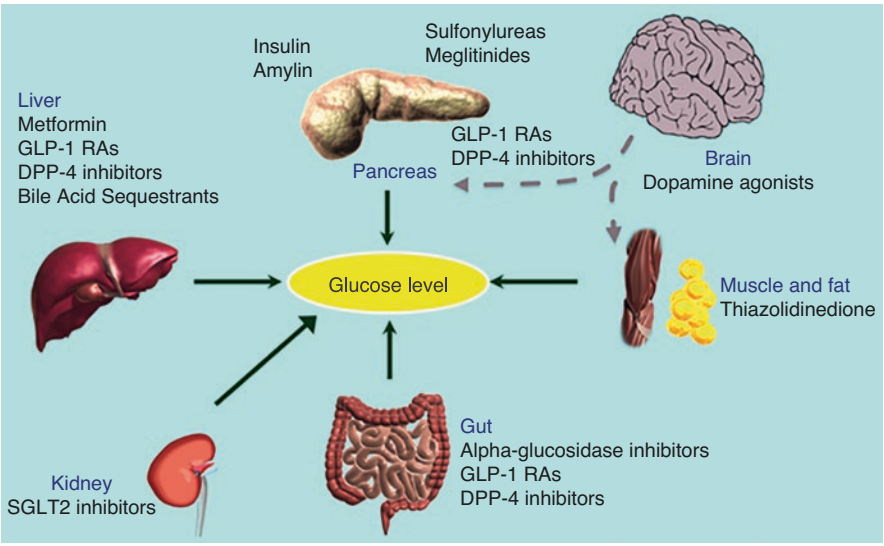

Fig. 40.1 Pathophysiologic abnormalities of the various organs that contribute to hyperglycemia in type 2 diabetes and how can they be targeted by different antidiabetic medications. Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor), glucagon-like peptide-1 receptor agonist (GLP-1 RA), sodium-glucose cotransporter 2 inhibitor (SGLT2 inhibitor)

circulating lipoproteins, high triglycerides, and low high-density lipoprotein (HDL). Adipose-driven recruitment of macrophages and release of abnormal adipokines and cytokines play a role in the low-grade cardiovascular inflammation found in T2DM.

In T2DM, the gastrointestinal tract exhibits abnormal secretion of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which account for 90% of the incretin effect that regulates insulin secretion and glucagon suppression. These incretin abnormalities particularly contribute to postprandial hyperglycemia in individuals with T2DM.

The kidneys also play a crucial role in glucose regulation by releasing glucose into the circulation via gluconeogenesis, particularly during the fasting state, and reabsorbing the filtered glucose. Both are adaptive mechanisms that ensure the availability of sufficient energy during fasting periods. The low-affinity, high-capacity glucose transport protein sodium-glucose cotransporter 2 (SGLT2) reabsorbs approximately 90% of the filtered glucose, while the high-affinity, low-capacity sodium-glucose cotransporter 1 (SGLT1) reabsorbs the remainder. A maladaptation in individuals with diabetes increases the expression and activity of SGLT2 in the proximal tubule causing increased glucose reabsorption and exacerbating the hyperglycemia.

Lastly, in T2DM and obesity, the normal negative feedback to the central nervous system by satiety signals from insulin and leptin is altered, further contributing to glycemic dysregulation.

In summary, multiple complex pathophysiologic disturbances involving different organs and endocrine and neurologic pathways contribute to hyperglycemia in T2DM (Fig. 40.1). Therefore, it is not surprising that combination therapy is necessary.

Treatment

Can Diabetes Be Prevented?

T2DM is a continuum preceded by prediabetes, a condition characterized by carbohydrate dysregulation and insulin resistance. Individuals with prediabetes tend to be more responsive to lifestyle interventions compared to those with long-standing, poorly controlled diabetes. Prediabetes, therefore, serves as a window of opportunity to prevent progression to T2DM. The Diabetes Prevention Program (DPP) showed that both metformin and intensive lifestyle changes are effective in reducing the incidence of T2DM [2].

How Can Patients Learn Diabetes Self-Care?

Well-structured programs, such as diabetes self-management education and support (DSMES), are crucial to patient education. Sporadic visits with a healthcare provider, who offers counseling on dietary changes, weight loss, and medications, while helpful, are less effective. By systematically teaching the information and skills needed for diabetes self-care and informed decision-making, structured DSMES programs have been shown to improve clinical outcomes and quality of life in a cost-effective manner [3].

How Has the Treatment Paradigm of T2DM Evolved?

Treatment of patients with T2DM requires a multidisciplinary approach. It is no longer glucocentric and needs to address all ASCVD risk factors, such as smoking, obesity, HTN, dyslipidemia, and antiplatelet therapy. As shown in the Steno-2 Study, the use of intensive multifactorial intervention to address modifiable risk factors such as hyperglycemia, hyperlipidemia, and HTN resulted in a 50% relative risk reduction of cardiovascular events with a gain of quality of life [4].

In recent years, guidelines have moved away from a “one size fits all” approach and toward a personalized, patient-centered approach [5]. Clinical inertia and the “too much, too late” approach of providing more intensive treatment after

complications have already occurred are changing to earlier tailored combination therapy. Following the results of cardiovascular outcome trials (CVOTs), the focus has shifted from stringent glycemic control to prevention or attenuation of atherosclerotic cardiovascular disease (ASCVD) and kidney disease. The aggressive use of hypoglycemic agents, especially in the elderly, simply to lower the A1c is discouraged due to the high risk of hypoglycemia [6].

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement emphasizes patient preference and individualized treatment. For instance, a younger individual with T2DM and comorbidities due to obesity should be treated with agents to improve glucose control together with medications that can also facilitate weight loss. Similarly, a person with T2DM, ASCVD, and early renal disease, like our patient in the case, should be treated with a regimen that is cardioprotective and renal protective. Another example is a patient with T2DM, obesity, dyslipidemia, and nonalcoholic steatohepatitis (NASH), a commonly associated complication of T2DM with insulin resistance. Such a patient will benefit from a combination therapy of metformin, pioglitazone, and glucagon-like peptide-1 receptor agonist (GLP1-RA), a regimen that attenuates the progression of liver disease even without a very elevated A1c. Regimens, therefore, are increasingly being designed according to the individual's phenotype and complications while focusing less on the A1c level and taking into consideration quality of life and affordability.

What Distinguishes Twenty-First Century Pharmacotherapy?

The extensive armamentarium available to lower blood sugars (Table 40.1) in patients with T2DM evolved at the turn of the century from mainly hypoglycemic agents such as insulin and sulfonylureas (SUs) to non-hypoglycemic antidiabetic agents, including metformin, thiazolidinediones (TZDs), and the newer GLP-1 RAs and SGLT2 inhibitors. Highly effective for an increasingly obese and insulin-resistant population, TZDs were extensively used until rosiglitazone (trade name Avandia) was attributed to increased ASCVD risk. Subsequently, in 2007, the FDA required a black box warning for cardiac risks followed by heavy restrictions on rosiglitazone. Although rosiglitazone was eventually reintroduced to the market after a lengthy and careful review, as a result of what was called the Avandia affair, the FDA has required that cardiac safety be demonstrated for all new T2DM therapies since December 2008. It mandated long-term CVOTs demonstrating safety and noninferiority when compared to placebo for major adverse cardiac events (MACE), classically defined as a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. Two classes of medications, GLP1-RA and SGLT2 inhibitors, have since shown that, when used in patients with advanced ASCVD, they are superior to conventional therapy. The CVOT results have strongly impacted guidelines recommending their use in those with comorbidities such as ASCVD, congestive heart failure (CHF), or chronic kidney disease (CKD) [7].

Table 40.1 Approved antidiabetic medications in the United States

Medication class	Brand name	Generic name	Route	Hypoglycemia	Weight
Insulins	Basal (intermediate and long acting)	Humans, analogues, biosimilars	Subcutaneous	YES	↑
	Prandial (short and rapid acting)	Humans, analogues, biosimilars			
	Fixed premixed combinations	Humans, analogues			
	Afrezza (ultra short acting)		Inhaled		
Sulfonylureas	Glucotrol	Glipizide	Oral	YES	↑
	Amaryl Diabeta/ Glynase/ Micronase	Glimepiride Glyburide			
Meglitinides (glinides)	Starlix	Nateglinide	Oral	YES	↑
	Prandin	Repaglinide			
Biguanide	Glucophage	Metformin	Oral	NO	↔
Alpha-glucosidase inhibitors	Precose	Acarbose	Oral	NO	↔
	Glyset	Miglitol			
Amylin analogue	Symlin	Pramlintide	Parenteral	NO/YES	↓↓
Bile-acid sequestrant	Welchol	Colesevelam	Oral	NO	↔
Dopamine D2 receptor agonist	Cycloset	Bromocriptine	Oral	NO	↓
Thiazolidinedione	Actos	Pioglitazone	Oral	NO	↑↑
Incretin mimetics: DPP-4 inhibitors	Januvia	Sitagliptin	Oral	NO	↔
	Onglyza	Saxagliptin			
	Tradjenta	Linagliptin			
	Nesina	Alogliptin			
Incretin mimetics: GLP-1 RAs	Byetta	Exenatide	Parenteral	NO	↓↓
	Bydureon	Exenatide ER			
	Victoza	Liraglutide			
	Trulicity	Dulaglutide			
	Ozempic	Semaglutide			
	Rybelsus	Semaglutide (oral)	Oral		
Combination (pen-syringe)	Soliqua 100/33	Glargine and lixisenatide	Parenteral	YES	↔
GLP-1 RA + basal insulin	Xultophy® 100/3.6	Degludec and liraglutide			
SGLT2 inhibitors	Invokana	Canagliflozin	Oral	NO	↓↓
	Farxiga	Dapagliflozin			
	Jardiance	Empagliflozin			
	Steglatro	Ertugliflozin			

DPP-4 inhibitors dipeptidyl peptidase 4 inhibitors (gliptins), *GLP-1 RAs* glucagon-like peptide-1 receptor agonists (GLPs), *SGLT2 inhibitors* sodium-glucose cotransporter 2 inhibitors (flozins)

Insulins. Discovered in 1921, insulin dramatically changed the lives of individuals with T1DM and continues to improve hyperglycemia in individuals with T2DM. Today, it is utilized as a supplement to overcome insulin resistance in a population with increasing adiposity, often after combination therapies have failed. The main side effects are weight gain and hypoglycemia.

Current insulin delivery systems are easier to administer and well accepted. Intensive insulin therapy requiring multiple daily injections with a basal insulin administered once or twice daily and a rapid-acting insulin administered with meals are sometimes required in those with T2DM and significant insulin deficiency. Inhaled rapid-acting insulin is available although not widely used. Insulin pump therapy, otherwise known as continuous subcutaneous insulin infusion, provides a continuous delivery of rapid-acting insulin throughout the day as well as variable amounts of insulin to match carbohydrate intake or correct high blood sugars.

Many patients are reluctant to start insulin, particularly as first-line therapy, for various reasons, including perceived stigma, aversion to injections, and concerns about side effects. Nevertheless, as T2DM tends to be a progressive disease with worsening glycemic control over time, insulin is added when glycemic control cannot be achieved on 2–3 agents; the A1c is >10% or >2% above target; or severe, persistent hyperglycemia with blood glucose levels >300 mg/dL is present. It is prescribed as initial therapy in catabolic patients who present with symptoms such as weight loss, polydipsia, or polyuria. Once blood sugars are better controlled and glucotoxicity resolves, patients may be switched to other non-insulin regimens.

Basal insulin alone is the most convenient initial insulin regimen. The ADA recommends a starting dose of 10 units or 0.1–0.2 units/kg/day and titrations by 10–15% or 2–4 units once or twice weekly until the fasting blood glucose is at the goal of 80–130 mg/dL [8]. Doses of 4–5 units/kg/day, or even higher, are often required in patients with high insulin resistance. Therefore, in individuals who are reliable and monitor their finger-stick blood sugars frequently, a more aggressive initial dose can be started. The chief action of basal insulin is to suppress the inappropriate excessive hepatic glucose production, limiting hyperglycemia, particularly overnight.

The use of prandial insulins has decreased when basal insulin is combined with SGLT2 inhibitors and GLP-1 RAs that have prandial effects. Nonetheless, when goals are not met, prandial insulins are necessary. The addition of prandial insulins can be done only before the largest meal or before each meal if necessary. The recommendations for initial prandial dose are 4 units, 0.1 units/kg, or 10% of the basal dose, which can then be titrated by 1–2 units or 10–15% every 2–3 days until the 2-hour postprandial glucose or next pre-meal glucose is consistently <140 mg/dL [8]. These recommendations offer a simple, safe, and stepwise approach to titrating insulin. While insulin is easy to prescribe, finding the correct dose is much more complicated as it requires frequent monitoring and dose adjustments. When significantly increasing the prandial insulin doses, particularly with the evening meal, consideration should be given to decreasing the basal insulin dose. In T2DM, rapid-acting insulin analogues do not differ from the less expensive human regular insulin in improving glycemic control [9].

Sulfonylureas (SUs) stimulate pancreatic β-cells to secrete insulin by binding to the ATP-sensitive potassium channels, leading to cell depolarization and subsequent insulin exocytosis. Currently, glipizide and glimepiride are the most commonly used. The main side effects are hypoglycemia and weight gain. Due to the risk of hypoglycemia, caution must be taken with SUs, particularly when used in the elderly or frail patient. Patients who have been treated with SUs for some time but fail to achieve better glycemic control indicate that they have lost β-cell function and need insulin therapy. When adding insulin in these patients, it is best to discontinue the SU as it has no added benefit but can increase the hypoglycemia risk.

Meglitinides are non-sulfonylurea insulin secretagogues with faster onset and much shorter duration of action compared to SUs. Hence, they are taken more frequently and 15–30 minutes before meals to reduce postprandial hyperglycemia. The two meglitinides available in the United States are repaglinide and nateglinide. Similar to SUs, meglitinides are dependent on functioning β-cells and, thus, become less effective over time as β-cell function declines. They share a similar side effect profile to SUs.

Biguanides do not have a clearly elucidated molecular mechanism of action (MOA). Metformin (dimethylbiguanide) decreases hepatic gluconeogenesis, reduces intestinal absorption of glucose, and may improve insulin sensitivity. Multiple potential mechanisms of action include inhibition of the mitochondrial respiratory chain complex I, activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), and inhibition of mitochondrial glycerophosphate dehydrogenase. A possible effect on gut microbiota has also been postulated. Since 1995, metformin has become the preferred initial drug for treatment of T2DM. Compared with SUs and insulin, it results in less weight gain, fewer hypoglycemic events, and potentially improved CVD outcomes as suggested by the United Kingdom Prospective Diabetes Study (UKPDS) sub-study [10]. Lactic acidosis, the most concerning side effect, is rarely observed when administered properly, but metformin should be avoided in patients with a GFR between 30 and 45 mL/min/m^2. Gastrointestinal side effects, such as abdominal discomfort, nausea, and diarrhea, are common and are the main reasons for discontinuation.

Alpha-glucosidase inhibitors delay carbohydrate degradation and absorption, thereby reducing postprandial hyperglycemia. The effect on A1c is modest, but their multiple prandial dosing and gastrointestinal side effects such as flatus and diarrhea markedly limit their use. CVD benefits have been found with acarbose in people with prediabetes and T2DM [11].

Thiazolidinediones (TZDs) improve insulin sensitivity by binding to the peroxisome proliferator activator receptors in the target cell nucleus. This class of medications was a major breakthrough in diabetes treatment as novel insulin sensitizers, but use has been limited by rosiglitazone's potential risk for increased cardiac events. In contrast, pioglitazone, which was approved before the FDA-mandated CVOTs, has been shown to have protective ASCVD outcomes. In a recent study done in individuals with prediabetes, pioglitazone was found to reduce the incidence of myocardial infarction or stroke by 24% [12]. It is very effective in those with

severe insulin resistance and is the best antidiabetic agent for nonalcoholic fatty liver disease (NAFLD), a condition highly associated with insulin resistance [13]. Common side effects are dose-related weight gain and edema, particularly when used concomitantly with insulin or SUs. It is contraindicated in patients with New York Heart Association (NYHA) class III/IV heart failure or symptomatic CHF.

Bromocriptine is a dopamine receptor agonist that was approved for use in T2DM in 2009. It reduces postprandial glucose levels, but its MOA has not been fully understood. It is thought to increase dopamine activity in the brain and inhibit excess sympathetic tone. It has not been widely used as an antidiabetic drug.

Colesevelam is a bile-acid sequestrant that reduces LDL cholesterol and glucose levels. It was approved by the FDA for the treatment of T2DM in 2008. Its MOA is not known, and it only has a modest effect on glycemic control. It too has not been widely used as an antidiabetic drug.

Amylin is a neuroendocrine hormone that is co-secreted with insulin by the pancreatic β-cells. Pramlintide, a synthetic analogue of amylin, was approved in 2005 as an adjunct to preprandial insulin therapy in T1DM and T2DM. It reduces prandial glucagon secretion, lowers postprandial glucose levels, delays gastric emptying, and causes weight loss. The most common side effect is nausea. Nowadays, this medication is less used due to the need to be co-administered with insulin and the availability of GLP-1 RAs, which have similar or better glycemic effects in addition to ASCVD benefits.

Three classes of medications were approved after 2008 and required the FDA-mandated CVOT: the two incretin mimetic agents, dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and the renally acting sodium-glucose cotransporter-2 (SGLT2) inhibitors. To date, none of these CVOTs have identified an increased risk of CV events, and some have demonstrated reduced risk in patients with T2DM and advanced ASCVD (Table 40.2). Consequently, rather than continuing to focus narrowly on cardiovascular safety, the FDA has begun to consider a more holistic assessment of safety in a diverse population representative of the diabetes community while avoiding barriers to new antidiabetic drug development.

DPP-4 inhibitors block the action of DPP-4, an enzyme which destroys incretin hormones. By increasing levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), they enhance insulin secretion and suppress glucagon release from pancreatic α-cells in a glucose-dependent manner during the prandial state. They have a low risk of hypoglycemia and are weight neutral. While they help reduce blood sugar levels, they tend to have a very modest glycemic effect when not combined with metformin. In patients with moderate or severe CKD, alogliptin, saxagliptin, and sitagliptin need to be renally dosed. In contrast, linagliptin, the only DPP-4 inhibitor primarily excreted via the hepatic route, does not require any dose adjustment. All DPP-4 inhibitors are well tolerated. Postmarketing reports of pancreatitis and pancreatic cancer are rare and have not been reported in the large CVOT. All the DPP-4 inhibitors showed safety in their CVOTs.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin mimetics, similar to DPP-4 inhibitors but more potent. They also work through enhancing

Table 40.2 Summary of the cardiovascular outcome trials (2008–2020)

Medication vs placebo	CVOT[ref]	FDA-approved for MACE superiority
Inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors)		
Saxagliptin	SAVOR TIMI 53 [32]	
Alogliptin	EXAMINE [33]	
Sitagliptin	TECOS [34]	
Linagliptin	CARMELINA [35]	
Linagliptin vs glimepiride	CAROLINA [36]	
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)		
Exenatide ER	EXSCEL [37]	
Liraglutide	LEADER [38]	✓
Semaglutide	SUSTAIN-6 [39]	✓
Semaglutide (oral)	PIONEER-6 [40]	✓
Dulaglutide	REWIND [41]	✓
Sodium-glucose cotransporter-2 (SGLT2) inhibitors		
Canagliflozin	CANVAS + CANVAS-R [42]	✓
Empagliflozin	EMPA-REG [43]	✓
Dapagliflozin	DECLARE TIMI-58 [44]	HFrEF only
Ertugliflozin	VERTIS-CV [45]	

CVOT cardiovascular outcome trial, *FDA* Food and Drug Administration, *MACE* major adverse cardiac events, *HFrEF* heart failure with reduced ejection fraction

glucose-dependent insulin secretion and suppressing glucagon secretion, mostly during a meal. They carry a low risk of hypoglycemia and help reduce body weight. Exenatide, the first GLP-1 RA, was approved as a twice daily injection in April 2005. Several agents exist that can be injected daily, such as liraglutide and lixisenatide, or weekly, such as dulaglutide and semaglutide. Semaglutide was also approved in 2019 by the FDA as an oral formulation.

Common side effects are gastrointestinal in nature, including nausea, vomiting, and diarrhea, and can be reduced by the once weekly formulations. Despite no causal relationship being proven, GLP-1 RAs are contraindicated in patients with a history of pancreatitis due to postmarketing reports of acute pancreatitis [14]. All GLP-1 RAs showed ASCVD safety in the CVOT studies, and some showed superiority when compared to placebo.

SGLT2 inhibitors exert their effects via the kidney, and their MOA involves inhibiting the SGLT2 protein in the proximal nephron, thereby reducing the inappropriately increased glucose reabsorption found in T2DM and increasing urinary glucose excretion. SGLT2 inhibitors are effective in improving glycemic control, decreasing weight, and reducing systolic blood pressure, with a low risk of hypoglycemia when not used in combination with hypoglycemic agents. As their action is independent of pancreatic function, they may be used at any stage of T2DM, even after insulin secretion has waned significantly.

Complications include increased risk of genital mycotic infections and a mildly increased incidence of lower urinary tract infections. A higher risk of diabetic ketoacidosis, the so-called euglycemic DKA as blood sugars can be normal or only modestly elevated, is found particularly in those with insulin deficiency and caloric restriction. The former FDA-issued black box warning for canagliflozin regarding an increased risk of lower limb amputations was removed in 2020. Use of SGLT2 inhibitors also has the potential to cause hypotension, particularly in older patients or those taking loop diuretics.

CVOTs that evaluated the effects of SGLT2 inhibitors on cardiovascular and renal outcomes have shown consistent benefits with respect to certain outcomes such as hospitalization for heart failure and progression of kidney disease [15]. Ertugliflozin, however, was found to be noninferior with respect to MACE in the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) [16]. The other three agents, canagliflozin, empagliflozin, and dapagliflozin, showed MACE superiority. SGLT2 inhibitor trials have notably demonstrated a robust class effect on reducing hospitalizations for heart failure, with the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial showing this benefit even in people without T2DM [17]. As heart failure is a common complication for individuals with T2DM, SGLT2 inhibitors serve as an effective therapeutic strategy [18].

Reducing CKD progression was another unexpected benefit of SGLT2 inhibitors. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the first renal outcome trial of an antidiabetic drug, studied the use of canagliflozin in patients with CKD (estimated glomerular filtration rate (eGFR) 30–90 mL/min/1.73 m^2) and albuminuria, who were already on maximally tolerated doses of ACE inhibitors or angiotensin receptor blockers (ARB). The trial was stopped prematurely due to an interim analysis showing clear benefit in the canagliflozin group with a 30% lower relative risk in the primary composite outcome consisting of end-stage kidney disease, doubling of creatinine, or renal or cardiovascular death [19]. Based on the findings of these CVOTs, the updated ADA/EASD consensus statement recommends the use of SGLT2 inhibitors in patients with T2DM and heart failure and/or CKD independent of A1c [20].

Does Combination Therapy Provide Additive Beneficial Effects?

Older studies, such as UKPDS, have shown that T2DM is a progressive disease marked by worsening β-cell dysfunction, resulting in increased difficulty achieving or maintaining glycemic control. Thus, regardless of the agent chosen, monotherapy fails sooner or later, as evidenced in A Diabetes Outcome Progression Trial (ADOPT) [21], and most patients eventually end up requiring combination therapy. While leading guidelines agree on initiating metformin monotherapy in conjunction with lifestyle modifications in newly diagnosed T2DM, there is not yet a clear consensus on the choice and timing of combination therapies. Some propose sequential

therapy to allow for a full assessment of the efficacy and risk-benefit profile of each agent as it is added on [22]. However, step up therapy results in clinical inertia, a chasing of the A1c and, ultimately, progression of the disease. In contrast, combination therapy at the time of diagnosis can lead to faster achievement of glycemic control, possibly better preservation of β-cell function, and certainly less diabetic complications.

The numerous advances in pharmacologic therapies for T2DM and the findings of the CVOTs have made plausible the notion of a synergistic effect in improving blood sugars, reducing weight, and providing cardioprotective and nephroprotective effects when a combination of these newer antidiabetic agents is used [23]. This option is particularly attractive as the mechanisms by which they exert cardiovascular and nephroprotective benefits differ. It is postulated that pioglitazone slows down or reverses atherosclerotic disease [24], whereas SGLT2 inhibitors improve cardiac hemodynamics, and GLP-1 RAs have anti-atherogenic or anti-inflammatory effects [25]. Three small, short-term trials, SUSTAIN 9, AWARD-10, and DURATION-8, demonstrated improvements in glycemic control and weight loss when a GLP-1 RA (semaglutide, dulaglutide, and exenatide, respectively) was added to an SGLT2 inhibitor in patients with poorly controlled T2DM treated with or without metformin. To date, however, no trial has addressed the efficacy of the combination of GLP-1 RA and SGLT2 inhibitor on cardiorenal outcomes, and future trials are much awaited [26].

In summary, we have entered into an exciting new era in the treatment of diabetes, when improvements in A1c can take place without hypoglycemia, weight gain, and frequent monitoring. The changing strategy of using combination regimens without hypoglycemic agents necessitates less monitoring and improves patients' well-being and quality of life. Using twenty-first-century medications is particularly important in those with advanced renal and/or ASCVD and in the elderly population, who are more vulnerable to hypoglycemia.

Do Single-Pill or Single-Injection Combination Therapies Exist?

Antihyperglycemic single-pill combinations (SPCs) have been developed in an effort to reduce pill burden and address adherence issues associated with combination pharmacotherapy in patients with T2DM while optimizing clinical outcomes [27]. Most SPCs contain metformin or a SU. In January 2020, the FDA approved the first oral therapy that combines three medications into one pill: the SGLT2 inhibitor empagliflozin, the DPP-IV inhibitor linagliptin, and metformin extended release.

The advent of combination pen devices that simultaneously deliver a basal insulin and a GLP-1 RA (glargine with lixisenatide and degludec with liraglutide) in 2016 (Table 40.1) has also reduced treatment burden while improving glycemic control with low risk of hypoglycemia and weight gain.

What Is the Ideal Regimen for Our Patient Described in the Case?

Our patient was sent home on an intense insulin regimen, requiring four injections daily, which was ineffective likely due to his severe insulin resistance and poor adherence. A better regimen in light of his comorbidities, which include obesity, NAFLD, CKD, and CHF, would have been an SGLT2 inhibitor in combination with metformin and a GLP-1 RA. Pioglitazone, while beneficial for the treatment of both T2DM and NAFLD, is contraindicated due to his heart failure. Instead, a GLP-1 RA, which may also be effective for NAFLD, is recommended [28]. Therefore, the patient's regimen was eventually changed to a once weekly injection of a GLP-1 RA and a once daily combination pill of metformin and an SGLT-2 inhibitor to decrease the number of pills and improve adherence. His weight improved, his A1c normalized to 6.3%, and his quality of life improved with fewer injections and finger-stick glucose monitoring.

Is Surgical Management of Diabetes an Option?

The term "metabolic surgery" refers to surgical procedures used to treat metabolic diseases, especially T2DM. Metabolic surgery is indicated for patients with T2DM who do not respond to lifestyle changes and/or pharmacotherapy and is currently typically used as a last resort to treat T2DM in individuals with class II obesity (BMI 35–39.9 kg/m^2) or class III obesity (BMI >40 kg/m^2). Recent innovations in surgical techniques have led to less invasive but metabolically successful laparoscopic procedures with fewer postoperative complications and quicker recovery times. These procedures involve gastric restriction by reducing the size of the stomach, malabsorption of nutrients, or a combination of both. The best-known metabolic surgery remains gastric bypass, but laparoscopic sleeve gastrectomy has become more common.

There is compelling evidence that the clinical benefits of metabolic surgery extend beyond correcting obesity and its direct complications, such as mobility and arthritic difficulties. In patients with T2DM and obesity, metabolic surgery can reliably achieve glycemic control with less pharmacotherapy and reduce hepatic, renal, and CVD risk. To date, it is the only treatment that results in durable weight loss and, in some individuals, complete remission of diabetes. The antidiabetic effect of metabolic surgery is largely mediated by weight loss, but several other hypotheses have been proposed for additional weight-independent mechanisms, including increased postprandial secretion of incretins such as GLP-1, impaired ghrelin secretion, and alterations in the gut microbiome.

In light of the safety and effectiveness of metabolic surgery, clinicians should consider it as an option for the management of T2DM. As the success of metabolic surgery depends on a commitment to lifestyle modifications, individuals undergo

extensive preoperative screening and preparation to determine if they are suitable candidates for surgical treatment. Therefore, the clinical decision to pursue metabolic surgery should always be patient-centered and based on a team approach [29].

Diabetes and COVID-19

The global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is here to stay, with important therapeutic implications for metabolic disorders. Both obesity and T2DM are well-known risk factors for greater COVID-19 disease severity.

How Can We Treat Individuals with T2DM and COVID-19 in the Outpatient Setting?

There is scant data regarding the most appropriate pharmacotherapy to use in the outpatient management of patients with T2DM infected by SARS-CoV-2. Despite ACE2 and DPP4 functioning as coronavirus receptors, pharmacotherapy targeted at ACE2- or DPP4-related pathways has shown no harm or benefit. While incretins, including DPP4 inhibitors and GLP-1 RAs, and metformin exert anti-inflammatory effects and decrease biomarkers of inflammation in individuals with diabetes, there is no clinical data to support better outcomes in COVID-19 [30]. TZDs have been hypothesized to be beneficial as adjuvant therapy in COVID-19 by limiting the differentiation of pulmonary lipofibroblasts into myofibroblasts, which have been implicated in pulmonary fibrosis and, hence, severe disease. However, no human studies have been performed to confirm this hypothesis [31].

Providers need to exercise caution when using antidiabetic agents in ill patients who are clinically unstable. In those who develop sepsis or severe renal dysfunction, metformin should be discontinued to minimize the risk of lactic acidosis, and the dose of DPP4 inhibitors should be adjusted. As SARS-CoV-2 infection is associated with poor oral intake and dehydration, SGLT2 inhibitors should also be discontinued to reduce the risk for further volume depletion and euglycemic DKA. Lastly, SUs are not advisable as they are not effective for stress hyperglycemia but carry a high risk of hypoglycemia.

Lessons Learned

1. T2DM is a complex metabolic disorder characterized by hyperglycemia and associated with a constellation of cardiovascular risk factors.
2. Treatment of T2DM has expanded to include newer classes of medications demonstrated to improve glycemic control and have additional cardio- and renal-protective effects.
3. Successful treatment of T2DM requires early diagnosis and treatment targeting ASCVD risk factors or complications rather than solely focusing on a lower A1c.

Multiple Choice Questions

1. Side effects associated with SGLT2 inhibitors include all of the following except:

   (a) Euglycemic DKA
   (b) Pancreatitis
   (c) Hypotension
   (d) Genital mycotic infections
   (e) Urinary tract infections

2. All of the following are requirements for initiation of insulin therapy except which of the following:

   (a) Persistent A1c above the goal on 2–3 agents
   (b) Persistent A1c greater than 10%
   (c) Persistent blood glucose between 250 and 290 mg/dL
   (d) Patient has weight loss and polyuria
   (e) Patient is hospitalized with diabetic ketoacidosis

3. A 63-year-old woman with T2DM, dyslipidemia, and albuminuria persistently has an A1c greater than 9% on a maximal dose of metformin and a low dose of glipizide for the past 6 months. What is the best next step in her diabetes management?

   (a) Provide additional nutritional counseling and continue the same pharmacotherapy
   (b) Increase the dose of glipizide
   (c) Continue glipizide and add insulin therapy
   (d) Stop glipizide, and start pioglitazone and an SGLT2 inhibitor

Answers to Questions

1. b
2. c
3. d

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Chapter 41
Inpatient Management of Type 2 Diabetes Mellitus

Hanna J. Lee

Objectives

1. To review the glycemic goals for inpatient hyperglycemia and type 2 diabetes mellitus
2. To describe optimal initiation of insulin therapy for inpatient hyperglycemia
3. To discuss the inpatient challenges of hyperglycemia and diabetes management in patients with COVID-19 infection

Case Description

A 67-year-old man with history of type 2 diabetes mellitus (T2DM) for more than 12 years, hypertension, hyperlipidemia, and chronic kidney disease presents from the outpatient clinic for hypertensive emergency. Initial BP is 211/112, HR 81, O_2 sat 92% (improved to 98% on nasal cannula), RR 18, and temperature 98.2 °F. His height is 164 cm, and he weighs 71 kg with a BMI of 26.4 kg/m^2. Upon admission, he was found to have acute diastolic heart failure due to uncontrolled hypertension, was initiated on a nicardipine drip, and was transferred to the intensive care unit. On exam, the patient appears comfortable while on BiPAP. The exam is notable for bilateral rales on lung exam, absence of jugular venous distention, and bilateral 2+ pitting edema of the lower extremities with palpable dorsalis pedis pulses. He has a history of medication nonadherence and admits to not taking his antihypertensives nor his diabetes medications that include glargine 12 units daily and dulaglutide 1.5 mg weekly. He reports infrequently checking his finger-stick glucoses at home

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but recalls glucoses are consistently greater than 200 mg/dL. Initial labs are notable for blood glucose 505 mg/dL, creatinine 1.91 mg/dL, estimated GFR 35 (worse than baseline GFR), anion gap 9, bicarbonate 25, pH 7.37, normal liver function tests, and hemoglobin A1c 11.2%. During the following 24 hours, the patient was noted to have persistent hyperglycemia for which the endocrinology team was consulted.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with increased morbidity and mortality in hospitalized patients. Individuals with T2DM are more likely to be hospitalized and have longer duration of hospitalization. Diabetes predisposes patients to various cardiovascular and peripheral vascular diseases, renal dysfunction, and infectious complications that require more frequent inpatient admissions and surgical procedures [1]. It has been estimated that diabetes accounts for approximately 25% of hospital inpatient days in the United States [2]. Even in the absence of diabetes, hyperglycemia occurs commonly in the hospital setting and is also associated with poorer outcomes. Up to 38% of patients in community hospitals and up to 44% of patients with heart failure and acute coronary syndrome have been noted to have sustained hyperglycemia [3–5]. Higher rates of infection, cardiovascular events, and prolonged disability have been linked to hyperglycemia even when adjusted for the severity of the underlying acute illness. This has been demonstrated especially in patients undergoing general surgery, surgical and percutaneous cardiac intervention, and in critically ill patients in the intensive care units (ICU) [6–8]. Acute hyperglycemia independently increases the risk for sepsis, organ failure, acute kidney injury, and in-hospital and long-term mortality. Hyperglycemia, at the time of admission, has even been shown to be an independent predictor of mortality [9]. The observed hyperglycemia may be initially triggered by the surge of stress hormones in acute illness, but it is often exacerbated by underlying diabetes, use of glucocorticoids, and enteral nourishment. Appropriate diabetes and glycemic management in hospitalized patients is needed to reduce short- and long-term clinical complications.

Glycemic Goals

Inpatient hyperglycemia is defined by a glucose level greater than 140 mg/dL [10, 11]. It is recommended that all patients with a known history of diabetes have an active hemoglobin A1c (HbA1c) checked within the past 3 months of hospitalization. Not only does the HbA1c provide insight into a patient's pre-admission glycemic status, but also it can potentially guide how to optimize a patient's outpatient diabetes regimen prior to discharge. The HbA1c should also be measured in all patients with a blood glucose in the hyperglycemic range as it can help differentiate between undiagnosed diabetes and stress-induced inpatient hyperglycemia. The standard HbA1c threshold of 6.5%, above

which is diagnostic for diabetes, may be less sensitive among the hospitalized population. One study reported that an HbA1c less than 5.2% reliably excluded a diagnosis of diabetes while an HbA1c above 6.0% had 100% specificity with an improved sensitivity of 57% for the inpatient diagnosis of diabetes [12]. Alternative glycemic markers to the HbA1c are serum fructosamine and glycated albumin [13]. Once patients with diabetes or hyperglycemia are identified, point-of-care (POC) glucose monitoring should be checked before each meal and at bedtime; if the patient is nil per os (NPO), POC glucoses should be monitored every 4–6 hours. Both HbA1c and glucose measurements are paramount to determining when to initiate hyperglycemia therapy, how to effectively adjust an inpatient regimen, and how to tailor a potential outpatient regimen at discharge.

What Are the Glycemic Targets for Critically Ill Patients in the ICU?

Consensus guidelines recommend a glucose target of 140–180 mg/dL in the ICU setting. This glycemic goal is derived from randomized controlled trials (RCTs) that have shown, although with inconsistency, that tighter glycemic control reduced morbidity and mortality among ICU, surgical, and cardiac patients. When critically ill surgical ICU patients, the majority of whom were post-cardiac surgical intervention, were randomized to either intensive insulin therapy with a glucose target of 80–110 mg/dL or conventional insulin therapy with a glucose target of less than 215 mg/dL, an impressive 32% risk reduction was observed in mortality in the intensive therapy group. This was primarily attributed to a decrease in sepsis-related multi-organ failure in patients who required more than 5 days of ICU treatment [6]. Significant reductions in septicemia, duration of antibiotic use, and onset of critical illness polyneuropathy were also observed in the intensive therapy cohort. Subsequent studies have shown conflicting results with the majority unable to demonstrate a mortality benefit with intensive insulin treatment; this inconsistency may be partly explained by variations in glucose targets, insulin treatment protocols, and patient populations [14–18]. Most other studies, however, demonstrate significant reductions in morbidity, ranging from decreased acute kidney injury and earlier weaning from mechanical ventilation to shorter ICU and hospitalization courses with intensive insulin treatment.

What Are the Risks of Inpatient Hypoglycemia?

Intensive insulin therapy with more aggressive glycemic targets can come at the cost of increased hypoglycemic events, as was observed in the multinational Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) study [17]. In this study, over 6000 patients in the surgical and medical ICU were randomized to intensive insulin therapy with

a glucose target of 81–108 mg/dL versus standard insulin therapy with a glucose target of less than 180 mg/dL. A significant increase in mortality, with an odds ratio of 1.14, was observed in the intensive glucose control group. Furthermore, this same group encountered significantly more hypoglycemia (defined by a glucose of 40 mg/dl or less) with an odds ratio as high as 14.7. A meta-analysis of fourteen trials comparing aggressive with conventional glycemic goals reported a pooled relative risk of 6.0 for hypoglycemia [16]. Hypoglycemia, like hyperglycemia, has been a predictor of poorer outcomes. High-risk cardiac patients presenting with an ST-segment elevation myocardial infarction (STEMI) and with hypoglycemia (blood glucose less than 81 mg/dL) were shown to have at least a threefold increased risk of death at 30 days [19]. Another retrospective study showed that hypoglycemia (blood glucose less than 55 mg/dL) occurring in diabetes patients presenting with acute coronary syndrome had at least a twofold increase in mortality at 2 years [20]. Hypoglycemia is clearly not a benign event and should not be overlooked.

What Are the Glycemic Targets for Non-critically Ill Patients in the Hospital?

Consequently, a modified intensive approach to glycemic control is recommended in order to minimize the adverse clinical outcomes associated with aggressive glycemic targets of less than 100 mg/dL and hyperglycemia above 180 mg/dL. These guidelines have been extended to the non-ICU inpatients. As such, in the non-critically ill patient population, it is generally recommended that the fasting, preprandial glucose target is 100 or 110–140 mg/dL while the postprandial glucose target is less than 180 mg/dL [10, 11, 21]. Although a clear and specific target glucose range has not been universally established, given the inconsistent conclusions from various studies, all agree that overt hypoglycemia and hyperglycemia need to be avoided.

Inpatient Treatment of Hyperglycemia and T2DM

Should Oral Antihyperglycemic Therapies Be Used in the Hospital Setting?

The American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE), and Endocrine Society guidelines discourage the use of oral hypoglycemia agents for hospitalized patients with T2DM. However, cautious continuation or resumption of non-insulin therapies may be considered in the select inpatient who is medically stable, eating a per os (PO) diet, not on acute glucocorticoid therapy, and not planned for any contrast studies or invasive procedures [7, 22]. Precautions must be taken with metformin in acute renal insufficiency, heart failure, sepsis, hypoxia, and hypoperfusion as its use can potentially cause lactic acidosis. Sulfonylureas can

potentially cause prolonged, severe hypoglycemia and may have harmful cardiovascular effects. SGLT2 inhibitors can potentially cause euglycemic diabetic ketoacidosis and need to be avoided in severe illness, renal dysfunction, ketonemia, or settings of prolonged fasting. Sitagliptin has been reported to be safely utilized and to be non-inferior to insulin in non-ICU patients with moderately uncontrolled T2DM [23]. Inpatient use of glucagon-like peptide-1 receptor analogs (GLP-1 RAs), intravenous and subcutaneous (SQ), has been shown to minimize the need for rescue insulin therapy but has been limited by its potential gastrointestinal side effects [24]. Further research is needed regarding the use of these incretin-modifying agents. Given the delayed and variable pharmacokinetics of non-insulin therapies in the hospital during which there is an unpredictability of renal and hepatic function, dietary status (NPO versus PO versus enteral feeds), and scheduling for invasive procedures, insulin therapy is the preferred method for effective glycemic inpatient management [24].

How Can Glycemic Control Be Achieved in the ICU?

In the ICU, continuous insulin infusions that follow a validated infusion algorithm or protocol are the standard of therapy. Intravenous (IV) delivery of insulin permits for rapid dose adjustments to efficiently reach specific glucose targets. Prospective RCTs in cardiac patients, either presenting with an acute myocardial infarction (as in the Diabetes Mellitus Insulin Glucose Infusuion in Acute Myocardial Infarction (DIGAMI) study) or post-coronary artery bypass grafting (CABG), showed that insulin infusions, compared to subcutaneous (SQ) insulin regimens, were significantly better at maintaining euglycemia and even resulted in significant reductions in in-hospital and long-term mortality [8, 25, 26]. When patients begin an oral diet or are ready for transfer out of the ICU, the insulin drip should be transitioned to a SQ insulin regimen. Select patients, without a history of diabetes and/or who required less than 1–2 U/hour of continuous insulin infusion, may not need further insulin therapy. Typically, the intravenous insulin infusion rate during the last 6–8 hours can be extrapolated to estimate the required 24-hour total daily dose (TDD) of SQ insulin [7, 22]. A 20–40% reduction of the calculated total daily insulin can then be divided proportionately between the basal insulin dose and the bolus pre-meal insulin doses (Fig. 41.1). Basal insulins typically are administered as a once-daily long-acting insulin or a twice-daily intermediate-acting insulin. Bolus insulins include rapid-acting or short-acting insulins and are administered with meals to minimize the anticipated postprandial hyperglycemia. Because the onset of action for basal insulins is approximately 2 hours, it is imperative to coordinate a 1–2-hour overlap between the insulin infusion and the first dose of basal insulin in order to prevent rebound hyperglycemia, which can occur post-infusion in up to 40% of patients [7, 11]. Another approach is to administer the long-acting basal insulin at the initiation of the insulin drip. Compared to the traditional stepwise transition from infusion to SQ insulin, one study showed significant reduction in rebound hyperglycemia among patients with diabetes when the basal insulin, glargine dosed at 0.25 U/kg, was administered at the time of initiation of the insulin drip [27]. Another group showed

that the immediate administration of glargine at 0.15 U/kg in patients without diabetes significantly shortened the mean duration of insulin infusion [28]. When administered simultaneously at the start of the insulin infusion, the weight-based doses of the long-acting basal insulin have typically ranged 0.15–0.3 U/kg.

How Can Glycemic Control Be Achieved in the Non-critically Ill Patient?

For most non-ICU patients, a scheduled SQ insulin regimen, often administered as a basal-bolus regimen, is recommended. Such regimens typically include a long- or intermediate-acting insulin that provides the basal, fasting insulin requirements plus a rapid- or short-acting bolus insulin, administered with each meal, that provides the prandial insulin requirements. Additional "correction insulin" doses of bolus insulin can be administered with each meal or every 4–6 hours to correct for any hyperglycemia [11, 24]. The use of "sliding scale" insulins, which involve a set of fixed doses of insulin regardless of food intake, is strongly discouraged. Several RCTs including the Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT-2) trial compared basal-bolus with sliding-scale insulin regimens, and have demonstrated that basal-bolus regimens achieve glycemic control earlier and more efficiently without increasing the risk of hypoglycemia [29–31].

When initiating a basal-bolus insulin regimen in non-critically ill patients in the hospital, the patient's weight, especially if insulin-naive, can provide guidance for

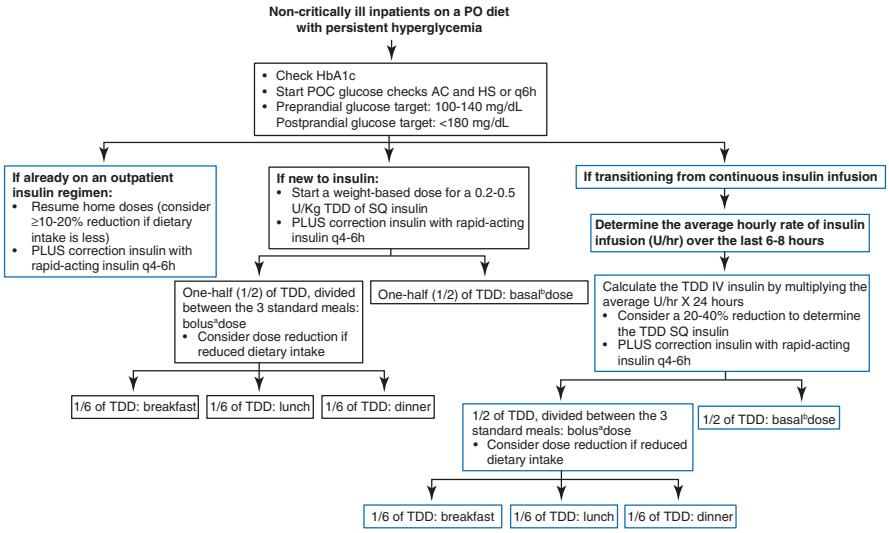

Fig. 41.1 Initiation of basal-bolus insulin in the non-critically ill hospitalized patient on a PO diet. TDD total daily dose, PO per os. [a]Bolus insulins include rapid-acting insulins or short-acting insulins; [b]basal insulins include long-acting or intermediate-acting insulins

the initial dose (Fig. 41.1). The total daily insulin required can often range 0.2–0.5 U/kg; approximately half can be administered as the basal insulin dose and the other half divided proportionately across the three standard meals of the day [11, 22]. If the patient is not new to insulin, the outpatient insulin regimen may be continued but often requires dose modifications, commonly at a 10–20% reduction, accounting for differences in the quantity and nutritional composition of hospital versus home food. Furthermore, clinical variables including renal insufficiency, hepatic dysfunction, prolonged NPO status, and even changes in insulin sensitivity may necessitate more conservative dosing [32]. For patients receiving enteral nutrition, the total daily insulin can also likewise be split between the basal insulin and the prandial bolus insulin. Depending on whether the enteral feeds are continuous or cyclical, the intermediate-acting Neutral Protamine Hagedorn (NPH) insulin, administered every 8–12 hours, or the short-acting regular insulin, administered every 6 hours, is commonly used to cover for the enteral nourishment [7, 22]. Inpatient insulin management is a dynamic process and requires continual reassessment and dose adjustments to ensure that appropriate glycemic targets are safely achieved.

How Is Glucocorticoid-Induced Hyperglycemia Managed?

Glucocorticoids can trigger and exacerbate persistent inpatient hyperglycemia with a prevalence up to 52% [33]. This is unsurprising in view of its metabolic effects: increased gluconeogenesis and increased insulin resistance at the level of the skeletal muscles, liver, and adipose tissue. The decreased peripheral glucose uptake leads to pronounced postprandial hyperglycemia. NPH, an intermediate-acting insulin, has pharmacokinetics that are similar to the onset and duration of hyperglycemia induced by once-daily prednisone and methylprednisolone. For moderate hyperglycemia, NPH, dosed at the time of daily glucocorticoid administration, may sufficiently control glycemic excursions. An RCT showed that the addition of NPH to a basal-bolus insulin regimen trended toward better glycemic control [34]. With long-lasting glucocorticoids such as dexamethasone or when glucocorticoids are dosed more than once daily with subsequent all-day hyperglycemia, basal-bolus insulin titration is preferred. However, for severe steroid-induced hyperglycemia, a continuous insulin infusion may be required to effectively achieve safe glycemic targets.

Has the COVID-19 Pandemic Changed How Inpatient T2DM and Hyperglycemia Are Managed?

Since early 2020, the SARS-CoV-2 (COVID-19) virus has and continues to devastate the world as a global pandemic. Soon after its outbreak, increased mortality and morbidity were observed in patients with diabetes mellitus as well as obesity, cardiovascular disease, hypertension, and chronic kidney disease. It has been estimated

that up to 34% of hospitalized patients with COVID-19 have diabetes [35, 36]. Severe hyperglycemia, insulin resistance, and hyperglycemic emergencies such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) have been particularly notable in these high-risk populations. The link between hyperglycemia, regardless of diabetes status, and poorer outcomes has already been well established. The mechanistic link between COVID-19 infection and marked hyperglycemia is yet to be clearly determined. A potential mechanism may involve the downregulation of ACE2, a functional receptor for the virus, that may possibly result in a cytokine storm of excessive inflammation, cellular damage and apoptosis, and decreased insulin release.

Standard glycemic management of critically ill patients with COVID-19 requires intensive glucose monitoring with continuous insulin infusion therapy. In light of limited hospital resources, personal protective equipment (PPE), and hospital staff, glycemic control has been particularly challenging during the pandemic. This has been further complicated by the frequent use of high-dose glucocorticoid therapy. Classically, infusion therapy necessitates hourly POC glucose checks and frequent titrations of the insulin infusion rate. Alternative methods have since been successfully adopted by some institutions that permit effective glucose control while minimizing the risk of exposure to the clinician. Variations of SQ insulin regimens have been implemented; each has been paired with rapid-acting correction insulin doses every 4–6 hours. Some have used once-daily basal insulin with prandial bolus insulin, while others have used intermediate-acting NPH insulin that is dosed more frequently [36].

The Food and Drug Administration (FDA) announced the temporary approval for using continuous glucose monitoring (CGM) devices in the hospital setting on March 20, 2020. The approval is only during the COVID-19 pandemic in order to allow for safe, noninvasive, and remote glucose monitoring. Currently, the Dexcom G6 and Abbott's FreeStyle Libre, both factory-calibrated devices, have been provided to hospitals for clinical use. This does not obviate the need for POC monitoring; treatment decisions should still rely on POC glucose values. Pre-pandemic studies, utilizing CGM telemetry systems, have demonstrated the potential for reduced hypoglycemic events and nurse time spent at patient bedside [37]. However, further research with large, powered trials in both the ICU and non-ICU settings is still needed.

How Was Our Patient's Uncontrolled T2DM and Hyperglycemia Managed in the Hospital?

Our patient was admitted to the ICU for new-onset heart failure in the setting of hypertensive emergency. Upon admission, the patient's outpatient T2DM medications were held, and he was initiated on a continuous insulin infusion, as per the hospital's validated infusion protocol. Hourly POC glucose checks and insulin rate adjustments were followed to achieve a glycemic goal of 140–180 mg/

dL. Once the patient's clinical status stabilized and he was ordered for a PO diet, the patient was planned for transition to an SQ basal-bolus insulin regimen. During the last several hours of the insulin drip, the infusion rate averaged 1.5 U/hour. This was extrapolated to be a total daily IV dose of 36 units (1.5 U/hour × 24 hours = 36 units), from which a 40% reduction resulted in an estimated total daily SQ insulin dose of 22 units. Half was designated for the basal insulin dose, 11 units (22 units/2 = 11 units), and the other half was designated for the bolus rapid-acting insulin dose, 3 units with each meal (11 units/3 = ~3 units). Due to the slight acute kidney injury (AKI), it was decided to initiate glargine 10 units once daily and lispro 3 units preprandially. Alternatively, a weight-based dose of 0.3 U/kg for a total daily dose of 21 units (71 kg × 0.3 U/kg = 21 U) could have been calculated. Or a dose close to the patient's home dose of basal glargine 12 units could have been initiated. In this example, all three estimations of the total daily SQ insulin happen to correlate. To prevent rebound hyperglycemia, the insulin infusion was discontinued at least 2 hours after the 10 U of glargine was administered. To correct for any subsequent hyperglycemia and to avoid hypoglycemia, the basal-bolus insulin regimen was supplemented by correction doses of lispro with every meal and at bedtime. Glycemic targets were modified to non-ICU glucose targets of fasting 100–140 mg/dL and postprandial less than 180 mg/dL. Close POC glucose monitoring was continued to allow for further daily insulin dose adjustments.

Lessons Learned

1. Inpatient hyperglycemia and hypoglycemia are both associated with poorer outcomes and increased mortality.
2. Weight-based insulin doses at 0.2–0.5 units/kg are recommended when initiating a basal-bolus insulin regimen. Supplemental correction doses of a rapid- or short-acting insulin are recommended while sliding scale insulin orders are discouraged.
3. T2DM patients are at increased risk for severe COVID-19 infections.

Questions

1. What are the recommended glycemic targets for the critically ill patient in the ICU?

   (a) 80–110 mg/dL
   (b) 100–140 mg/dL
   (c) 140–180 mg/dL
   (d) Less than 200 mg/dL

2. When transitioning from a continuous insulin infusion to a subcutaneous (SQ) insulin regimen, which of the following is NOT recommended?

   (a) The insulin infusion needs to overlap with the SQ basal insulin by at least ~2 hours
   (b) The total daily dose of SQ insulin can be estimated from the insulin infusion rate

(c) A "sliding scale" insulin regimen can be initiated
(d) A basal-bolus insulin regimen can be initiated in the patient who is eating
(e) All of the above

3. Which of the following clinical parameters must be considered when determining an insulin regimen for a hospitalized patient?

(a) Patient's outpatient diabetes medications
(b) Dietary status and intake
(c) Renal function
(d) Weight
(e) All of the above

Answers to Questions

1. c
2. c
3. e

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Part XI
Lipid Abnormalities

Chapter 42
Introduction to Lipid Abnormalities

Neil J. Stone

This edition's lipid cases represent a potpourri of genetic abnormalities leading to striking lipid and lipoprotein profiles. These cases were chosen to illustrate instances where algorithms directed at lowering elevated levels of lipids can be misleading. It is important to reduce lipid and lipoprotein burdens in the patient, but detailed understanding of the genetic basis and specific pathophysiology is crucial for a complete understanding and, more importantly, appropriate management. These cases also point out the importance of various clinical and laboratory clues that can further guide the clinician. The importance is high. Lack of a correct diagnosis may lead to inadequate therapy or lack of appropriate family screening.

In the first case, Dr. Conrad Blum presents the successful long-term management of heterozygous familial hypercholesterolemia (HeFH). So often when patients present with markedly elevated total and low-density lipoprotein (LDL) cholesterol (LDL-C), patients have considerable worry about their ultimate prognosis. Over the past three decades, LDL-lowering drugs from statins to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have successfully reduced elevated LDL-C concentrations to lower levels. The association of lower life expectancy with HeFH needs no longer be a reality.

This case underscores the value of early diagnosis and effective implementation of LDL-C-lowering therapies. Its recommendation of cascade screening for those with HeFH is an integral part of best practice for the management of HeFH.

Patients who present with mixed hyperlipidemia and/or severe hypertriglyceridemia (HTG) usually have a combination of genetic and acquired causes that must be considered for appropriate management. When severe hypertriglyceridemia is found, the focus shifts to preventing not only adverse cardiovascular outcomes but also when Trigyceride level (TG) rises above 1000–2000 mg/dL, the potential for

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hyperlipidemic pancreatitis. The latter can be recurrent and lead to diabetes, pancreatic insufficiency, and death.

Drs. Daniel Soffer and Eugenia Gianos present a man with lifetime elevations of cholesterol and triglycerides with significant diagnostic and therapeutic challenges. They skillfully dissect the case showing the barriers of partial treatment, missing family data, and inadequate tools to achieve the exact diagnosis. They guide us expertly through a differential diagnosis first based on their patient's lipid and lipoprotein patterns and then a consideration of possible hyperlipidemia syndromes as well as potential genetic abnormalities. This thoughtful approach indicated that their patient had a combined genetic disorder. Achieving a more precise genetic diagnosis led to appropriate lipid management including all-important cascade screening.

Finally, the last of our three lipid cases is a case that may elude correct diagnosis unless the clinician's focus goes beyond control of blood glucose and markedly elevated triglyceride levels. Dr. Abhimanyu Garg presents a case of recurrent hyperlipidemic pancreatitis in a nonobese patient with diabetes mellitus in her late 30s requiring high doses of insulin and severe hypertriglyceridemia. He skillfully points out the characteristic features found on physical examination including marked loss of subcutaneous fat from characteristic sites including the gluteal region that point to a specific genetic diagnosis. His careful description of familial partial lipodystrophy (FPLD) of the Dunnigan variety proven by specific genetic analysis underscores the importance to the clinicians of genetic testing guided by a characteristic clinical presentation. I have noted over the years in seeing patients with severe hypertriglyceridemia in the hospital that important clues are missed unless the patient is examined after turning over on their abdomen. One can easily see eruptive xanthomas on the back side of the neck, back, and buttocks that occur in many forms of severe hypertriglyceridemia (chylomicronemia syndromes) and would otherwise be missed. Looking on the back side also displays the prominent gluteal fat loss that is a more specific sign of FPLD.

These cases nicely summarize a clinical point I have emphasized while seeing patients in the clinic and hospital with students, house staff, and fellows. Advanced lipid testing doesn't make a lipidologist. The best use of "advanced lipid thinking" is to guide the testing ordered. As these cases demonstrate, understanding the increasing importance of genomics can make an important difference.

Disclosures Dr. Stone served as vice-chair of the 2018 AHA-ACC Multisociety Cholesterol Guidelines.

Chapter 43
A Case of Heterozygous Familial Hypercholesterolemia: Success of Long-Term Management

Conrad B. Blum

Objective To understand the pathophysiology, clinical presentation, and modes of therapy for heterozygous familial hypercholesterolemia (HeFH).

Case Presentation SL is a 60-year-old woman who presented in 1985 at age 25 with a history of hypercholesterolemia first documented prior to age 10. She reported that her father was hypercholesterolemic and had prominent corneal arcus. He was a nonsmoker, and he did not have diabetes mellitus. He developed angina pectoris in his mid-30s and died of an acute myocardial infarction at age 42. Her brother when age 22 years and treated with lovastatin 20 mg/day had total cholesterol of 329 mg/dl, HDL cholesterol (HDL-C) 40 mg/dl, LDL cholesterol (LDL-C) 269 mg/dl, and triglyceride 100 mg/dl.

She is a nonsmoker, and she exercised 5–10 hours weekly. Her diet was rich in fruits and vegetables, nonfat dairy products, and fish. It was limited in red meat fats, milk fats, and egg yolks.

When she first presented, her weight was 116 lbs, height 64 inches, BMI 19.9 kg/m^2, BP 115/75, and heart rate 92/min. She had corneal arcus, Achilles tendon xanthomas, and xanthomas of the extensor tendons of her hands. There was no cardiac murmur.

She had normal results for tests of liver function and thyroid function. There was no proteinuria.

She was given a diagnosis of heterozygous familial hypercholesterolemia (HeFH). Over the years since 1985, she has developed no undue exertional dyspnea and no chest discomfort. She has continued to exercise regularly—1 hour 2–3 times weekly in recent years.

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Table 43.1 Chronologic summary of pharmacologic therapy and lipid response (patient SL)

Date	Total cholesterol	Triglyceride	HDL-C	LDL-C	Medication	Notes
1984				231	None	Assuming 15% reduction in LDL-C with colestipol 15 g/day
05/01/1985	268	59	60	196	Colestipol 15 g/day	
08/20/1985	238	49	76	152	Colestipol 25 g/day Niacin 3 g/day	
						3 pregnancies
12/03/1993	166	32	55	106	Colestipol 30 g/day Niacin 1 g bid Lovastatin 40 mg bid	Lp(a) 112 mg/dl
05/18/10	170	38	64	98	Niacin 1.5 g/day Rosuvastatin 40 mg/day Ezetimibe 10 mg/day	
01/26/2016	127	54	72	42	Alirocumab 150 mg 2×/month Rosuvastatin 40 mg/day Ezetimibe 10 mg/day	

Prior to her first visit, she had initiated treatment with the bile acid sequestrant colestipol 15 g/day. A chronology of her pharmacologic treatment is summarized in Table 43.1. Bile acid sequestrants were the mainstay of pharmacologic treatment of elevated LDL-C in the pre-statin era. Fasting cholesterol on colestipol was 268 mg/dl, triglyceride 59 mg/dl, HDL cholesterol (HDL-C) 60 mg/dl, and LDL-C 196 mg/dL. Assuming that she had a usual response to treatment with this dose of colestipol (LDL-C reduction ~15%), her baseline level of LDL-C prior to starting lipid-lowering medication would have been ~231 mg/dl.

Lp(a) was 112 mg/dl (ULN 25 mg/dl) in 1993.

Genetic testing in 2015 showed her to have a pathogenic mutation of LDLR, the gene encoding the LDL receptor (c. 654_656delTGG (p.Gly219del)). This mutation impairs transport of newly synthesized LDL receptors from the endoplasmic reticulum to the Golgi apparatus, thereby reducing delivery of LDL receptors to the cell surface.

Nicotinic acid 1.5 g bid was added to her regimen, and colestipol increased to 25 g/day in 1985, resulting in a reduction of LDL-C to 152 mg/dl. She had three pregnancies (1987–1992) during which time her lipid-lowering therapy was limited

colestipol, which is not absorbed from the intestine. In 1993, lovastatin was added, and the combination of lovastatin, niacin, and colestipol resulted in LDL-C 106 mg/dl and HDL-C 55 mg/dl. Over the next several years, as more potent statins became available, lovastatin was replaced by atorvastatin (2002) and then by rosuvastatin (2005). The cholesterol absorption inhibitor ezetimibe was added in 2003, shortly after it received FDA approval. Constipation and bulky stools caused her to discontinue treatment with bile acid sequestrants. Ichthyosis and cutaneous flushing caused her to reduce niacin to 1.5 g/day.

Thus, in 2010, she was taking rosuvastatin 40 mg/day, ezetimibe 10 mg/day, and niacin 1.5 g/day. On this regimen, a fasting lipid panel showed LDL-C 98 mg/dl and HDL-C 64 mg/dl.

In 2016, niacin was discontinued and she initiated treatment with the PCSK9 antibody alirocumab. On a regimen of alirocumab 150 mg twice monthly, rosuvastatin 40 mg/day, and ezetimibe 10 mg/day, total cholesterol was 116 mg/dl, HDL-C 56 mg/dl, and LDL-C 46 mg/dl.

By 2016, xanthomas had completely resolved. Corneal arcus persisted.

An echocardiogram showed fibrocalcific changes in the aortic valve and mild aortic regurgitation but no aortic stenosis (2013). Left ventricular function and regional wall motion were normal. A carotid Doppler study demonstrated an absence of plaque and normal intimal-medial thickness (2013). A coronary artery calcium (CAC) score was 24 Agatston units (2016).

How the Diagnosis Was Made

Familial hypercholesterolemia (FH) is an autosomal codominant disorder caused by a pathogenic allele in any of three genes involved in the function of the LDL receptor pathway for clearance of LDL from plasma and, therefore, resulting in accumulation of high levels of LDL-C in plasma. These three genes are LDLR (encodes the LDL receptor), APOB (encodes apolipoprotein B, the ligand in LDL that is recognized by the LDL receptor), and PCSK9 (encodes proprotein convertase subtilisin kexin 9, which chaperones the LDL receptor to lysosomal degradation preventing the receptor from being recycled to the cell surface). Until 10–20 years ago, the term "familial hypercholesterolemia" indicated only those conditions caused by a mutation of LDLR. More recently, it has generally subsumed conditions caused by a pathogenic mutation of any of these three genes. More than 2300 unique mutations of APOB have been identified, and at least 1900 are likely or clearly pathogenic. Fewer likely pathogenic or clearly pathogenic mutations have been reported for APOB ($n = 30$) and PCSK9 ($n = 26$) [1].

Mutations of LDLR are the most common cause of genetically diagnosed FH, accounting for ~90% of such individuals. Pathogenic mutations of APOB (5–10%) and PCSK9 (~1%) are much less common. FH caused by pathogenic mutation of APOB or PCSK9 also tends to cause less severe elevation of LDL-C than FH due to mutation of LDLR.

HeFH has a prevalence of 1/200 to 1/250. However, in some populations, it has been shown to be more frequent (e.g., French Canadians in northeastern Quebec, Afrikaners, Ashkenazi Jews, Druze, Christian Lebanese, Tunisians) [2]. Among patients with acute coronary syndromes ≤60 years of age, the prevalence of HeFH is reported as 7%, and among those ≤45 years of age, the prevalence of HeFH is 14% [3].

Clinically, HeFH is characterized by lifelong elevations of LDL-C (generally 200–500 mg/dl in adulthood), premature coronary heart disease, tendon xanthomas, and corneal arcus. A study performed during the pre-statin era involving 116 kindred with FH showed that the probability of a fatal or nonfatal CHD event by age 60 in those with FH was 52% for men and 33% for women [4].

Furthermore, those with HeFH who have undergone percutaneous coronary intervention (PCI) have a worse prognosis than similar patients without HeFH. In a 2019 report of 6-year follow-up after PCI in 77 patients with a clinical diagnosis of definite or probable HeFH vs 1141 patients unlikely to have HeFH, the hazard ratio for a major adverse coronary events (MACE) during follow-up was 1.9 for HeFH patients compared to those without HeFH [5]. Similarly, the hazard ratio for 5-year mortality and MACE after myocardial infarction was ~2.0 in a 2020 report of 146 HeFH patients vs 5001 non-HeFH patients [6].

Homozygous FH is rare (prevalence 1/500,000–1/1,000,0000) and causes much more severe elevation of LDL-C (generally 500–1000 mg/dl). When untreated, it causes death due to myocardial infarction by age 20 years and often before age 10 years.

Homozygosity of the gene LDLRAP1 (also called ARH) is a very rare cause of a syndrome of homozygous FH and yields elevations of LDL-C in a range similar to that seen with homozygosity for pathogenic mutations of LDLR, APOB, or PCSK9. LDLRAP1 encodes for the LDL receptor adapter protein, which tethers LDL receptors to clathrin in the coated pits of the cell surface. Coated pits are the specialized regions of the cell surface for endocytosis. Homozygous FH caused by pathogenic mutation of LDLRAP1 is also known as autosomal recessive hypercholesterolemia since heterozygosity for a pathogenic mutation of LDLRAP1 has no impact on LDL-C levels. A single copy of a normal allele of LDLRAP1 produces a sufficient quantity of the LDL receptor adapter protein to allow normal functioning of the LDL receptor pathway.

The diagnosis of HeFH can be based on clinical and routine laboratory findings (phenotypic diagnosis) or on identification of pathogenic genetic mutation of LDLR, APOB, or PCSK9 (genotypic diagnosis).

Three different sets of criteria have been widely used for phenotypic diagnosis of HeFH: the Dutch Lipid Clinic Network criteria, the Simon Broome criteria, and Medical Pedigrees with FH (MEDPED FH) criteria (Tables 43.2, 43.3, and 43.4). Patient SL satisfies each of these criteria for a phenotypic diagnosis of HeFH. Additionally, she was found to have a pathogenic mutation of LDLR. Thus, she has both phenotypic and genotypic diagnoses.

Table 43.2 Dutch lipid clinic network criteria for diagnosis of familial hypercholesterolemia

Criterion	Points
Family history:	
1st-degree relative with premature CHD (<55 y/o men, <60 y/o women) or 1st-degree relative with LDL-C >95th percentile	1
1st-degree relative with tendon xanthomas or corneal arcus or children <18 y/o with LDL-C >95th percentile	2
Clinical history:	
Patient with premature CHD (men <55 y/o, women <60 y/o)	2
Patient with premature cerebrovascular disease or peripheral artery disease (men <55 y/o, women <60 y/o)	1
Physical examination:	
Tendon xanthoma	6
Corneal arcus before age 45	4
LDL cholesterol levels:	
≥330 mg/dl	8
250–329 mg/dl	5
190–249 mg/dl	3
155–189 mg/dl	1
DNA analysis:	
Pathogenic mutation in LDLR, APOB, or PCSK9	8
Diagnosis (based on number of points)	
Definite FH	>8
Probable FH	6–8
Possible FH	3–5
Unlikely FH	0–2

Benn et al. [19]

Table 43.3 Simon Broome criteria for diagnosis of familial hypercholesterolemia

	Criterion
A	Total cholesterol >290 mg/dl or LDL-C >190 mg/dl in adult Total cholesterol >260 mg/dl or LDL-C >155 mg/dl in child <16 y/o
B	Tendon xanthoma in patient or in first- or second-degree relative of patient
C	DNA-based evidence of pathogenic mutation in LDLR, APOB, or PCSK9
D	MI before 60 y/o in first-degree relative or before 50 y/o in second-degree relative
E	Total cholesterol >290 mg/dl in adult first- or second-degree relative Total cholesterol >260 mg/dl in child or sibling ≤16 y/o
Diagnosis: Definite FH—criteria A and B or criterion C Possible FH—criteria A and D or criterion E	

Austin et al. [20]

Table 43.4 Medical Pedigrees with FH (MEDPED FH) diagnostic criteria for familial hypercholesterolemia

Age	If first-degree relative with FH	If second-degree relative with FH	If third-degree relative with FH	General population
<20	220	230	240	270
20–29	240	250	260	290
30–39	270	280	290	340
≥40	290	300	310	360

Williams et al. [21]
FH is diagnosed if total cholesterol (mg/dl) exceeds these cut points

There are limitations both to genotypic diagnosis and to phenotypic diagnosis. A genotypic diagnosis is not identified in approximately 30% of patients with a phenotypic diagnosis of HeFH [7]. This does not negate the possibility of monogenic FH; it may be that the responsible mutation has not yet been identified. Alternatively, these individuals may have polygenic hypercholesterolemia.

There appears to be substantial overlap of LDL-C distribution of normal individuals with that of patients with genetic HeFH. For instance, Huijgen reported that 23% of patients with genotypic diagnosis of HeFH had LDL-C levels below the 90th percentile for the general population in a cross-sectional study of 26,406 persons in the Netherlands [8]. Garcia-Garcia noted that decreased penetrance of HeFH resulted in the finding of normal LDL-C concentrations in 7% of carriers of pathogenic mutations of LDLR or APOB [9]. Khera et al. have reported on whole exome sequencing in 26,025 individuals who participated in 12 cohort or case/control studies. In this group, they identified 164 persons with pathogenic mutation of LDLR, APOB, or PCSK9; 44 (27%) of these had LDL-C <130 mg/dl. Many of these would, therefore, fail to receive a phenotypic diagnosis of FH. However, they found that at any given stratum of LDL-C down to <130 mg/dl, the presence of a pathogenic mutation of LDLR, APOB, or PCSK9 caused a substantial increase in cardiovascular risk (Fig. 43.1). The explanation for increased ASCVD risk associated with a genotypic diagnosis of HeFH above and beyond risk predicted by current LDL-C level is probably that these patients have had *lifelong elevations of LDL-C* [10].

Overlap at the upper end of the LDL-C distribution of genotypically diagnosed patients with the LDL-C distribution of the general population also occurs. Only ~2% of those with LDL-C >190 mg/dl have a pathogenic mutation of LDLR, APOB, or PCSK9 [10].

Cascade family screening is recommended after identification of a patient with HeFH. This initially involves screening of first-degree relatives of the index case (the first case identified in a family) in order to identify additional cases of HeFH. If additional cases are found, their first-degree relatives are screened, and the process is repeated until all HeFH cases have been identified—thus, the term "cascade." Because it is not rare for patients with a pathogenic mutation of LDLR, APOB, or PCSK9 to fail to satisfy criteria for a phenotypic diagnosis of HeFH, genetic testing is an important part of the evaluation of index cases. When a pathogenic mutation has been found in the index case, genetic testing should be targeted to that causative

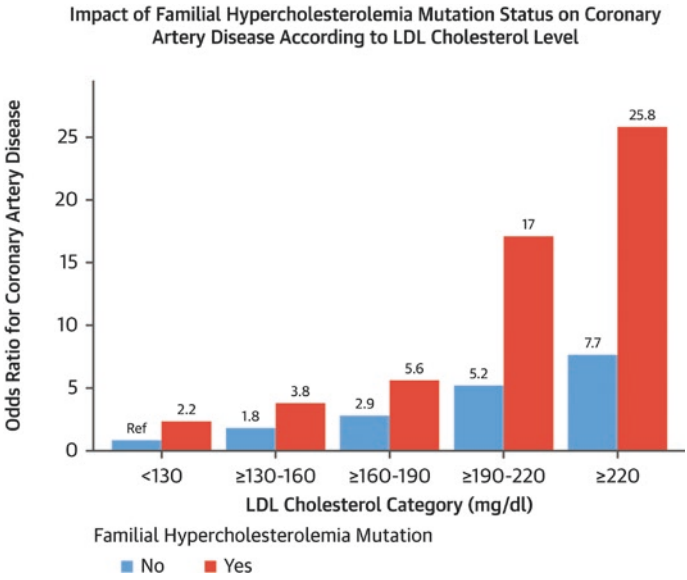

Fig. 43.1 Odds ratio for coronary artery disease stratified by LDL-C concentration in patients with and without FH mutation. (Modified from Khera et al. [10])

mutation in the course of cascade screening. This is cost-effective. It provides clinically useful information because the presence of an HeFH mutation indicates an increased risk of ASCVD beyond the risk expected on the basis of LDL-C alone. Of course, if DNA testing fails to identify a known pathogenic mutation in the index case, cascade screening should proceed without DNA analysis and must be limited to phenotypic diagnosis.

Lessons Learned

This patient provides an example of the responsiveness of patients with HeFH to intensive treatment with currently available medication to reduce LDL-C concentrations. She is now nearly 30 years older than her father had been when he first developed symptomatic ASCVD, and she shows no evidence of ASCVD.

The ability of LDL-reducing treatment to prevent ASCVD in her is particularly striking in view of her elevation of Lp(a). Not only did SL begin life with increased CHD risk because of FH, but also an elevation of Lp(a) further increased her risk. Lp(a) is a cholesterol-rich lipoprotein, the protein moiety of which is a molecule of apoB linked by a disulfide bond to a molecule of apo(a). Lp(a) levels are predominantly determined by a person's genetics; diet has no impact on Lp(a) levels. Statins may slightly increase Lp(a) levels; PCSK9 inhibitors reduce Lp(a) by ~30%. The mechanisms whereby an elevation of Lp(a) concentration may increase ASCVD events involve effects on blood clotting and on atherogenesis. Apo(a) has homology to plasminogen; it can thereby interfere with fibrinolysis; Lp(a) also has the capacity to deliver cholesterol to the vascular wall [11]. Elevated levels of Lp(a) have

been shown to cause increased risk of ASCVD events in patients without HeFH and in those with HeFH. Two Mendelian randomization studies in the general population have estimated the change in Lp(a) that would produce the same change in ASCVD risk as a change in LDL-C of 38.7 mg/dl (1 mM/L): this has been estimated as 67 mg/dl change in Lp(a) in the report of Lamina et al. [12] and as 102 mg/dl in the report of Burgess et al. [13]. Although the overwhelmingly powerful risk factor in patients with FH is usually elevation of LDL-C, other factors including elevated Lp(a) levels (as well as age, male sex, current smoking, diabetes mellitus, HDL-C <40 mg/dl, and xanthomas) can further increase risk in patients with HeFH [14–16]. In patient SL, the elevation of Lp(a) (112 mg/dl) would, thus, yield an increased cardiovascular risk equivalent to that resulting from an additional 42–64 mg/dl of LDL-C. The 2018 ACC/AHA Multisociety Guideline on the Management of Blood Cholesterol considers elevated Lp(a) to be a risk-enhancing factor that is useful when decisions about therapy are uncertain [17].

A CAC score (0 vs >0 Agatston units) is often useful in refining assessment of ASCVD risk. However, CAC is difficult to interpret in statin-treated patients such as SL. Paradoxically, statin treatment increases CAC [18], although statin treatment has been definitively shown to reduce atherosclerosis volume, high-risk plaque features, and ASCVD events. For this reason, the 2018 ACC/AHA Multisociety Guideline advises that "CAC measurement has no utility in patients treated with statins" [17].

The 2018 guideline recommends consideration of a PCSK9 inhibitor in patients with HeFH who have LDL-C ≥130 mg/dl despite maximally tolerated statin an ezetimibe therapy. SL had LDL-C 98 mg/dl when taking rosuvastatin, ezetimibe, and niacin. The discontinuation of niacin was expected to result in LDL-C >130 mg/dl. Because of this and the increased risk implied by her high Lp(a) concentration, she initiated treatment with alirocumab and achieved excellent control of LDL-C.

Questions

Correct Answers in Bold Italics

1. Which of the following statements about familial hypercholesterolemia is TRUE:

   (a) In FH, the level of LDL-C is so high that other factors such as cigarette smoking and hypertension, when present, do not make a significant additional contribution to risk of atherosclerotic cardiovascular disease (ASCVD).
   (b) Most patients with LDL-C >190 mg/dl have an identifiable FH mutation.
   (c) FH has autosomal recessive inheritance.
   (d) ***FH is caused by a pathogenic mutation in LDLR, APOB, or PCS9.***

2. Which of the following statements about familial hypercholesterolemia is TRUE:

   (a) In nearly all patients with a clinical diagnosis of FH, a pathogenic mutation of LDLR, APOB, or PCSK9 can be identified.
   (b) ***Pathogenic mutation of LDLR is the most common cause of FH.***

(c) Adult patients with a genetic diagnosis of FH will almost never have LDL-C <190 mg/dl in the absence of treatment with lipid-lowering medication.
(d) Assessment of coronary artery calcium is a useful way of monitoring the benefit of treatment with statins, particularly in patients with FH.

3. Which of the following statements is TRUE:

(a) The risk of ASCVD in FH is similar to that seen in non-FH patients with a similar elevation of LDL-C.
(b) Genetic testing should generally be avoided in the course of family cascade screening because it adds little to clinical diagnosis by validated protocols such as the Dutch Lipid Clinic Network criteria.
(c) Lp(a) contains apoB and apoC-III as its protein components.
(d) ***Lp(a) can interfere with thrombolysis by virtue of homology of apo(a) to plasminogen.***

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Chapter 44
Familial Partial Lipodystrophy Presenting as Extreme Hypertriglyceridemia and Acute Pancreatitis

Abhimanyu Garg

Objectives

1. To recognize patients with familial partial lipodystrophies presenting with extreme hypertriglyceridemia
2. To make a clinical diagnosis of familial partial lipodystrophy
3. To confirm the diagnosis of familial partial lipodystrophy with genotyping of the candidate genes

Case Presentation

F200.11. This 40-year-old white female presented with recurrent episodes of acute pancreatitis due to extreme hypertriglyceridemia (type 5 hyperlipoproteinemia) (Fig. 44.1a, b). Clinical data of this patient have been reported in brief previously [1]. She first noted prominent muscles in extremities at the age of 18 years. Her appearance in early childhood was normal. She had chylomicronemia-induced acute pancreatitis at age 18 years. Since then, she had multiple recurrent attacks of abdominal pain and acute pancreatitis. Fatty tumors were removed from the right inguinal area at age 19 years and from left axilla at age 30 years. She had menarche at age 13 years and had regular menstrual periods. She had five unassisted pregnancies. The patient lactated normally, after deliveries. At age 34 years, she had a total hysterectomy and bilateral oophorectomy for heavy vaginal bleeding. She had cholecystectomy at age 35 years for gallstones. She developed diabetes mellitus at age 38 years. She took oral sulfonylureas initially but, because of poor glycemic control, was switched to

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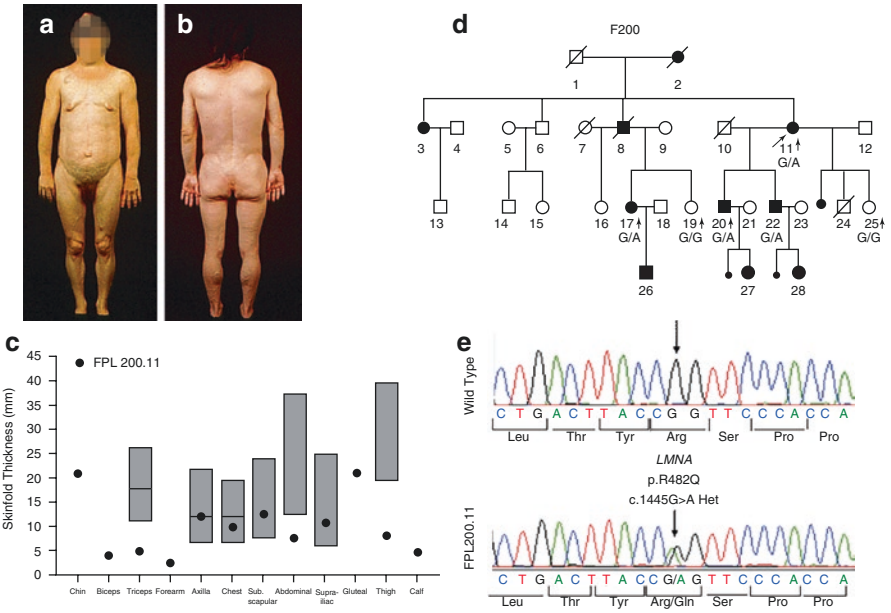

Fig. 44.1 Clinical features, skinfold thickness measurements, pedigree of the patient, and chromatogram for *LMNA* Sanger sequencing. (**a**, **b**) Anterior and posterior views of a 43-year-old female with familial partial lipodystrophy of the Dunnigan variety (FPLD2). There is marked loss of subcutaneous fat from both the extremities and gluteal and anterior truncal area with prominent veins and underlying musculature. There is excess subcutaneous fat deposition in the face, chin, neck, upper back, and labia majora. (These two figures are reproduced from Peters et al. [11]). (**c**) Skinfold thickness at various anatomical sites in our patient with FPLD2. The bars represent the median and 10th and 90th percentile values of skinfold thickness for the normal women, aged 18–55 years [8]. The patient had considerably reduced peripheral skinfold thickness at the triceps, anterior abdomen, and anterior thigh regions, while she had normal skinfold thickness in the axilla, chest, subscapular, and supra-iliac regions. (**d**) Pedigree of our patient with FPLD2. Circles denote females and squares represent males. Slanting arrow indicates the proband. Filled black symbols indicate affected subjects based on clinical information, and unfilled symbols indicate unaffected subjects. Filled gray symbols indicate indeterminate phenotype in children. A diagonal line across a symbol indicates a deceased subject. The genotypes of the subjects for whom DNA was available (vertical arrows) are given under the symbols. Subjects with heterozygous c.1445G>A pathogenic *LMNA* variant are shown as G/A and those with wild type as G/G. (**e**) Sequence electropherograms from Sanger sequencing of exon 8 of *LMNA* showing the wild-type sequence and the heterozygous c.1445G>A, p.Arg482Gln pathogenic variant in the proband, FPL200.11. The arrow indicates the site of the variant

insulin therapy. Despite 195 units of total insulin subcutaneously daily, diabetes was not well controlled. She was also on gemfibrozil 600 mg twice daily orally.

Physical examination revealed blood pressure of 134/84 mm Hg and pulse rate of 84 beats per minute. Her height was 1.57 m and weight was 58 kg with a body mass index of 23.6 kg/m^2. She had a well-built, muscular appearance; round face; and double chin, with prominent supraclavicular fat pads but no buffalo hump. She

had acanthosis nigricans in the neck, axillae, and groin. The liver and spleen were palpable, 6 and 4 cm below the costal margins, respectively. Cardiovascular and pulmonary examinations were within normal limits. Neurological examination revealed loss of knee and ankle reflexes suggestive of peripheral neuropathy. She had marked loss of subcutaneous (SC) fat from both the upper and lower extremities and from the gluteal region with prominent muscles and subcutaneous veins. Fat loss was also evident from the anterior part of the chest and abdomen, with breast atrophy and prominent recti abdominis. She had no clitoromegaly or excess facial or body hair. At the age of 43 years, she had numerous eruptive and plantar xanthomas. Skinfold thickness measurements revealed a triceps skinfold of 5 mm and anterior mid-thigh skinfold of 6 mm (Fig. 44.1c). Her total body fat by underwater weighing was 22.6%. A whole-body dual-energy X-ray absorptiometry (DXA) scan for regional body fat determination was not done.

Her older sister and older brother's daughter also had diabetes mellitus and type 5 hyperlipoproteinemia (Fig. 44.1d). She had two living sons, both of whom had muscular appearance and a healthy daughter.

Laboratory data revealed fasting blood glucose of 353 mg/dL (19.6 mmol/L), serum triglycerides of 14,100 mg/dL (159.2 mmol/L), and cholesterol of 262 mg/dL (6.76 mmol/L). Her alanine aminotransferase and aspartate aminotransferase and gamma glutamyl transferase levels were normal. Hemoglobin A1c was 9.1%. A whole-body magnetic resonance imaging revealed marked subcutaneous fat loss from the arms, legs, and hips but preservation of subcutaneous fat in the face, anterior and posterior neck, submental region, intra-abdominal region, and labia majora [1]. The fat in the intermuscular fasciae was also preserved [1]. Sanger sequencing of lamin A/C (*LMNA*) gene revealed a heterozygous c.1445G>A, p.Arg482Gln pathogenic variant establishing the diagnosis of familial partial lipodystrophy of Dunnigan variety (FPLD2) (Fig. 44.1e).

How the Diagnosis Was Made

FPLD2 is a rare autosomal dominant disorder with an estimated prevalence of 1 in 100,000 to 1 in 1 million. However, in some populations, it has been found to be more prevalent such as from Quebec, Canada, and Reunion Island in Indian Ocean, France. FPLD2 is characterized by progressive loss of subcutaneous (SC) body fat from the extremities and gluteal region starting during early or late childhood [2] and accompanied by excess SC fat deposition in the face, submental region (chin), supraclavicular fossae, dorso-cervical region (causing buffalo hump), intra-abdominal region, and labia majora [1]. Some subjects thus develop a Cushingoid appearance and may be suspected of having Cushing's syndrome. Loss of SC fat results in muscular appearance of the extremities and prominence of SC veins which is especially unusual for affected females. Since affected subjects have normal body fat distribution at birth and during early childhood, it is difficult to diagnose FPLD2 during early childhood by physical examination. FPLD2 is also difficult to diagnose in adult males as many normal males have reduced

SC fat in the extremities. Furthermore, affected females develop more metabolic complications such as diabetes, hypertriglyceridemia, hepatic steatosis, and atherosclerotic vascular complications such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease [3].

Lack of SC fat from the extremities and gluteal region limits the triglyceride storage capacity of the adipose tissue, and excess dietary triglycerides instead are deposited in ectopic sites such as the liver and skeletal muscle causing steatosis and insulin resistance. Other manifestations of insulin resistance are also more prevalent such as acanthosis nigricans in the neck, axillae, and groin as well as hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus [3]. Some women with FPLD2 may present with gestational diabetes as the initial metabolic complication. Approximately 25% of the females with FPLD2 also have irregular menstrual periods due to polycystic ovarian syndrome. Some affected females may also develop hirsutism, clitoromegaly, and acne vulgaris. Hepatic steatosis can cause excess very low-density lipoprotein production by the liver and contribute to hypertriglyceridemia. Uncontrolled diabetes can further exacerbate hypertriglyceridemia and chylomicronemia and result in repeated episodes of acute pancreatitis accompanied by eruptive, tuberous, and planar xanthomas.

Some patients with FPLD2 also develop cardiomyopathy, muscular dystrophy, and progeroid features due to inheriting specific *LMNA* variants [4, 5]. These patients should be carefully followed for signs of congestive heart failure or arrhythmias or conduction system disturbances. Some of them require pacemakers, whereas others may need cardiac transplantation during early adulthood.

Major causes of mortality in FPLD2 patients include coronary heart disease, cardiomyopathy, congestive heart failure, arrhythmias, steatohepatitis progressing to cirrhosis and liver failure, kidney failure due to diabetic nephropathy, and acute pancreatitis due to extreme hypertriglyceridemia [6, 7].

The diagnosis of FPLD2 should be suspected in patients presenting with lack of SC fat on the extremities, muscular appearance, prominent SC veins on the extremities, severe acanthosis nigricans, cardiomyopathy, and Cushingoid and progeroid appearance [8]. It should also be suspected in patients with diabetes mellitus with extreme insulin requirements (>200 units/day or 2 units/kg/day) and polycystic ovarian syndrome, nonalcoholic hepatic steatosis or steatohepatitis in nonobese individual, and in those with severe hypertriglyceridemia [8].

Clinical diagnosis of FPLD2 can be based on history, physical examination, body composition, and metabolic status. Measurement of skinfold thickness at the mid-triceps (<6 mm in adult males and <11 mm in adult females) and anterior midthigh (<8 mm in adult males and <19.5 mm in adult females), which are below the 10th percentile of normal values, can increase the diagnostic suspicion for FPLD2 [8]. Measurement of regional body fat by whole-body DXA scan can also be helpful. Recent data suggest that in adult females, lower-extremity fat of <1st percentile of age-specific normal values from the National Health and Nutrition Examination Survey (NHANES) is 99.5% specific and 100% sensitive for diagnosis of FPLD2 [9]. Serum leptin levels do not establish or exclude the diagnosis of FPLD2 [8]. Confirmation of diagnosis requires genetic testing.

FPLD2 is caused by heterozygous, mostly missense variants in the lamin A/C (*LMNA*) gene [7]. In our experience, ~75% of patients with FPLD2 have a missense variant affecting the arginine residue at 482 position (p.R482Q, p.R482W, or p.R482L), and these patients are considered to have "typical" FPLD2, which usually presents with severe loss of SC fat from the extremities [7]. Other FPLD2 patients harboring variants in other positions of lamin A/C are considered to have "atypical" variety, and some of these patients may have milder loss of SC fat [7, 10]. Patients with variants affecting the amino-terminal region of lamin A/C are more likely to develop associated cardiomyopathy [4, 5].

There are several genotypically distinct varieties of FPLD (Table 44.1). The autosomal dominant FPLD is caused by heterozygous pathogenic variants in *LMNA*, *PPARG*, *PLIN1*, *ADRA2A*, or *AKT2* genes [7]. Extremely rare autosomal recessive subtypes of FPLD have been reported due to biallelic pathogenic variants in *CIDEC*, *PCYT1A*, *MFN2*, or *LIPE* genes [7]. FPLD2 due to *LMNA* variants is the most

Table 44.1 Classification of familial partial lipodystrophies

Subtype	Inheritance	Gene	Function of encoded protein(s)	Comments
FPLD1	AD	Unknown	Unknown	Loss of subcutaneous fat from the extremities
FPLD2	AD	*LMNA*	Nuclear lamina structure and function	Most prevalent subtype. Associated with cardiomyopathy, myopathy, or progeroid features in some patients. About 500 patients reported
FPLD3	AD	*PPARG*	Transcription factor important for adipocyte differentiation	Second most common subtype. Milder loss of SC fat than seen in classical FPLD2. About 70 patients reported
FPLD4	AD	*PLIN1*	Structural lipid droplet protein	Eight families reported. Acromegaloid features
FPLD5	AR	*CIDEC*	Lipid droplet protein	Single patient reported
FPLD6	AR	*LIPE*	Hormone-sensitive lipase enzyme involved in lipolysis	Associated with multiple symmetric lipomatosis and myopathy. Six families with 12 patients reported so far
FPLD7	AD	*ADRA2A*	Adrenergic receptor 2 alpha	Single family reported. Excess subcutaneous fat in the face and neck
FPLD8	AD	*AKT2*	Downstream insulin action	Single patient reported
FPLD9	AR	*PCYT1A*	Enzyme-converting phosphocholine to CDP-choline	Two patients reported. Also had short stature
FPLD10	AR	*MFN2*	Mitochondrial protein	Associated with multiple symmetric lipomatosis. Fourteen patients reported so far. Also associated with cystic bone lesions

AD autosomal dominant, *AR* autosomal recessive

common subtype of FPLD, followed by FPLD3 due to *PPARG* variants [7]. Therefore, in our research laboratory, we first conduct Sanger sequencing for *LMNA*, followed by *PPARG* in a patient presenting with FPLD, and if no pathogenic variants are found in the two candidate genes, we proceed to whole exome sequencing. There are commercial laboratories, which provide a "lipodystrophy panel" and sequencing of many lipodystrophy genes.

Lessons Learned

1. A detailed physical examination including visual inspection for fat loss from the hips, legs, and arms is critical for suspecting familial partial lipodystrophy.
2. Measurement of skinfold thickness, especially of the thigh and triceps region, can assist in further confirmation of the clinical diagnosis.
3. Whole-body DXA scan can provide further support for diagnosis of FPLD2 in females if the lower-extremity fat percentile is less than the age-specific 1st percentile.
4. Whole-body MRI can be used to further characterize body fat distribution of FPLD patients in details.
5. Final confirmation of diagnosis is dependent on genotyping of the candidate genes.

Multiple Choice Questions

Correct answer is in the bold font.

Question 1

Individuals with familial partial lipodystrophy are predisposed to the following:

(a) Hypertriglyceridemia
(b) Diabetes mellitus
(c) Hepatic steatosis
(d) **All of the above.**

Question 2

Familial partial lipodystrophy of the Dunnigan variety (FPLD2) is due to pathogenic heterozygous missense variants in the following gene:

(a) *PPARG*
(b) ***LMNA***
(c) *PLIN1*
(d) *ADRA2A*

Question 3

The following tests can be used for clinical diagnosis of familial partial lipodystrophy of Dunnigan variety (FPLD2):

(a) Loss of subcutaneous fat from the upper and lower extremities with increased muscularity and prominent subcutaneous veins on physical examination
(b) Reduced anterior thigh skinfold thickness below the 10th percentile of normal values

(c) Reduced lower-limb fat by dual-energy X-ray absorptiometry below 1st percentile of age-specific normal value in adult females
(d) **All of the above**

Question 4

Affected individuals with familial partial lipodystrophy of Dunnigan variety (FPLD2) have increased prevalence of:

(a) **Hypertriglyceridemia**
(b) High levels of low-density lipoprotein cholesterol
(c) High levels of high-density lipoprotein cholesterol
(d) None of the above

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Chapter 45
Severe Combined Hyperlipidemia and Multiple Medication Sensitivities

Daniel E. Soffer and Eugenia Gianos

Abbreviations

AP	Acute pancreatitis
apoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
CACS	Coronary artery calcium score
CM	Chylomicron
CMr	Chylomicron remnant
FCHL	Familial combined hyperlipidemia
FCS	Familial chylomicronemia syndrome
FDBL	Familial dysbetalipoproteinemia
FED	Fish-eye disease
FH	Familial hypercholesterolemia
FHTG	Familial hypertriglyceridemia
FLD	Familial LCAT deficiency
HDL	High-density lipoprotein
LCAT	Lecithin cholesterol acyltransferase
LDL	Low-density lipoprotein
LP	Lipoprotein
Lp(a)	Lipoprotein(a)
LpX	Lipoprotein X
MCS	Multifactorial chylomicronemia syndrome

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NMR	Nuclear magnetic resonance
TC	Total cholesterol
TG	Triglycerides
ULP	Ultracentrifugation lipoprotein

Objectives
Review diagnostic approaches to enhance clinical management in a patient with severe combined hyperlipidemia.

Case Presentation

DS is a 53-year-old overweight nonsmoker who presents for management of severe combined hyperlipidemia. He was first diagnosed at age 8 with total cholesterol (TC) of approximately 900 mg/dL and triglyceride (TG) levels above 3000 mg/dL by his report. He has been under the care of lipid specialists since that time until transferring his care to our program. He does not recall being given a specific lipid or lipoprotein (LP) diagnosis in the past beyond being told that he has severe combined hyperlipidemia.

He does not have clinical atherosclerotic cardiovascular disease (ASCVD). There is no history of acute pancreatitis (AP) or unexplained skin rashes. There is no history of kidney or liver disease, no history of thyroid dysfunction, no autoimmune or inflammatory diseases (rheumatoid arthritis, lupus, or psoriasis), and no history of infection with the human immunodeficiency virus (HIV).

He follows a Mediterranean diet and does not drink alcohol. He works at a desk job and does not have an exercise regimen. DS is of Eastern European descent. Details about his family history are not available, but there is no history of premature ASCVD events in his parents or siblings. He has three sons (ages 14, 11, and 4) who he describes as healthy; they have not had their lipid profiles examined.

Treatment History

DS has taken multiple lipid-lowering medications in the past and was deemed to be "statin intolerant." He reports a history of his medications being effective at impacting the lipids, but he has had variable attention to therapeutic lifestyle modification. He recalls having taken cholestyramine, niacin, multiple different statins, ezetimibe, and lomitapide in the past. He reports being on lipid-lowering medication approximately 50% of his lifetime since age 8. He is presently taking evolocumab 140 mg subcutaneous injection every 2 weeks (for more than 2 years).

Current Status

DS is 5′8″, weighs 190 lbs, and has body mass index (BMI) of 29 kg/m^2 with normal adipose distribution. Blood pressure is 120/80 and pulse 80 beats per minute. There are no xanthomas, xanthelasma, or corneal arcus. There is no rash or palmar discoloration. Cardiovascular and lung exams are normal; there are no vascular bruits. Abdominal examination is unremarkable.

Resting electrocardiogram is normal.

Laboratory results are reported in Table 45.1, and results from coronary artery calcium score (CACS) by computed tomography (CT) are in Table 45.2, with representative image demonstrating a long heterogeneous calcified coronary plaque in the left anterior descending (LAD) artery on CT in Fig. 45.1.

Table 45.1 Laboratory results

Lab Results (mg/dL)	6/28/2018	9/19/2018	1/25/2019	8/21/2019	2/19/2020
Lipid-lowering meds	Evolocumab 140 mg q2wk				
TC	364		220	275	236
TG	334		180	273	186
HDL-C	46		52	45	47
LDL-C (Friedewald/Martin-Hopkins)	251/261		132/136	175/181	152/157
Non-HDL-C	318		168	230	189
ApoB		146		96	87
Fasting blood glucose, serum creatinine, urinalysis, hepatic function panel, thyroid-stimulating hormone	Normal				

Key: *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *apoB* apolipoprotein B

Table 45.2 Coronary artery calcium score (CACS) by computed tomography (CT)

Vessel	No. of calcifications	Calcium volume (Agatston)	Calcium score
LM	0	0	0
LAD	4	118	126
LCx	2	35	28
RCA	6	141	152
Total	**12**	**294**	**306**

Results from coronary artery calcium score, reported in Agatston units. *LM* left main, *LAD* left anterior descending, *LCx* left circumflex, *RCA* right coronary artery

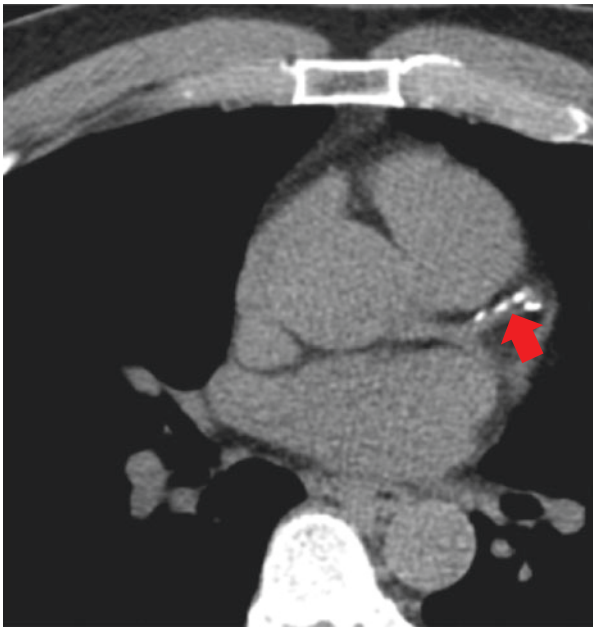

Fig. 45.1 Coronary artery computed tomography image demonstrating coronary artery calcification. Focused image from coronary CT; note calcified lesions in proximal and mid-left anterior descending (LAD) coronary artery (red arrow)

Review of How the Diagnosis Was Made

DS has a history of severe combined hyperlipidemia and high atherosclerosis burden after approximately 40 years of on/off pharmacotherapy and variable attention to lifestyle. Going forward, the clinical team was faced with the concerns of optimizing ASCVD and lipid management and performing appropriate cascade screening of family members. He has not tolerated multiple pharmacologic therapies and is not willing to consider apheresis at this time. Dietary intervention and novel pharmacotherapy, as well as investigational therapy, are available to him. A specific lipid/LP diagnosis may enable optimization of ongoing care.

Hyperlipidemia management can be improved by clarification of the LP excess and characterization of a specific syndrome and genetic profile. We will review the similarities and differences and how each approach will inform diagnosis in DS's care and for his family.

The Lipid Approach

Clinical lipid specialists have to understand lipids; however, the lipid profile may not "tell the whole story." Lipids must be transported in lipoproteins with variable amounts of TG and cholesterol in each LP species and variable levels of circulating LP.

The 2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol (aka the 2018 Guidelines) [1] is lipid-oriented and provides an evidence-based approach for managing cholesterol and triglycerides for the general population.

The guidelines stress the importance of lifestyle intervention, clinician-patient discussion, long-term monitoring, and tailoring intensity of care to the severity of ASCVD risk. They support the use of pharmacotherapy (high-intensity statins) for individuals with severe primary hypercholesterolemia/LDL-C >190 mg/dL. For individuals with elevated TG levels, after appropriate attention to secondary causes and dietary modification, pharmacotherapy should be considered based upon ASCVD risk (statins) and severity of TG elevation for prevention of acute pancreatitis (with high-dose omega-3 fatty acid supplementation and/or fibric acid derivatives).

Not all individuals with severe hypercholesterolemia have high LDL-C. In fact, the calculated LDL-C may severely misrepresent the actual LDL-C in particular circumstances (e.g., dysbetalipoproteinemia, LpX, sitosterolemia, hyperchylomicronemia), and not all patients with severe hypertriglyceridemia have high risk for ASCVD (e.g., isolated hyperchylomicronemia), so a clear understanding of the lipid diagnosis is essential. ApoB, phytosterol/stanol, and TG levels, along with clinical evaluation +/− specialized testing for free cholesterol and viscosity in the case of LpX, are necessary to clarify the proper diagnosis and treatment for those conditions.

DS has had TC as high as ~900 mg/dL. This can be seen in individuals with homozygous (HoFH) or compound heterozygous familial hypercholesterolemia (HeFH) variants (e.g., *LDLR, APOB, PCSK9, LDLRAP*) or when LDL-C is mistakenly reported based upon incorrect assumptions from the Friedewald equation. TC and LDL-C levels do not change dramatically in the case of HoFH or compound/double HeFH patients and would be expected to have been in that range his entire life. In those cases, treatment typically requires polypharmacy and lipoprotein apheresis.

Nephrotic syndrome or severe liver disease may lead to severe cholesterol elevations associated with high LDL-C +/− elevated LpX in the case of biliary obstructive disease. Whether to treat the hypercholesterolemia in this case and expectations of response to therapy in individuals with severe secondary hypercholesterolemia is complicated and decision-making should be customized to the individual needs.

DS has severe hypercholesterolemia and hypertriglyceridemia that has improved to moderate elevations in both while taking PCSK9 monoclonal antibody monotherapy. He also has a high atherosclerosis burden and would benefit from intensification of lipid lowering and need to address every aspect of atherosclerosis to optimize ASCVD risk reduction. Treatment options are limited because of prior side effects and personal reluctance.

The Lipoprotein Approach

Since lipids circulate in lipoproteins (LP), hyperlipidemia is due to excess LP. Donald Fredrickson and colleagues at the NIH devised a system in the 1960s for expressing LP excess in patients with hyperlipidemia, based upon laboratory

Table 45.3 Fredrickson-Levy-Lees (FLL) classification of hyperlipoproteinemia [3]

	I	IIa	IIb	III	IV	V
High TG	x		x	x	x	x
CM	x					x
LDL		x	x			
VLDL			x		x	x
TRLr				x		

x signifies lipoprotein class in excess, *TG* triglycerides, *CM* chylomicron, *LDL* low-density lipoprotein, *VLDL* very low-density lipoprotein, *TRLr* TG-rich lipoprotein remnant

methods from John Gofman's seminal work in the 1950s [2]. The Fredrickson-Levy-Lees (FLL) classification system [3] (see Table 45.3) identifies hyperlipidemia based upon the four main apoB-containing lipoproteins in circulation: low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), chylomicrons (CM), and TG-rich LP remnants (TRLr). Perturbations in normal metabolism result in elevated levels of one or two different LPs and are signified by a Roman numeral in the FLL system (I, IIa, IIb, III, IV, V). Three of the phenotypes are due to single LP excess that include CM (I), LDL (IIa), and VLDL (IV), and two of the described phenotypes are due to a combination of two LPs in excess: LDL/VLDL (IIb) and CM/VLDL (V). Type III phenotype has high levels of cholesterol-enriched TRLr (CM remnants and intermediate density lipoprotein (IDL) or partially lipolyzed VLDL) and relatively low apoB levels. Notably, all are associated with elevated TG except for IIa.

The pairing of elevated levels of LDL and CM would only be expected to be seen in the event of rare combined inherited abnormalities. In addition, rare inheritance patterns may result in poly-LP excess (LDL, VLDL, CM, TRLr) and will not be characterized by the FLL system. Low levels of HDL and LDL and high levels of phytosterols, Lp(a), and LpX are not characterized by this system either.

Individuals with specific inherited syndromes may manifest different LP phenotypes in the course of their life, and rarely does a specific LP phenotype define a specific syndrome. For example, an individual with familial chylomicronemia syndrome (FCS) due to homozygous lipoprotein lipase (LPL) deficiency may develop secondary diabetes mellitus (DM) with insulin resistance and convert from predominant type I to type V phenotype as a consequence of secondary DM or even just as part of normal aging. However, the converse can be very specific. Individuals who present with types I and III LP phenotypes have pathognomonic phenotype for FCS and familial dysbetalipoproteinemia (FDBL), respectively. Therefore, there is value in characterizing an individual phenotype when considering the diagnosis, and we will discuss how this information can inform clinical management in the next section "The Syndrome Approach".

Since LP phenotype can vary in an individual due to environmental factors, the phenotype should not be used as a diagnosis, but, rather, as a descriptor to characterize the present state. Despite its potential clinical utility, contemporary diagnosis

and management strategies tend to proceed without use of the FLL LP classification for a variety of reasons.

The FLL classification system has fallen out of favor since the 1990s because of the following:

1. The *FLL system requires complicated testing* with beta quantification after agarose gel electrophoresis or paper apheresis from preparative ultracentrifugation (ULP), a technique that is time- and work-intensive and available at very few centers. Furthermore, paper apheresis is largely qualitative rather than quantitative and has limited clinical utility. Nuclear magnetic resonance (NMR) spectroscopy and ion mobilization techniques enable more accessible tools for LP quantification, though clear standards and prespecified classification systems do not exist for these measurements and additional cost to testing is not always covered by health insurers.
2. *Estimating which LP is in excess is imprecise* without those tools and requires judgment by an experienced clinician that cannot be easily validated.
3. *Lipid and apoB analysis* without consideration of the specific LP excess *can still enable appropriate care and diagnosis*, especially when complementary clinical data (e.g., ASCVD, acute pancreatitis, skin/tendon manifestations, and genetic profile) are available.
4. *Available therapeutic interventions impact non-HDL-C or TG that is not LP-specific, so the LP phenotype does not typically inform treatment plan.*

In this case, neither ULP nor NMR was available and lipid-based rather than LP-based treatment was favored. The severe combined hyperlipidemia at age 8 does suggest initial presentation with either type V or III phenotypes at the time, however. The most recent lipid profile suggests IIb or IIa phenotype, while incorporation of the apoB level suggests type III (according to the 2007 Sniderman algorithm [4]). This level of uncertainty when characterizing phenotype without ULP or NMR is an example of the shortcoming of this approach.

The Syndrome Approach

Multiple lipid/LP syndromes have been described. A lipid/LP syndrome is characterized by persistent lipid and LP abnormalities with specific clinical manifestations reflecting an underlying inherited or acquired pathology. Table 45.4 describes some of the important characteristics of syndromes.

By confirming that an individual has a diagnosis in the Group 1 (monogenic) syndromes, care can be customized. For example, individuals with FCS tend to have inadequate response to the present FDA-approved pharmacotherapy but will respond to dietary modification aimed at limiting CM production which is a different diet than that needed for reducing VLDL production, whereas FH patients require targeted LDL lowering including a diet that reduces LDL-C; pharmacotherapy that enhances LDL clearance (or, in the case of HoFH, inhibits synthesis

Table 45.4 Hyperlipidemia syndromes

Syndromes	Monogenic/ polygenic	High LDL-C	High TG/CM	High TRLr	High apoB	Xanthoma	ASCVD risk	AP risk	Other clinical features	Specific treatment available	Family cascade screen recommended
Group 1 – monogenic											
FCS	Monogenic		+++/+++			+ (Eruptive)		+++	Lipemia retinalis, abdominal pain	Dietary; plasma exchange; gene therapy (previously available in Europe)	
FH	Monogenic	+++			+++	+ (Tendinous)	+++		Corneal arcus, aortic valve stenosis	Specific FDA-approved pharmacotherapies (e.g., PCSK9 mAb's, bempedoic acid); LP apheresis; lomitapide and evanacumab for HoFH	+
FDBL	Monogenic		+to+++/−	+++		+ (Tuberous, palmar striae)	++	+	PAD	Remnant-targeted; diet- and environment-sensitive	
Sitosterolemia	Monogenic	++			+	+ (Tendinous)	+		Serum sterols	CAI and/or BAS; dietary	
LALD	Monogenic	++	+/−		+		+		Microvesicular steatohepatitis	Enzyme replacement tx	

LpX	Monogenic (LCAT only); more commonly secondary to biliary obstruction					+			High free cholesterol; hyperviscosity; corneal opacity in FLD and FED	Plasma exchange; treat underlying cause	
Lp(a)	Monogenic						++		Aortic valve stenosis	LP apheresis for progressive ASCVD	+
Group 2 – polygenic											
FCHL	Polygenic	+	+/ Variable		+++		+++	+			+/−
FHTG	Polygenic		+/ Variable		+		+	+			
MCS	Polygenic		+/+++			+/− (Eruptive)	+	+++		Responds to meds and environmental change; plasma exchange	

FCS familial chylomicronemia syndrome, *FH* familial hypercholesterolemia, *HoFH* homozygous FH, *HeFH* heterozygous FH, *FDBL* familial dysbetalipoproteinemia, *LALD* lysosomal acid lipase deficiency, *CAI* cholesterol absorption inhibitor, *BAS* bile acid sequestrant, *LCAT* lecithin cholesterol acyltransferase, *FLD* familial LCAT deficiency, *FED* fish-eye disease, *FCHL* familial combined hyperlipidemia, *FHTG* familial hypertriglyceridemia, *MCS* multifactorial chylomicronemia syndrome

with lomitapide); and, in some cases, apheresis to remove LDL from the circulation. Some pharmacotherapy is explicitly (but not necessarily exclusively) FDA-approved for use in patients with FH, including PCSK9 monoclonal antibodies, bempedoic acid, and lomitapide, and recently, evinacumab (AngPTL3 monoclonal antibody). FH patients who have identifiable codominant genetic variants should also follow through with cascade screening of relatives for the same variant.

Furthermore, novel pharmacotherapy is under investigation for targeting treatment of individuals with specific syndromes (e.g., antisense oligonucleotide (ASO) therapy for apolipoprotein C3 (apoC3) inhibition in FCS patients; ASO and monoclonal Ab against AngPTL3 for HoFH; ASO and inhibitory RNA against apolipoprotein(a) for patients with high Lp(a)). Therefore, individuals may only be able to access these novel therapies in clinical trials or soon after approval if they are identified by syndrome.

Since hypertriglyceridemia is almost always caused by a combination of recessive gene and environment interactions, the family history does not typically reveal a specific pattern in patients with hypertriglyceridemia. In DS's case, which is very common in typical clinical management, the family history is vague, but does not suggest a particularly virulent ASCVD predisposition or history of severe lipid disorder. The authors believe that the benign family history and his lack of adverse events to date have contributed to DS's ambivalence about intensification of therapy. A syndromic diagnosis and demonstration of significant coronary atherosclerosis by CT were meant to inform recommendations for DS to intensify his treatment.

We have considered whether a more complete syndromic diagnosis would affect his interest in intensification of care. The highest lipid levels reported at age 8 suggested the presence of hyperchylomicronemia but with extreme hypercholesterolemia accompanying which makes FCS less likely, especially in light of subsequent effective treatment with PCSK9 mAb and maintenance of TG levels below 500 mg/dL without a fat-restricted diet. Therefore, MCS (Group 2) and FDBL may explain his presentation better. Furthermore, while FH can be associated with severe hypercholesterolemia and would respond well to PCSK9 mAb, elevated TG levels are not part of that syndrome, so either DS does not have FH or he has FH plus another inherited syndrome.

Given the childhood presentation without having developed clinical ASCVD or acute pancreatitis (AP) or the progression of secondary identifying factors like liver disease or nephrotic syndrome, we can conclude that DS does not have HoFH, FCS, LALD, or LpX. FDBL, sitosterolemia, and high Lp(a) remain possible, so additional testing of apoB, sterol levels, Lp(a), and genetic markers including *ABCG5/G8* and *APOE* will enable distinction of these syndromes respectively. In fact, based upon the clinical scenario, we do not have a complete sterol panel, and Lp(a) is not mentioned. We can thus still conclude that FH plus additional hypertriglyceridemia condition is possible, as is FDBL.

The childhood presentation and severe combined hyperlipidemia eliminate conditions associated with a single lipoprotein excess, so FCS, FH, and FHTG are only possible if an additional diagnosis is coincident. Thus, FDBL (monogenic) and

MCS (polygenic) or combined defects (always polygenic) are the only syndromes left to explain DS's condition with a single diagnosis.

If a single lipid syndrome is not possible, then consider whether there are multiple syndromes present.

FDBL is quite rarely reported in children as its manifestation requires a "2nd hit" and should have physical stigmata reported. Similarly, MCS in the absence of severe insulin resistance, obesity, or endocrinopathy is not expected to occur by age 8, nor was this described in DS's history, suggesting that a combined defect is the likeliest explanation.

The Genetic Approach

Individuals with the FH phenotype (LDL-C >190 mg/dL or >160 mg/dL in younger patients or those with enhancing risk factors and historical characteristics) should undergo genetic testing, and if a monogenic cause is found, then first-degree relatives are encouraged to be tested as well [5]. Genetic testing for non-FH causes can be considered as well when canonical FH genotype is not found (i.e., pathogenic variants in the *LDLR, APOB, PCSK9, LDLRAP*) and may include testing for *APOE*, sitosterolemia, LALD, and Lp(a). Genetic testing for polygenic causes of the FH phenotype is not commercially available yet but may also inform clinical care when monogenic cause is not found. Similarly, genetic testing is recommended for those with severe hypertriglyceridemia when FCS is suspected. While the majority of patients with severe hypertriglyceridemia will be found to have polygenic causes, monogenic causes associated with severe reductions in lipoprotein lipase (LPL) activity do require specific lifelong dietary intervention, are known to have minimal or no response to the present available pharmacotherapy, enable access to participation in clinical trials with novel therapy, and may inform specific approach to plasma exchange or even gene therapy (formerly available in Europe). In addition, identification of the genetic background may identify whether FDBL is present, though the phenotype should always dictate the care in these patients.

In the case of inherited LP syndromes, only FH requires cascade testing for family members since it is the only monogenic autosomal codominant hyperlipidemia syndrome.

Widespread use of genetic testing without lipid or LP information is not recommended. The genetic profile may suggest a particular risk for disease, but will not define the lipid or LP condition, which is always highly susceptible to environmental factors. For example, we know that individuals who have inherited genotypes associated with FH may have greater risk for ASCVD [6, 7]; however, the presence of the genotype does not dictate specific therapy at this time according to the FH genotype algorithm by Sturm et al. [8], from the National Lipid Association (NLA) position statements on genetic dyslipidemia [5] or based upon Lp(a) alone [9]. However, a heightened vigilance for ASCVD risk is supported for those individuals

who have known inherited genetic susceptibility for those conditions. In the case of Lp(a), genetic testing is not recommended beyond a test for Lp(a) levels.

With respect to high TG syndromes, monogenic FCS (due to homozygous or compound heterozygous inheritance of variants in *LPL, LMF1, GPIHBP1, APOA5, APOC2*) should be considered and evaluated because of clinical implications already mentioned. Furthermore, FDBL due to *APOE* variants should also be considered; though similar to FH, it is the lipid/LP phenotype that will dictate care, not the genotype [5].

Of the remaining cases where genotyping is used, only LALD has significant clinical implications since enzyme replacement therapy is available for this condition and severe liver disease is expected without treatment. Sitosterolemia management will depend upon the lipid/LP and clinical characteristics and can be established without genotyping but is reasonable to pursue in the right clinical scenario.

Genetic testing clarifies the diagnosis.

DS was found to have a combined genetic disorder. Contemporary NexGen sequencing of the *LDLR, APOB, PCSK9,* and *LDLRAP1* genes was completed, and he was found to have a pathogenic deletion mutation of three nucleotides in succession in exon 4 of the *LDLR* gene (a known variant most common amongst Ashkenazi Jewish people). In addition, using polymerase chain reaction (PCR) and fluorescence monitoring using hybridization probes, he was also found to have *APOE2* homozygosity, the genotype most commonly associated with FDBL. Since FDBL requires homozygous inheritance of the common apo-e2 allele (or inheritance of other rare *APOE* mutations), family cascade screening is not necessary in FDBL. However, because FH is due to a codominant inheritance pattern, FH is a strong indication for family cascade screening as suggested by the Scientific Expert Panel [8] and by the NLA Scientific Statement [5].

Additional lifestyle and genetic counseling, as well as therapy with aspirin 81 mg daily, bempedoic acid 180 mg daily (still pending outcomes trial data), and LP apheresis, have all been offered to DS, and he continues to follow up for ongoing care. He has not yet followed through with cascade screening of his children or siblings.

Lessons Learned

While most cases of combined hyperlipidemia are thought to be the result of both inherited and environmental factors [5], the relative impact of a lipid/LP syndrome may affect clinical decision-making, prognosis, and family cascade screening. The advent and availability of affordable genetic testing enable a higher degree of precision and should be offered to all individuals with severe LDL and/or TG elevations.

Whether or not a confirmation of LP excess is possible, diagnosis of a particular syndrome through testing may enable targeted treatment that is better informed and more precise than a lipid description alone. In this case, the LP designation was not available, and the mixed lipid condition did not clearly define a syndrome. However, both FH and FDBL genotypes are present, and this enabled clarification of the underlying physiology and expected phenotype, informed ongoing treatment, and family cascade screening.

With respect to his dietary and pharmacologic treatment, because DS has FH and FDBL, he requires treatment aimed at both LDL and TRLrs. The LDL is targeted with reduction of dietary saturated fat and cholesterol, whereas dietary counseling for individuals with FDBL is aimed at mitigating insulin resistance and abdominal/visceral weight gain by limiting total calories, processed food (especially added sugars), sugar-sweetened beverages, alcohol, starches, and simple carbohydrates. Thus, a Mediterranean-style diet with limitation of saturated fat was recommended. Total fat may have to be limited if TGs rise >1000 mg/dL.

With respect to pharmacotherapy, LDL-directed treatment (statin, ezetimibe, PCSK9 mAb, bempedoic acid, and bile acid sequestrant) is critical for FH, and the diagnosis of FH does enable insurer-approved access to specific therapies that are limited to those individuals with that diagnosis (PCSK9 mAb, bempedoic acid) and absent clinical ASCVD. Pharmacotherapy for managing FDBL targets VLDL synthesis and optimizing TRL clearance (e.g., fibric acid derivative, high-dose omega-3, statin, possibly ezetimibe, PCSK9 mAb, bempedoic acid, and avoidance of bile acid sequestrants (BAS) because of high TG). Of note, lomitapide and evinacumab are not indicated unless there is HoFH or severe HeFH (e.g., compound or double HeFH) or functional HoFH. One could make the case here that DS has functional HoFH based upon the severity of his early presentation and height of calculated LDL-C.

Since both FH and FDBL are present, combination pharmacotherapy is warranted. Prior side effects and experiences have left DS wary of rechallenge with older therapies, but he appears willing to consider novel therapies (e.g., bempedoic acid). If current therapies are exhausted and he has not achieved optimal lipid levels, apheresis can again be discussed. We do not yet know the role of anti-apoC3 or anti-AngPTL3 therapies for a patient like this. LP apheresis or even plasma exchange may be considered given the very high residual ASCVD risk in this case.

Based upon what we have learned from genetic testing DS, his sons, siblings, and parents should all undergo genetic testing for inheritance of the same *LDLR* variant since its presence portends a worse ASCVD prognosis and may inform their clinical care beyond the standard lipid profile. Additional testing may be considered if family members also have hypertriglyceridemia. Cascade screening could improve the health and longevity of DS's family, altering the poor outcomes often seen in patients with severe lipid disorders.

Multiple Choice Questions [3–5]

1. Which lipoprotein phenotype is expected to have normal triglyceride (TG) levels?

    1. I
    2. IIa
    3. IIb
    4. III
    5. IV
    6. V

2. Which lipid/lipoprotein syndrome is associated with a codominant trait?

    1. Familial chylomicronemia syndrome (FCS)

2. Familial hypercholesterolemia (FH)
3. Familial dysbetalipoproteinemia (FDBL)
4. Familial hypertriglyceridemia (FHTG)
5. Lipoprotein X

3. A very low-fat diet is recommended to treat which lipoprotein syndrome?

1. Familial chylomicronemia syndrome (FCS)
2. Familial hypercholesterolemia (FH)
3. Familial dysbetalipoproteinemia (FDBL)
4. Familial hypertriglyceridemia (FHTG)
5. Lipoprotein X

4. High levels of apolipoprotein B (apoB >120 mg/dL) are expected in which lipoprotein syndrome?

1. Familial chylomicronemia syndrome (FCS)
2. Familial hypercholesterolemia (FH)
3. Familial dysbetalipoproteinemia (FDBL)
4. Familial hypertriglyceridemia (FHTG)
5. Lipoprotein X

5. Statin therapy is the first-line option as treatment for which lipoprotein syndrome?

1. Familial chylomicronemia syndrome (FCS)
2. Familial hypercholesterolemia (FH)
3. Familial dysbetalipoproteinemia (FDBL)
4. Familial hypertriglyceridemia (FHTG)
5. Lipoprotein X

Multiple Choice Answers

1. All of the FLL phenotypes have high TG except for type IIa (see table), due to excess in TRL. The *correct answer is 2*.
2. FH is transmitted as a codominant trait even when associated with polygenic cause; thus, the *correct answer is 2*. The other syndromes listed are associated with either known recessive genes or genes with limited penetrance. In the case of FHTG, the genetics are not consistent, and some argue that it should not be considered a specific syndrome since genetic transmission is always due to polygenic cause. LpX occurs as a result of LCAT deficiency (a rare autosomal recessive condition associated with severely reduced HDL-C levels, ophthalmologic and renal manifestations) or acquired as a result of biliary obstruction from any cause.
3. A very low-fat diet is indicated to limit chylomicron production by enterocytes. Individuals with FCS have inherited defects in lipoprotein lipase (*LPL*) or critical cofactors (*APOA5, APOC2, GBIHBP1, LMF1*). This syndrome is characterized by very low LPL activity and inability to clear CM (and other TRL) from the circulation. It tends to be refractory to contemporary approved pharmacotherapy (e.g., fibrates and high-dose omega-3) but responds to a very low-fat diet

by limiting CM production; the *correct answer is 1*. Investigational products show promise in treating this condition. Reduced fat diets (~30–40% of calories) are typical of a healthy dietary pattern appropriate for patients with FH, FDBL, and FHTG as long as the TG levels are <1000 mg/dL. There is no specific diet recommended for LpX.

4. The 2007 Sniderman review identified that LP phenotypes IIa and IIb were both associated with high levels of apoB (>120 mg/dL); the *correct answer is 2*. FCS is associated with low level. FDBL and FHTG have low or normal apoB, though FDBL will have significant discordance and even low apoB levels. LpX does not contain apoB, so an elevated level would suggest the presence of other LPs in circulation.
5. High-intensity statins are recommended in the 2018 AHA/ACC/MS cholesterol guidelines for individuals with persistent LDL-C >190 mg/dL or if FH is suspected/diagnosed; the *correct answer is 2*. Statins are not indicated to treat FCS which is characterized by excess CM. Statins can have a role in management of FDBL and FHTG depending upon the ASCVD risk, but are not typically first-line options. Statins are contraindicated to treat LpX when it is due to advanced hepatobiliary disease but may be considered early in the course of the disease in individuals who have hypercholesterolemia due to LpX as long as there is high apoB; these individuals require close monitoring and dose reduction or cessation if hepatobiliary disease progresses. Statins are not indicated in individuals who have LpX due to LCAT deficiency.

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Part XII
Obesity

Chapter 46
Introduction

Katherine Samaras

The Obesity Epidemic

Obesity Literacy in Endocrine Practice: The Physiology of Energy Homeostasis and Mechanisms Driving Weight Gain and Weight Regain

Understanding how human beings have survived environmental catastrophes such as famine, war, food insecurity due to crop failures, climate change, or hostile food or trade blockades helps us understand how human beings have evolved over millennia with the energy storage and food searching capabilities to overcome such significant privations. For example, consider the conditions of relatively recent historical episodes in human history such as the Dutch famine, the Siege of St. Petersburg, World War II internment or concentration camps, the Great Chinese Famine and other famine or war conditions that have led to mass migrations under significant survival duress: Cambodia, Sudan, Eritrea, Ethiopia, and Syria. This list is only representative and not at all comprehensive. Then, consider shifts in food agricultural practices and food cultures: the impact of attrition of small-holding effort-intensive farming, transitions to industrialized food production and mass production, the advent of "fast food" and highly refined energy-dense (often nutrient-poor) foods, and the loss of family food literacy and cooking skills and their devaluing. Consider the contemporary circumstances many people living in industrialized nations find themselves: ease of access to cheap, energy-dense foods; challenges in sourcing nutrient-rich, less energy-dense foods; and reduced physical effort to economically survive: less movement in the workplace and in travelling to

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the workplace and living environments where physical activity is not encouraged, whether through poor planning or being perceived unsafe. Consider the impact of the recent coronavirus pandemic on physical activities with lockdowns and movement restrictions, the advent of working from home, and online work environments where only our fingers do the walking. The energy balance equation is stacked toward excess energy consumption in circumstances where our opportunities for energy expenditure seem to diminish. Those with stronger genetic predisposition are at risk of the greatest weight gain and obesity.

With that background, it is easy to see how human beings, in an environment of chronic energy balance disequilibrium, will become obese. Overweight and obesity (body mass index exceeding 25 and 30 kg/m^2, respectively) afflict approximately 37% of adult men and 30% of women and 23–24% of children worldwide [1]. Rates in industrialized nations are substantially higher. The United States has the highest overweight and obesity prevalence rates internationally at two in three adults [2]. Modelling based on rising prevalence rates has estimated that 85% of American adults will be overweight or obese by 2030 [3]. Obesity is now the major driver of cancer in countries where smoking rates have declined, particularly esophageal, endometrial, breast, and prostate [4]. Obesity is a major contributor to type 2 diabetes mellitus, ischemic heart disease, cirrhosis, gastroesophageal reflux disease, obstructive sleep apnea, degenerative joint disease, and polycystic ovary syndrome and infertility [5]. In other words, obesity impacts every area of medical and surgical practice, and many health conditions will be improved, if not ameliorated, by obesity intervention. It is imperative for every endocrinologist to understand the assessment of obesity with evaluation of promoting factors and obesity interventions: nutritional intervention, psychological intervention, pharmacotherapy, and bariatric surgery and work in partnerships with our general medicine and specialist colleagues and our patients.

An understanding of obesity requires a knowledge of obesity physiology and adipose tissue homeostasis. As endocrinology is a speciality grounded in regulation and feedback mechanisms, endocrinologists are well placed in grappling with why it is so difficult for obese people who have lost weight to maintain that weight loss for the longer term. Readers are referred to a comprehensive review of the homeostatic mechanisms that promote weight regain in those who have successfully lost weight [6]. Understanding these mechanisms assists clinicians in understanding that obesity treatment involves long-term (if not our work-lifelong) commitment to our patient for sustained intervention. The clinical imperative and commitment to our obese patients is to motivate and guide them through successes, plateaus, and slides, modifying, escalating, and supporting multipronged interventions, drawing in the support of our allied health profession colleagues and not failing our patients with our own treatment nihilism. Our role is to maintain vigor and rigor in our clinical

capabilities to inspire and treat patients to battle their survivor physiology which seeks to drive their weight upward.

Obesity Literacy in Endocrine Practice: Management Strategies and the Long Haul of Physician Engagement

The three cases below are aimed at encouraging standards of endocrine practice to a wholistic evaluation of the person living with obesity. The fundamentals of history taking and physical examination and aspects of treatment individualization. No two people with obesity have had the same journey to their current condition, nor will they have the same therapeutic pathway. While there are common features (a chronic excess of energy intake over energy expenditure), the factors driving eating choices, eating behaviors, and sedentariness will vary as widely as will the health consequences which will require comprehensive evaluation and addressing.

How should the endocrinologist involved in the care of a person with obesity consider themselves? There are numerous hats, each of which can expand the exercise of physician's skills and job satisfaction: expert assessment of physical health issues and addressing each one, expert and adept use of pharmacology, detective work in understanding the drivers of unhelpful eating behaviors and scaffolding several approaches to provide alternative stimulus outcomes which undermine a patient's motivation or progress. Life coach, counsellor and advisor, role model, team cheerleader. Consider the physician's role in your patient's recovery from obesity as someone who walks along the pathway, supporting the journey, which will have traps, landslides, and regressions. Our role is to guide, support, and use our skills, knowledge, and understanding to remediate this pervasive condition. Beyond this individualized role, do we have others? My view is yes: we hopefully share our knowledge with peers, trainees, and students and inspire them not to be afraid or fatigued by addressing obesity. We stimulate ourselves and others not to be victims of therapeutic nihilism, to never give up, and to never to judge. We need to remind ourselves that obesity management is chronic disease management which is multidisciplinary, multifaceted, and professionally rewarding. There may be roles for us in advocacy: within hospitals to obtain an equitable share of resources such as access to expert dietetic and psychology intervention; advocacy in lobbying our town planners and politicians in considering the layouts of town centers, public transport, and safe areas for physical activity; advocating for parity in access to unprocessed whole foods (both physical and financial); parity of access of expensive pharmaceuticals and bariatric procedures. It is a partnership with our patients and for our patients. With these philosophies and commitments in mind, the next three case vignettes illustrate the steps in assessing and individualizing obesity interventions and tackling dietary interventions, physical activity prescription, and psychological interventions (including diversional approaches), pharmacotherapy, the principles and safe application of very low-energy diets, and bariatric surgery in

people with an array of comorbid conditions including insulin-requiring diabetes, severe heart failure, renal impairment, and severe mental illness. These vignettes are stimulus points to consider and discuss management issues frequently encountered in our patients with obesity.

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Chapter 47
Obesity Case Management: Bariatric Surgery

Bon Hyang Lee and Katherine Samaras

Objectives

1. Review indications of bariatric surgery in the management of obesity, and briefly describe surgical procedures
2. Discuss the preoperative and post-operative management of bariatric surgery
3. Consider the long-term benefits and risks of bariatric surgery

Case

A 51-year-old male presented for obesity management. He had been obese since childhood, with a strong family history affecting both parents and his siblings. Background medical history included prediabetes, non-alcoholic fatty liver disease (FibroScan score of 35 kPa and a steatosis score of 400), obstructive sleep apnoea, gout, osteoarthritis and hypovitaminosis D. Depressive or anxiety symptoms were denied. His only medications were metformin and cholecalciferol. He lived with his partner and worked in the civil service in a sedentary position. He walked a short distance to his work place but otherwise inactive. He ate café or restaurant meals at

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five weekday lunches and 3–5 nights weekly; he consumed 4–8 standard alcohol-containing beverages every day, sometimes more. He was a life-long non-smoker.

He had attempted to lose weight on numerous occasions in his adult life, using a variety of caloric restriction plans, but was unsuccessful at sustained weight loss due to irregular short- and long-term adherence, particularly with alcohol restraint. Furthermore, increasing physical activity was constrained by osteoarthritis.

Clinically, he weighed 190 kg, with height of 1.72 m, a BMI of 62 kg/m^2 and waist circumference of 145 cm. His blood pressure was 132/84 mmHg. There were no features of Cushing's syndrome, hypothyroidism or hypogonadism. Cardiovascular, respiratory and gastrointestinal examinations were unremarkable. Screening investigations excluded secondary causes of obesity (normal thyroid function, 24-h urine free cortisol, testosterone). Lipids showed mixed hyperlipidaemia; liver function showed an elevation of hepatocellular enzymes. The HbA1c was in the prediabetic range at 45 mmol/mol (6.3%).

His treatment program included a tailor-made eating program that addressed his eating habits and portion control, improving choices when purchasing prepared food outside of home and particularly reduction of ethanol consumption. In particular, his alcohol intake was unpacked, including examining the triggers of excessive ethanol consumption and strategies for limiting consumption. An exercise physiologist was consulted to construct an individualised physical activity program that considered his physical limitations. He was commenced on glucagon-like peptide-1 receptor agonist therapy. Due to financial factors, he elected for an off-label trial of exenatide 5 mcg twice daily, which was increased to 10 mcg twice daily, with reasonable benefits on reducing food intake. Bariatric surgery was discussed in his obesity management plan, and he was deemed a suitable candidate.

Review of the Bariatric Surgery in the Management of Obesity

Indications for bariatric surgery are BMI ≥40 kg/m^2 or ≥35 kg/m^2 with one or more obesity-related complications including type 2 diabetes, hypertension, non-alcoholic fatty liver disease, obstructive sleep apnoea, knee or hip arthritis and urinary incontinence [1].

Common bariatric surgeries include sleeve gastrectomy; Roux-en-Y gastric bypass; and, less commonly, biliopancreatic diversion with or without duodenal switch (Fig. 47.1). Restrictive surgeries such as sleeve gastrectomy and, less commonly, gastric banding have less anatomical and physiological alterations to the gastrointestinal system with minimal risk of malabsorption. Roux-en-Y bypass is both restrictive and potentially malabsorptive, as it creates a small gastric pouch with the gastric content bypassing the duodenum. The risk of malabsorption with

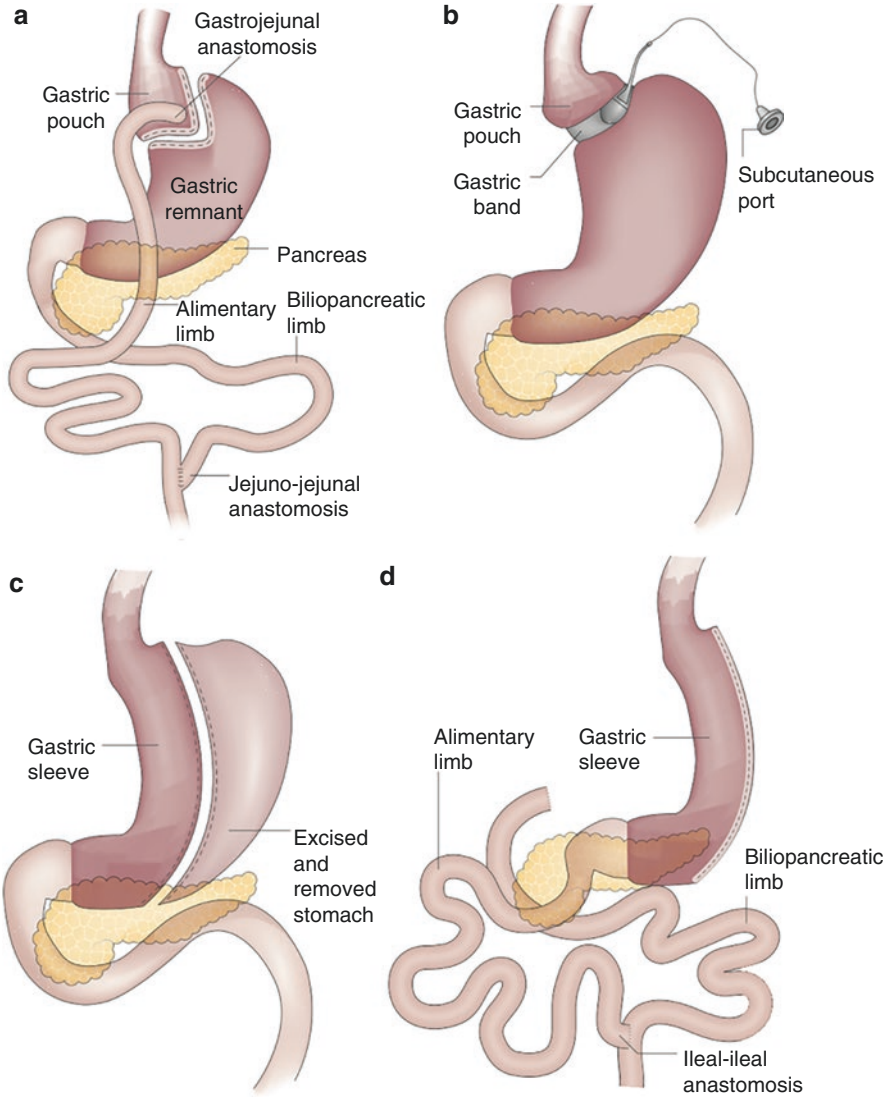

Fig. 47.1 Common bariatric surgical procedures. (**a**) Roux-en-Y gastric bypass. (**b**) Adjustable gastric band. (**c**) Sleeve gastrectomy. (**d**) Biliopancreatic diversion with duodenal switch [2]

the bypass appears to be dependent on the length of the intestinal loop and the small intestinal absorptive surface area that is bypassed. Biliopancreatic diversion is primarily a malabsorptive surgery bypassing a significant portion of the small intestine, with the greatest risk of significant nutritional deficiencies.

Preoperative Considerations

Prospective bariatric candidates are ideally placed on a very low-energy diet (VLED) for about 2 weeks preoperatively, with the aim of reducing the size of the liver which is often enlarged through ectopic fat deposition in obesity; this strategy assists with reducing intraoperative risk during the laparoscopic bariatric procedure in dealing with an enlarged liver that often has to be lifted and supported whilst the surgery is undertaken. In people with diabetes, glycaemic control should be optimised for 1–2 weeks preoperatively to reduce the risk of impaired immune function and infection. Candidates should undergo micronutrient assessment (vitamin B12, folic acid, vitamin D, iron studies), and any deficiencies should be addressed. In people on glucose-lowering medications, regular glucose monitoring should be performed during preoperative caloric restriction with adjustment and titration of glucose-lowering medications to mitigate the risk of hypoglycaemia. It is a reasonable approach to halve glucose-lowering medications such as sulfonylureas or insulin at the start of the VLED preparation. Further reductions are likely within 3 days of VLED commencement, when reductions in hepatic steatosis, hepatic insulin resistance and hepatic gluconeogenesis result in further decreased blood glucose levels. Bariatric candidates on glucose-lowering medications should be educated once again on the symptoms of hypoglycaemia and how to appropriately treat it. For some, they may never have experienced it. Bariatric candidates on diuretic therapy will require a check on electrolytes during VLED since there can be a significant diuresis 3 days into a VLED. Electrolytes should be checked on day 3 and then weekly, particularly in those people with heart failure who may require significant adjustment of diuretic therapy. Consideration should also be given to the specific anaesthetic needs of bariatric candidates with heart failure. In the setting of severe heart failure, specific and special perioperative management protocols exist, including intraoperative and intensive care-situated post-operative monitoring of pulmonary wedge pressures for early detection of cardiac decompensation. Needless to say, in this special needs group, surgery should be undertaken in centres with this specialised anaesthetic and cardiac expertise.

Post-operative Considerations and Monitoring

People undertaking bariatric surgery should be educated in the life-long commitment to dietetic monitoring and counselling, in addition to medical monitoring of electrolytes and micronutrients, with the possible need for micronutrient supplementation. Bariatric candidates where binging has characterised their eating patterns should also receive regular psychological assistance.

Close medical monitoring in the weeks to year after surgery will likely result in a reduction of multiple medications, not limited to adjustments in glucose-lowering, antihypertensive and lipid-lowering medications.

Current guidelines recommend multivitamins with minerals, elemental calcium, vitamin D and vitamin B12 in all [3]. Iron/ferritin, vitamin B12, folate, calcium, parathyroid hormone (PTH), vitamin D and albumin levels should be regularly monitored post malabsorptive surgeries, with vitamin A, vitamin B1 and zinc when deficiencies are suspected [3]. Ongoing multidisciplinary input to reinforce positive behavioural and dietary changes is crucial to avoid weight regain.

Roux-en-Y surgery and biliopancreatic diversion can result in dumping syndrome-like symptoms within an hour of food intake. This appears to be due to rapid transit of the food and subsequent intraluminal fluid shifts, possibly with gut hormone release. It is often accompanied by prominent gastrointestinal and vasomotor symptoms. Postprandial hyperinsulinaemic hypoglycaemia or late dumping syndrome can also occur within a few hours of food ingestion, especially after Roux-en-Y gastric bypass surgery. Simple dietary modifications can reduce early dumping syndrome, including small meals. Minimisation of simple carbohydrates and careful portion measures of complex carbohydrate can mitigate against the strong hyperinsulinaemic responses that promote postprandial hypoglycaemia.

Rapid weight loss is associated with bone mass reduction, which appears greater with malabsorptive bariatric surgeries where vitamin D and calcium absorption may be negatively impacted or where intake of these essential nutrients has been suboptimal. Whether this bone mass reduction is associated with increased risk of fragility fractures is yet to be delineated. It is recommended that vitamin D, calcium, phosphate, parathyroid hormone and alkaline phosphatase levels are monitored every 6 months. Measures of bone densitometry using dual-energy x-ray absorptiometry would be useful in documenting bone mineral losses [3]. Sufficient vitamin D and calcium supplementation should be well pursued to avoid secondary hyperparathyroidism and minimise bone loss; individualisation will be necessary, rather than application of recommended daily intakes, since obese people are at much higher risk of hypovitaminosis D for a variety of reasons.

The risk of cholelithiasis is increased post bariatric surgery due to rapid weight loss, although the exact mechanism is not well understood. Whilst ursodeoxycholic acid reduces the incidence of cholelithiasis and is recommended for patients post malabsorptive bariatric surgeries [1], simple measures such as ensuring some dietary fat is present daily will mitigate this risk, as it does with VLED. A simple procedure is addition of one tablespoon of olive oil to a daily meal.

A high concentration of urinary oxalate from enteric oxalate malabsorption can also increase the risk of nephrolithiasis post bariatric procedure. To prevent nephrolithiasis, patients should remain well hydrated and avoid oxalate-rich foods whilst ensuring adequate calcium intake.

Dysphoria is reported after bariatric surgery and may explain the increased rates of suicide and accident death that have been reported in long-term outcome studies [4]. Long-term follow-up and support strategies of medical and allied health professional staff should evaluate mood at each visit, considering that what has often been the main pleasure in life or a coping strategy in stress is now absent. Psychological strategies for preventing dietary behaviour relapses may be informed by understanding for each individual the role food and certain eating behaviours play in each

individual's life and then scaffolding appropriate strategies that may substitute for old pleasure, treat and coping behaviours. People with binge eating disorders (which are frequently down played or denied) will likely require specialised and long-term psychological intervention and support.

Finally, it is important that both physician and patient understand that bariatric surgery is not a 'once applied, then cured' approach and the path to recovery requires long-term engagement with medical and allied health professional support for consistent, life-long behaviour change.

Bariatric Surgery Outcomes

The benefits of bariatric surgery are well established, resulting in significant weight loss and improved cardiometabolic and cancer outcomes. An increasing number of long-term data support the durability of these beneficial effects. Here, we summarise the outcomes from three seminal papers.

An observational, prospective 12-year follow-up study post Roux-en-Y gastric bypass surgery showed sustained weight loss between 6 years and 12 years. There were higher remission rates and lower incidence rates of obesity-related complications, including type 2 diabetes, hypertension and dyslipidaemia, compared to those who did not have surgery at 12 years. In particular, more than half of the participants with type 2 diabetes had remission, with higher rates observed for those with fewer oral medications at baseline without insulin [5].

Another case-controlled trial featuring a 10-year follow-up study post biliopancreatic diversion in patients with newly diagnosed type 2 diabetes showed demonstrated maintained weight loss with higher type 2 diabetes remission and lower renal and cardiovascular complications compared to the matched control group at 10 years [4].

The Swedish Obese Subjects Study with a 15-year follow-up post gastric banding, vertical banded gastroplasty or gastric bypass showed higher remission rates of diabetes and lower microvascular and macrovascular complications. The weight loss was greatest at 1 year in the surgical group, though significant weight loss was maintained at 15 years compared to baseline, with the greatest weight loss observed in the gastric bypass group [6].

Additional benefits include clinically important improvements in obstructive sleep apnoea, hypertension control and congestive cardiac failure. Data also show 50–60% reductions in the incidence rates for cardiac disease and cancers.

Questions

1. Which of the following statements is true regarding bariatric surgery?

   A. It should be considered in patients with BMI $\geq$35 kg/m^2 without significant comorbidities
   B. Sleeve gastrectomy is mainly a malabsorptive procedure

C. Risk of malabsorption is dependent on the length of the intestinal loop post surgery
D. Nutritional deficiencies are uncommon with sleeve gastrectomy and Roux-en-Y
E. None of the above

2. Which of the following statements is true regarding the post bariatric surgical course?

A. Rapid weight loss can be associated with declines in bone mass.
B. Small complex carbohydrate meals can reduce the risk of postprandial hyperinsulinaemic hypoglycaemia following some bariatric surgeries
C. Ursodeoxycholic acid may be necessary for patients following malabsorptive bariatric surgeries to reduce the risk of cholelithiasis
D. Daily multivitamins, elemental calcium and vitamins D and B12 are recommended to minimise the risk of nutritional deficiencies
E. All of the above

3. Which of the following micronutrient(s) are at risk of malabsorption post bariatric surgery?

A. Vitamin D
B. Vitamin B12
C. Ferritin
D. Vitamins A and B1
E. All of the above

Answers to Questions

1. Answer: C. Bariatric surgery is indicated in patients with BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 with one or more obesity-related complications. Gastric sleeve surgery is mainly a restrictive procedure with a lower risk of malabsorption. Nutritional deficiencies are uncommon with sleeve gastrectomy but common with Roux-en-Y surgery.
2. Answer: E. Rapid weight loss is associated with bone loss; thus, it is important to optimise vitamin D and calcium intake, especially after malabsorptive bariatric surgery. Larger, simple carbohydrate meals can have strong insulin secretor effect; therefore, modifying diet with small complex carbohydrate can reduce the risk of postprandial hyperinsulinaemic hypoglycaemia. Multivitamins with minerals, calcium and vitamins D and B12 are recommended by the current guidelines to minimise the risk of nutritional deficiencies.
3. Answer: E. Bariatric surgeries, especially malabsorptive type, can increase the risk of micronutrient deficiencies. It is recommended to routinely screen for iron/ferritin, vitamin B12, folate, calcium, PTH, vitamin D and albumin. Vitamins A and B1 and zinc should be monitored if deficiencies are suspected.

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Chapter 48
Obesity Assessment and Management Using an Illustrative Case in Severe Mental Illness

Lisa M. Raven and Katherine Samaras

Objectives

1. To review the diagnosis of obesity in people with severe mental illness
2. To understand the contributing factors to weight gain and obesity in people with severe mental illness
3. To review the management of obesity, with a focus on people with mental illness

Case

A 44-year-old female presented with concerns about her weight gain. She had a long-standing history of schizophrenia which was managed at that point with risperidone injections fortnightly; however, due to instability in her mental health with prominent delusions, there was a plan from the psychiatric team to transition to clozapine therapy if her mental health deteriorated further. She reported her weight had been stable over many years, but she did not formally weigh herself.

She was accompanied by a mental health case worker and received an Australian federal government disability support pension with a fortnightly monetary

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allowance. She had minimal social supports, with no family or close friends that she could identify.

She had no known comorbidities. She smoked two packets of cigarettes per day.

Dietary history revealed breakfast consisted of black coffee only; morning tea was reported as two to three slices of white or multigrain sandwich bread with cheese, sour cream or a takeaway chicken roll; lunch consisted of processed fast-food chicken nuggets or fish with salad; and dinner consisted of takeaway pasta with chicken or bacon and mushroom or Asian-style fast food accompanied by noodles or rice. She also reported snacking on tinned fruit, up to 1 L over a 2–3-day period. She enjoyed fruit juice and carbonated sugar-sweetened drinks and would consume 2 L every 2–3 days. Once per fortnight, she consumed two fast-food burgers.

On physical examination, her blood pressure was 125/80 mmHg. Her weight was 222 lbs (101 kg) with a height of 5′7″ (1.7 m) and body mass index 35.0 kg/m^2. Her waist circumference was 40 inches (101 cm). She did not have any striae or bruising to suggest Cushing's syndrome nor significant hirsutism or androgenic alopecia. No acanthosis nigricans was present in the neck or axillary folds. The liver was not enlarged and there were no stigmata of cirrhosis. Dentition was adequate.

Laboratory findings demonstrated impaired fasting glucose at 109 mg/dl (6.1 mmol/L), with glycated haemoglobin 41 mmol/mol (5.9%). There was evidence of dyslipidaemia with total cholesterol of 239 mg/dl (6.2 mmol/L), HDL 42 mg/dl (1.1 mmol/L), LDL 170 mg/dl (4.4 mmol/L) and triglyceride level 142 mg/dl (1.6 mmol/L). TSH was normal at 1.8 μIU/ml.

Her intervention programme consisted of a multipronged approach focusing on the following:

(i) Caloric restriction with diet quality optimisation and strategies to increase food literacy
(ii) Pharmacotherapy to address her hyperlipidaemia, prediabetes and obesity
(iii) Strategies to reduce sedentariness and increase planned and incidental physical activity
(iv) Behavioural and diversional strategies to address food overconsumption in response to boredom and stress

Separately and importantly, she was encouraged to reduce or cease smoking. She received an individualised eating plan tailored to her food preferences and cooking skills and foods that she has ready access to. She also received advice on breaking the patterns of sedentariness identified and a physical activity prescription requesting she accrue at least 10,000 steps per day using a smartphone application. She was commenced on simvastatin 10 mg for treatment of her dyslipidaemia. Metformin 500 mg bd was also commenced, given the prediabetes but also because of evidence of its benefit in managing antipsychotic-associated weight gain.

Over the initial 6 months, she lost 13 lbs (6 kg) with the above interventions. She was able to maintain this weight over the following 12 months. Her lipids and fasting glucose improved.

Unfortunately, her mental health deteriorated, and she transitioned from antipsychotic therapy to clozapine. She rapidly regained 15 lbs. In addition to ongoing lifestyle advice, she was commenced on the glucagon like peptide-1 receptor agonist exenatide 10 mcg bd by self-administered subcutaneous injection.

Review of the Diagnosis

Obesity Classification

Obesity is defined as excessive fat accumulation and is calculated through body mass index (BMI) over 30. BMI is a standard measure using weight and height as listed in Table 48.1 [1].

$$\begin{aligned}\text{BMI} &= \text{weight}(\text{kg}) / \text{height}(\text{m})^2 \\ &= 704 \times \text{weight}(\text{lbs}) / \text{height}(\text{in})^2\end{aligned}$$

Elevated BMI is a major risk factor for cardiovascular disease, diabetes mellitus, musculoskeletal disorders and some types of cancers.

Another system for classification of obesity is the Edmonton Obesity Staging System (EOSS) which is listed in Table 48.2 [2]. This classification system takes

Table 48.1 Body mass index classification, modified from the World Health Organisation [1]

BMI (kg/m^2)	Classification
<18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
>40	Obesity class III

Table 48.2 Edmonton Obesity Staging System, modified from Sharma et al. [2]

EOSS stage	Conceptual definition	Examples of definition
0	No obesity-related risk factors, no physical symptoms, no psychopathology, no functional limitations and/or impairment of well-being	No EOSS factors reported
1	Presence of obesity-related subclinical risk factors, mild physical symptoms (e.g. dyspnoea on moderate exertion, occasional aches and pains, fatigue), mild psychopathology, mild functional limitations and/or mild impairment of well-being	Hypertension, impaired fasting glucose, elevated liver enzymes Dyspnoea on moderate exercise, occasional aches and pains, fatigue
2	Presence of established obesity-related chronic disease, moderate limitations in activities of daily living and/or well-being	Hypertension, type 2 diabetes, sleep apnoea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder
3	Established end-organ damage, significant psychopathology, significant functional limitations and/or impairment in well-being	Myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis
4	Severe disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well-being	

into account metabolic, physical and psychological parameters. There is evidence that the EOSS is a better predictor of mortality than BMI.

Metabolic syndrome is a collection of risk factors for cardiovascular disease, including increased waist circumference, hypertriglyceridemia, low HDL levels, hypertension and hyperglycaemia. The presence of at least three of the risk factors leads to the diagnosis of metabolic syndrome. The more risk factors present, the higher the risk of cardiovascular disease.

Obesity and Severe Mental Illness

People living with severe mental illness, including schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder, have reduced life expectancy, largely due to increased risk of premature cardiovascular disease. The life expectancy disparity has been estimated at over 20 years of life lost. There is an increased prevalence of obesity, diabetes, ischaemic heart disease, dyslipidaemia, hypertension and polycystic ovary syndrome in those with severe mental illness [3]. Medications used to treat severe mental illness have been associated with weight gain and metabolic syndrome. A summary of the metabolic effects of antipsychotic, antidepressant and mood-stabilising medications is listed in Table 48.3 [4]. Many people with severe mental illness may be on other medications that also promote weight gain and diabetes. Second-generation antipsychotic medications, a mainstay of treatment for mental illness, are associated with weight gain due to increases in appetite and reduced satiation, explaining the increased risk for obesity and associated metabolic disorders. Medications commonly used such as clozapine and olanzapine have a strong association with weight gain and metabolic syndrome. This association has been attributed to the effects of antipsychotic

Table 48.3 Metabolic effects of medications used to manage severe mental illness

	Antipsychotic medications	Antidepressant medications	Mood-stabilising medications
Weight gain	Marked effect: Clozapine Olanzapine Some effect: Quetiapine Risperidone	Some effect: Mirtazapine Paroxetine Tricyclic antidepressants	Moderate effect: Lithium Sodium valproate
Increased glucose levels	Marked effect: Clozapine Olanzapine Some effect: Quetiapine Risperidone Haloperidol Aripiprazole	Possibly some effect	Moderate effect: Sodium valproate

Modified from Correll et al. [4]

medication on dietary behaviours, with reports of increased appetite and cravings for sweet foods and decreased satiety. A proposed contributing mechanism for weight gain is from antagonising effects of antipsychotic medication on histamine 1 receptors and that affinity for the receptor is associated with increased appetite. When the diet of people with severe mental illness has been evaluated, evidence shows a marked increase in calorie intake, as well as increased sodium intake, with overall reduced quality of the diet [5].

Examination

Examination should focus on assessment of the diagnosis of obesity, as well as potential underlying pathology and complications and associated pathology.

Initial measurements should include weight, height and waist circumference.

Potential underlying pathology can include hypothyroidism and Cushing's syndrome. Hypothyroidism can clinically present with dry skin, cool peripheries and reduced reflexes, with or without a thyroid goitre. Signs that would suggest Cushing's syndrome include abdominal striae, bruising, intrascapular fat pad and increased fat deposit in the face.

Complications from obesity and associated pathology include insulin resistance, polycystic ovarian syndrome and liver disease. Signs of insulin resistance include acanthosis nigricans in the neck or axillary folds. Signs of polycystic ovarian syndrome include hirsutism or androgenic alopecia. Signs of liver disease include change in liver size on palpation and stigmata of liver cirrhosis.

Initial Investigations

Investigations should include screening for underlying pathology which may be contributing to weight gain, as well as screening for complications. A summary of suggested investigations are listed in Table 48.4.

Of note, thyroid function should be assessed in people with a history of severe mental illness as a screen for organic pathology. Lithium, a medication that can be used for the treatment of bipolar disorder, has been associated with increased risk for thyroid dysfunction and hypothyroidism.

Appropriate Interventions

A holistic approach to intervention for obesity management is depicted in Fig. 48.1.

Poor diet is an important modifiable risk factor for obesity and metabolic syndrome. A multidisciplinary team approach is beneficial to optimising diet. Intensive

Table 48.4 Suggested investigations

Screening for potential underlying pathology	Thyroid function test If clinically indicated, screening for Cushing's syndrome
Screening for complications	Fasting glucose level HbA1c Fasting cholesterol Liver function tests

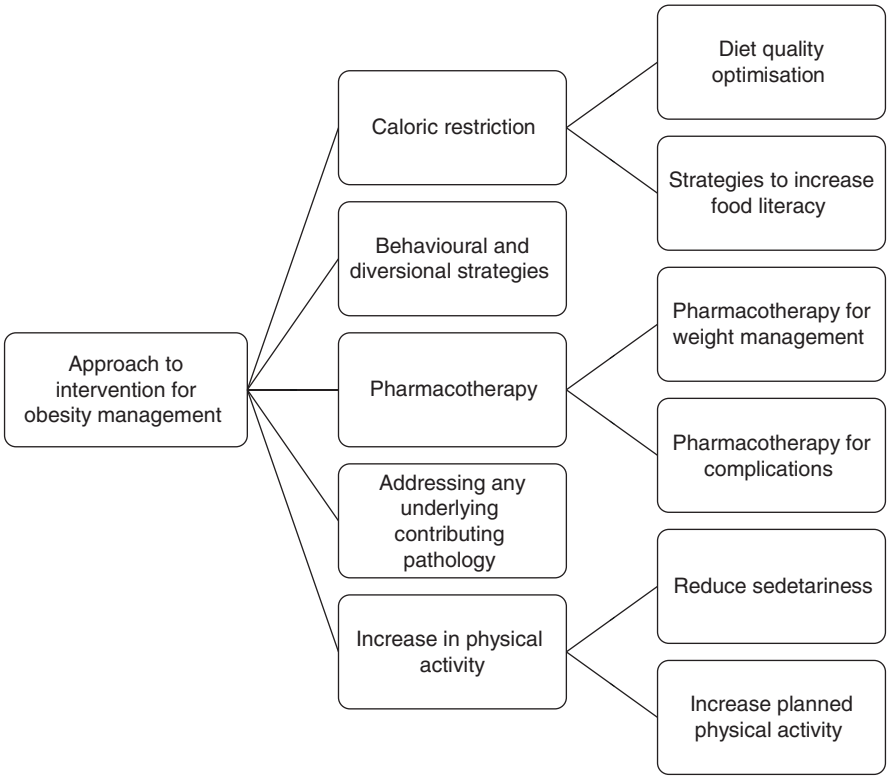

Fig. 48.1 Flow chart of an approach to intervention for obesity management

dietitian involvement with structured consultation and follow-up has been shown to be effective in improving nutrition in people living with severe mental illness [6]. For example, the Keeping the Body in Mind lifestyle and life skills intervention is a therapeutic and educational intervention that focuses on upskilling participants to improve their lifestyle choices. This programme included practical components such as group shopping tours, group cooking tuition and recipe sharing.

A major challenge in people living with severe mental illness is that antipsychotic medications can be extremely sedating. Many will drink copious amounts of coffee or caffeinated sugar-sweetened beverages to stimulate themselves into

wakefulness. Obviously, these add to the caloric intake; these factors need to be specifically detected and addressed.

Along with improved diet and caloric restriction, physical activity is an important lifestyle intervention. There is less data to guide this intervention; however, World Health Organisation recommendations on physical activity should be followed. This includes at least 150–300 minutes of moderate-intensity aerobic physical activity or at least 75–150 minutes of vigorous-intensity aerobic physical activity, per week, along with muscle-strengthening activities. Whilst this is the ideal, it may be challenging to simply break the sedentariness associated with the sedating effects of antipsychotic medication and issues such as safety to exercise based on where people with severe mental illness may reside. The difficult sociodemographic circumstances of people with severe mental illness may provide major hurdles to physical activity initiation, including insecure accommodation, and living in unsafe areas. It is well known that people living in unsafe areas walk less, particularly women. Simple strategies such as a step counter on a smartphone could be used to incentivise walking activity.

Pharmacological therapy can be used as an adjunct to lifestyle intervention. Metformin, an oral antihyperglycaemic agent, has been shown to be an effective treatment for the prevention and treatment of weight gain associated with antipsychotic therapy [7]. The combination of lifestyle intervention with metformin use was shown to be superior to either intervention alone.

Glucagon-like peptide-1 (GLP-1) analogues, such as semaglutide, have been shown to be effective in achieving weight loss in people with obesity, regardless of diabetes status [8]. However, at the time of publication, the use of most available GLP-1 analogues for weight loss in people without diabetes is off-label use, other than liraglutide. Further studies of the use of GLP-1 analogues in patients with mental illness are ongoing.

An ongoing dialogue between physicians and psychiatrists is encouraged, considering a number of patient-focused questions which might include the following: When might it be appropriate and safe to reduce antipsychotic doses? Could an obesity-inducing antipsychotic be swapped for another with lesser weight effects? Any medication transition requires careful observation for the well-being and safety of the person living with severe mental illness. It is important to recognise that people with severe mental illness can become ‘locked in’ to an antipsychotic medication regimen enduringly and without review. The physician simply raising the question advocating for use of less metabolically harmful treatment regimens is a degree of patient advocacy that may result in tangibly more positive health outcomes.

Lessons Learned

1. Severe mental illness with antipsychotic medication use is a significant risk factor for obesity and premature cardiometabolic sequelae and death.
2. Lifestyle intervention including dietary optimisation and increased physical activity are the mainstay of preventing and managing obesity. Where possible, the expertise of the multidisciplinary team should be utilised, including psychia-

trists, physicians expert in obesity management, dietitians, exercise physiologists, diversional therapists and mental health case workers.
3. Pharmacological therapy can aid in weight management.

Questions

1. What is the body mass index (BMI) of the patient described in the case when she first presented?

   A. BMI 30 kg/m^2
   B. BMI 33 kg/m^2
   C. BMI 35 kg/m^2
   D. BMI 40 kg/m^2
   E. BMI 45 kg/m^2

2. Which of the following medications are most strongly associated with weight gain?

   A. Clozapine and risperidone
   B. Clozapine and olanzapine
   C. Olanzapine and haloperidol
   D. Risperidone and aripiprazole
   E. Aripiprazole and haloperidol

3. What strategies should be considered for the management of obesity in people with mental illness?

   A. Asking a diet history
   B. Dietary advice
   C. Exercise advice
   D. Discussion about medications including metformin
   E. All of the above

Answers to Questions

1. Answer: C

   The patient presented above initially had a BMI of 34.8, which when she lost 13 lbs reduced to a BMI of 32.8. Use the equation listed above to calculate BMI.
2. Answer: B

   Clozapine and olanzapine are most strongly associated with weight gain. The other medications have a modest effect on weight gain.
3. Answer: E

   Taking a diet history is important to be able to tailor advice about areas of improvement. Lifestyle intervention, including both diet and exercise advice, is a mainstay of managing obesity. Pharmacological therapy can be used as an adjunct to aid weight management.

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Chapter 49
Obesity Management and Use of Very Low-Energy Diets

Ruth Frampton and Katherine Samaras

Objectives

1. To review the indications for commencement of a very low-energy diet (VLED) for management of obesity
2. To understand the principles of management of electrolytes when commencing a VLED
3. To be able to make appropriate adjustments to medications, including antihypertensives, diuretics and diabetes medications (including insulin) when commencing a VLED
4. To understand the need for and principles of nutritional monitoring while on a VLED

Case Presentation

A 46-year-old obese man presents to the metabolic clinic for assessment and management of his obesity, accompanied by his wife. His comorbidities included longstanding type 2 diabetes mellitus and decompensated heart failure on a background

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of ischaemic cardiomyopathy for which he has required multiple hospital admissions in the past year. He had undergone coronary artery bypass grafting in 2015, initially with symptomatic improvement. He was not known to have any microvascular complications of his diabetes, and his only known vascular disease was cardiac. He also has atrial fibrillation and obstructive sleep apnoea. He had two teenage children and was unable to work due to his health conditions.

A detailed dietary history revealed that most meals were consumed in the home with his family. He snacked regularly, including biscuits (cookies) and multiple servings of fruit between meals most days. He was on a fluid restriction of 1.2 litres per day due to his cardiac disease, with a preference for carbonated sugar-sweetened beverages.

On physical examination, his weight was 306 lbs (139 kg) with height 5′8″ (1.72 m), giving him a body mass index (BMI) of 47 kg/m^2. Blood pressure was 125/75 mmHg. Cardiovascular examination reveals normal heart sounds with mildly elevated jugular venous pressure (JVP) and mild pedal oedema.

He subsequently developed severe left ventricular dysfunction with a left ventricular ejection fraction of 24% without evidence of a new ischaemic event. Bariatric surgery had been planned as an outpatient in order to try to achieve eligibility for heart transplantation; however, his anaesthetic risk was considered too high to proceed despite local expertise in cardiac anaesthesia in severe heart failure and transplantation.

At assessment, medications were metformin 1 g bd, dapagliflozin 10 mg daily, bisoprolol 1.25 mg bd, sacubitril/valsartan 24/26 mg bd, frusemide 80 mg bd, hydrochlorothiazide 25 mg daily, spironolactone 25 mg bd and amiodarone 200 mg daily. He is also taking concentrated insulin glargine (300 units/mL) 60 units at bedtime and insulin aspart 20 units with meals.

Laboratory findings showed suboptimal diabetes control with glycated haemoglobin 72 mmol/mol (8.7%). Full blood count, renal and liver functions tests and electrolytes were within the normal reference ranges.

He was prescribed a very low-energy diet (VLED) with the aim of maximising weight loss, both to improve cardiac function and reduce anaesthetic risks in the prelude to bariatric surgery and to allow access to cardiac transplantation (since a BMI >35.0 kg/m^2 is an absolute contraindication). Glucagon-like peptide-1 (GLP-1) receptor agonist therapy was initiated with exenatide, initially at a dose of 5 mcg bd, increasing to 10 mcg bd after 4 weeks.

On starting the VLED, insulin aspart was ceased and insulin glargine reduced by 50% of usual dose. Eventually, all insulin was able to be ceased entirely. Dapagliflozin was ceased during the intensive phase of the calorie-restricted diet due to risk of euglycaemic ketoacidosis in the fasted state. Frusemide dose was reduced to 40 mg bd and hydrochlorothiazide ceased on initiation of the VLED.

He lost over 24 lbs (11 kg) over the ensuing 12 months. Unfortunately, his cardiac failure continued to progressively decline, and he required an implanted left ventricular assist device. He is currently on a wait list for bariatric surgery with a view to being placed on the heart transplant wait list once his BMI reduces to <35.0 kg/m^2.

Background

Very low-energy diets (VLEDs) are defined as diets in which less than 800 calories (3350 kJ) are consumed per day. A range of commercial preparations are available; however, these range in quality and the capacity to adequately meet recommended intakes of macronutrients and micronutrients. It is essential that any preparations contain adequate protein to avoid protein-calorie malnutrition which, in extreme cases, can lead to cardiac failure and death [1]. Generally, the diet is continued in an 'intensive phase' for a period of 8–16 weeks before transitioning to more conventional eating habits. However, for those who find meal replacement an easier option, it is possible to continue a VLED beyond this period, given the carefully constructed and balanced nutritional content of some of these meal replacements. Reports exist of successfully using this approach for 1 year and beyond without any adverse effects [2].

A typical composition for a VLED meal replacement shake based on acceptable and widely available commercial preparations is included in the Table 49.1.

During the initial intensive phase, meal replacements can be consumed 3–4 times per day, with additional protein if required to reach 1 mg/kg of adjusted ideal body weight (IBW). Ideal body weight (IBW) is defined as body weight at BMI 25 for a given height. In those with BMI >35, adjusted IBW = [(Actual Body Weight − IBW) × 0.25] + IBW should be calculated to determine protein requirements.

Following the intensive phase, conventionally prepared meals can be gradually reintroduced. Weaning off a diet consisting entirely of prepared supplements to calorie-restricted eating with conventionally prepared meals can be difficult for some patients, and clinician guidance is important during this crucial phase to prevent loss of any territory gained. Previous unhelpful patterns of eating may re-establish themselves as foods are reintroduced, and regular support is essential in ensuring transition and prevention of pre-existing eating behaviours, food choices and portion size selection difficulties. There is considerable individual variation in what may suit patients at this critical juncture, and various options should be discussed depending on a range of individual factors which may include work and family circumstances and patient preferences. Complimentary strategies such as time-restricted eating can be introduced if desired at this point.

Indications for Treatment

Patients suitable for consideration of VLED include those with BMI >30 kg/m^2 or those with BMI >27 kg/m^2 who have an additional reason for requiring weight loss, e.g. prior to surgery, or with medical conditions which may be improved by weight loss such as diabetes, hypertension or obstructive sleep apnoea.

Table 49.1 Nutritional composition of a typical and nutritionally appropriate meal replacement VLED product

	Units	Quantity per serving
Energy	kJ Cal	840 201
Protein	g	20
Fat		
Total	g	4.5
Saturated	g	0.9
Linoleic acid	g	1.2
Alpha-linoleic acid	mg	196
Carbohydrate	g	18.2
Sugars	g	9.5
Lactose	g	9.0
Dietary fibre	g	3.6
Sodium	mg	215
Vitamin A	mcg RE	345
Thiamine (B1)	mg	0.58
Riboflavin (B2)	mg	0.74
Niacin	mg NE	8.7
Pantothenic acid	mg	2.7
Vitamin B6	mcg	1.0
Biotin	mcg	10.6
Folic acid	mcg	110
Vitamin B12	mcg	1.1
Vitamin C	mg	46
Vitamin D	mcg	3.7
Vitamin E	mg TE	7.4
Vitamin K	mcg	31.8
Calcium	mg	408
Chromium	mcg	19
Copper	mg	1.2
Fluoride	mcg	340
Iodine	mcg	98
Iron	mg	8.2
Magnesium	mg	168
Manganese	mg	0.9
Molybdenum	mcg	18.6
Phosphorus	mg	360
Selenium	mcg	40
Zinc	mg	4.3
Potassium	mg	955
Chloride	mg	280

Absolute contraindications to treatment of obesity with VLED include use in childhood, pregnancy or lactation; porphyria; and acute medical conditions including recent myocardial infarction and acute kidney injury and advanced liver disease. Elderly patients may be unsuitable candidates due to the increased propensity for loss of lean muscle in this group and higher dietary protein requirements. Use of VLED in those with severe psychological disturbance and/or misuse of alcohol or other substances should also be carefully considered and, if used, supervised.

With appropriate monitoring and adjustment of medications, many patients with medical comorbidities including renal failure, cardiac failure and insulin-requiring diabetes mellitus can be successfully managed with VLED.

Initial Investigations and Monitoring

Prior to commencement of a VLED, initial investigations should be ordered including a full blood count, electrolytes, renal function, uric acid, liver function tests, fasting glucose, lipid profile, iron studies, vitamin D level and thyroid-stimulating hormone level. These tests should be repeated at least every 6 weeks until the conclusion of the intensive phase and more often if the patient is unwell or at particular risk of complications due to comorbid medical conditions. Blood pressure and weight should also be measured regularly through the intensive phase.

Rapid weight loss may induce formation of gallstones. Many preparations now contain adequate fat to stimulate gallbladder emptying; however, in those predisposed, ursodeoxycholic acid may be used. Serum uric acid may also increase on commencement, which should be considered in those with a history of gout.

VLEDs are lower in salt than the average Western diet, and in addition, their low-carbohydrate nature leads to a diuresis. The risk of hypokalaemia and other electrolyte disturbances is increased in those with comorbidities, particularly if on diuretic medications. Though it is generally recommended that patients on a VLED should drink up to 2 litres of fluid per day, patients on a fluid restriction need to consume less than this. In the intensive phase of VLED, electrolytes should be measured twice per week initially in patients who are on a fluid restriction due to renal or cardiac disease or in those patients taking diuretic medications.

Despite increased consumption of energy, micronutrient deficiencies are common in the obese population [3]. This may be due to consumption of foods that are high in calories but nutrient-deficient. However, metabolic changes in patients with obesity may also increase nutrient requirements. Evidence for routine supplementation is scarce, and this approach risks over-replacement. Screening for common deficiencies such as iron and vitamin D and supplementing as required appear as a reasonable approach, as well as remaining alert to the possibility of other micronutrient deficiencies.

Adjustment of Medications on a VLED

Given the diuretic effect of VLED with potential for postural hypotension, antihypertensive medications should generally be ceased unless there is a history of severe and resistant hypertension requiring multiple agents. Blood pressure should be checked regularly and antihypertensive medication reintroduced as required. Diuretic medications may also need to be dose reduced or even ceased completely. Regular examination of fluid status should be undertaken for high-risk patients.

Major changes to diabetes medications are necessary when commencing a VLED. Indeed, weight loss achieved through a VLED has been shown to reverse type 2 diabetes in many patients. For example, the UK DiRECT trial found that 46% of participants in the VLED intervention group achieved remission of diabetes, defined as HbA1c <6.5% after at least 2 months off diabetic medications [4].

If HbA1c is near target prior to commencement, sulfonylureas should be dose reduced or ceased due to the potential for hypoglycaemia. Medications in the SGLT2 inhibitor class should also be stopped to minimise the risk of euglycaemic ketoacidosis. Metformin can generally be continued if renal function allows. Dipeptidyl Peptidase-4 (DPP-IV) inhibitors and GLP-1 receptor agonists can be continued, though clinicians should be mindful of pancreatitis risk. Indeed, GLP-1 receptor agonists may be useful in adherence due to their effect on appetite.

Insulin doses may require large reductions. For type 2 diabetes, ceasing short-acting insulin and reducing basal insulin to 50% of previous dose are reasonable starting points; however, regular blood glucose monitoring should be used for further dose titration. VLED can also be used in obese patients with type 1 diabetes. In this circumstance, basal insulin doses may require a small reduction, e.g. down to 80% of previous dose. Again, large reductions or cessation of short-acting insulin may be necessary.

Lessons Learned

1. VLEDs using meal replacement products can be useful tools for intensive weight loss in a wide range of circumstances.
2. Transition from the intensive phase of a VLED to reintroduction of conventional foods is a challenging time and requires planning and support for the patient to prevent relapsing into previous unhelpful habits.
3. Micronutrient deficiencies are common in patients with overweight and obesity and should be actively screened for and addressed.
4. VLEDs remain an option for weight loss in patients with comorbidities, including heart failure and diabetes. However, careful monitoring and adjustment of medications are required.

Multiple Choice Questions

1. Which of the following is NOT a contraindication to use of a VLED?

   A. Normal body weight
   B. Pregnancy
   C. Porphyria
   D. End-stage renal failure on dialysis
   E. End-stage liver failure

2. For a patient with weight of 306 lbs (139 kg), height of 5′8″ (1.72 m) and body mass index of 47, how much protein is required per day on a VLED?

   A. 20 g
   B. 300 g
   C. 90 g
   D. 40 g
   E. 110 g.

3. Which of the following is NOT a known effect of a VLED

   A. Increased blood pressure
   B. Decreased weight
   C. Increased uric acid level
   D. Formation of gallstones
   E. Decreased insulin requirements

Answers to Questions

1. Answer: D
   Patients with end-stage renal failure on dialysis can safely undertake a VLED; however, this should be done in close consultation with the patient's nephrologist, and additional monitoring is required.
2. Answer: C
   BMI = weight/height^2, so ideal body weight (BMI 25) for height 1.72 m = 25 × 1.72^2 = 74 kg. Adjusted IBW = [(Actual Body Weight − IBW) × 0.25] + IBW = [(139–74) × 0.25] + 74 = 90 kg. Therefore, at 1 mg/kg, daily protein intake should be 90 g.
3. Answer: A
   Patients on a VLED will generally have decreased blood pressure due its diuretic effect and are likely to require cessation or reduction in antihypertensive medications.

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Part XIII
Polycystic Ovary Syndrome

Chapter 50
Introduction to Polycystic Ovary Syndrome

Sidika E. Karakas

Abbreviations

17OHP	17-hydroxyprogesterone;
AMH	Anti-Mullerian hormone
DHEA-S	Dehydroepiandrostenedione sulfate
FSH	Follicle-stimulating hormone
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
IVF	In vitro fertilization
LH	Luteinizing hormone
METS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
SGLT-2	Sodium-glucose cotransporter-2
T	Testosterone
T2D	Type 2 diabetes

Introduction

Four percent of lean and 14% of the obese women of reproductive age have PCOS [1]. The cardinal findings of PCOS are oligomenorrhea and/or anovulation, clinical or biochemical androgen excess, and polycystic ovarian morphology (PCO). Various combinations of these cardinal findings have been used as *diagnostic criteria* over

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the years. In 1990, the NIH criteria required the presence of androgen excess and oligomenorrhea/oligo-ovulation but did not require PCO morphology. In 2003, the Rotterdam criteria required any two out of three of the cardinal findings.

In 2009, Androgen Excess and PCOS Society required androgen excess along with any one of the other two findings. These definitions resulted in four different *phenotypes*:

A. Hyperandrogenism + anovulation + PCO
B. Hyperandrogenism + anovulation
C. Hyperandrogenism + PCO
D. Anovulation + PCO

Among these, phenotype D is the most challenging because women with hypogonadotropic hypogonadism can have PCO morphology and be erroneously diagnosed as PCOS [2]. Since PCOS is a common disorder, many pathologies presenting with oligomenorrhea, amenorrhea, hirsutism, infertility, and/or even obesity can be mislabeled as PCOS. The opposite is also true. Oligomenorrhea caused by PCOS can be attributed to youth or stress. The next section will summarize the information to help make the correct diagnosis.

What Is the Typical Menstrual Pattern?

Average age of menarche is 12 years. Three years after menarche, 90% of girls have regular monthly periods. If a young woman is still having irregular, infrequent periods 3 years after menarche, she deserves medical attention. Oligomenorrhea is having periods at longer than 35-day intervals and/or having 4–9 periods/year. Primary amenorrhea is not having a period by age 16 years. Secondary amenorrhea is absence of menses for longer than 6 months. Girls with PCOS may have oligomenorrhea from the menarche or may develop oligomenorrhea when they gain weight. Alternatively, they may have frequent vaginal bleeds. Menstrual cycles with shorter than 21-day intervals are typically anovulatory.

What Is Clinical Androgen Excess?

Hirsutism refers to growth of terminal hair, which is coarse and pigmented. It curls, lifts, and separates from the skin; it can be in the upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, and upper arms. Each area is graded using modified Ferriman-Gallwey Score from 0 to 4, and a total score >8 is considered significant hirsutism. Vellus hair, which is soft and lays flat on the skin, should not be mistaken for hirsutism; it is usually seen in amenorrhea caused by anorexia associated with hypogonadotropic hypogonadism.

What Is Biochemical Androgen Excess?

In women, androgens are produced in the ovaries and adrenals. In PCOS, the primary abnormality is increased ovarian androgen excess. Approximately one-third of the women with PCOS have adrenal androgen excess as well, but this finding does not alter the diagnosis.

The major ovarian androgen testosterone (T) is produced by the theca cells in the stroma (Fig. 50.1). The preferred method for measuring T is liquid chromatography tandem mass spectrometry (LCMS/MS); automated direct immunoassays are not accurate enough for women. Most importantly, measurement of total-T alone is not adequate and can be misleading. Biologically active components of T are free-T and bioavailable-T. Approximately 65% of T, which is bound to sex hormone-binding globulin (SHBG), is not bioactive. Women with PCOS can have five- to tenfold difference in SHBG concentrations. Consequently, two women who have similar total-T can have very different bioavailable-T and free-T (Table 50.1). Obese, insulin-resistant women usually have very low SHBG. Hence, when they have normal total-T, they can have elevated bioavailable-T and free-T. Notably, low SHBG is a strong biomarker for insulin resistance [3, 4]. In contrast, oral contraceptive therapy raises SHBG concentrations and decreases bioavailable-T and free-T. Women on oral contraceptives can have elevated total-T but normal bioavailable-T and free-T.

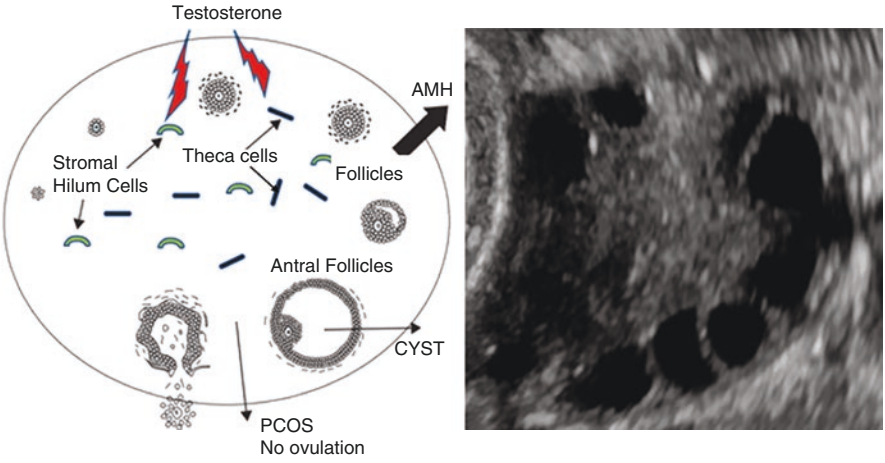


Fig. 50.1 During each menstrual cycle, many primordial follicles progress to become primary, preantral, and antral follicles. One of the antral follicles becomes dominant and ovulates. In PCOS, due to follicular arrest and anovulation, antral follicles persist. When examined by ultrasound, these follicles appear as cysts. Small follicles secrete AMH, and the serum concentration of AMH reflects follicle reserve. Stromal theca and hilum cells produce testosterone which is converted to estradiol by the aromatase in the granulosa cells. In PCOS, stroma is enlarged, and testosterone is overproduced. (Adapted from PCOS: Getting the Right Medical Care. Sidika E. Karakas, MD [5])

Table 50.1 Effects of sex hormone-binding globulin concentration on bioavailable testosterone and free testosterone

	Reference range	Patient 1	Patient 2
Total testosterone	11–56 ng/dl	50	50
SHBG	30–135 nmol/L	24	185
Bioavailable testosterone	4–23 ng/dl	27	6
Free testosterone	1–9 ng/ml	11	2

How to Assess Ovarian Morphology?

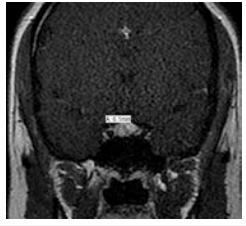
Recent evidence indicates that serum anti-Mullerian hormone (AMH) can be a very useful biomarker for assessing ovarian cysts [6]. Anti-Mullerian hormone is secreted by the granulosa cells in the primordial follicles and reaching its peak in the preantral and small antral follicles (Fig. 50.1) [7]. The larger follicles become FSH-dependent, and their AMH production decreases. In PCOS, the number of ovarian follicles as well as serum AMH is elevated [8, 9]. Serum AMH >5 ng/ml (35.7 pmol/L) is typical for PCOS [10, 11]. Concerns have been raised about the use of AMH as a diagnostic tool in adolescents because they can have PCO morphology without having the other components of the syndrome [12]. However, when adolescents who developed PCOS in adulthood were compared to those who did not develop PCOS, the former group had higher serum AMH during adolescence (6.0 ng/ml vs. 2.5 ng/ml). Use of ultrasound as a diagnostic tool is also limited during adolescence: Ultrasound should not be used until 8 years after menarche (approximately until age 20 years) [1]. Even though AMH is a practical, noninvasive, cost-effective biomarker, it is not yet accepted as a diagnostic test for PCOS.

Initial Test Cases

The following four patients were initially diagnosed as having PCOS. Their pertinent clinical information and initial and follow-up tests are shown in Table 50.2. Try and match the correct diagnosis to each patient. This includes PCOS, prolactinoma, hypogonadotropic hypogonadism, and premature ovarian failure.

Patient 1 presented with all the clinical findings of PCOS. She has elevated total-T, bioavailable-T, and free-T, indicating ovarian androgen excess. She had AMH >5 ng/ml, suggesting PCO morphology. In this case, the necessary and sufficient testing confirms PCOS. Initial evaluation of PCOS should also include the following tests: 17-hydroxyprogesterone (17OHP) is measured to rule out adult-onset congenital adrenal hyperplasia caused by 21 hydroxylase deficiency. If 17OHP measured during the follicular phase of the menstrual cycle is >200 ng/dl, Cortrosyn stimulation test is carried out. If 17OHP reaches >1000 ng/dl during the Cortrosyn stimulation, the diagnosis of 21OH deficiency is confirmed and can be validated by

Table 50.2 Differential diagnosis of PCOS. Match each patient with the correct diagnosis

Cases	1	2	3	4
Clinical parameters (*pertinents only*)	31 yo Oligomenorrhea + hirsutism: chin, chest, upper arms, and thighs	19 yo Amenorrhea for 17 mo Menarche 13 yo No hirsutism BMI: 36.5	18 yo Only one period in life No hirsutism Height: 4′11″ BMI: 31.2 Normal thyroid Acanthosis + breast exam: refused	25 yo Menarche: 12 yo Oligomenorrhea till age 19 Amenorrhea since age 19 BMI: 17.7
Basic laboratories (*reference values*) T: 9–55 ng/dl SHBG: 30–135 nmol/L Bioavail-T: 4.1–25.5 ng/dl Free-T: 1.3–9.2 pg/ml AMH:	T: 93 SHBG: 40 Bioavail-T: 39.7 Free-T: 14.0 AMH: 9.167	T: 23 AMH: <0.003	T: 11 SHBG: N.A. Bioavail-T: 5.5 Free-T: 1.8 AMH: 2.1	T: 25 SHBG: 122 Bioavail-T: 5.4 Free-T: 1.6 AMH: 8.299
Additional tests (*reference values*) FSH: 3–8.1 IU/L TSH: 0.35–3.3 mIU/l Prolactin: <19.5 ng/ml Growth H: 0.05–8 ng/ml IGF-1: 165–585 ng/ml		FSH: 50.2	FSH: 6.5 TSH: 1.22 Prolactin: 194 Growth H: 0.12 IGF-1: 277	FSH: 3.8 LH: 0.6 Prolactin: 4.7 Estradiol: <0.5 TSH: 1.52
Imaging/special testing		Karyotype: Balanced reciprocal translocation between chromosomes X and 4		
Correct diagnosis? (a, b, c, d)				

genetic testing. In this case, 17OHP was 40 ng/dl. Her prolactin, thyroid function tests and DHEA-S were also normal.

Patient 2 presented with amenorrhea and obesity but not hirsutism. Testosterone was normal. AMH <0.003 indicated absence of ovarian follicles. This information is adequate to make the diagnosis of premature ovarian failure. FSH >50 confirms the diagnosis. The next step was to determine the cause of premature ovarian failure, i.e., autoimmune vs. genetic. In the medical history, presence of Hashimoto's thyroiditis, hypothyroidism, and insulin-requiring diabetes points to autoimmune etiology. The genetic testing to evaluate premature ovarian failure includes karyotyping, to rule out Turner syndrome, and Fragile X testing. In this case, premature ovarian failure was caused by a mutation affecting X chromosome.

Patient 3 presented with amenorrhea, obesity, and short stature. Her physical examination was consistent with insulin resistance (acanthosis nigricans). Lack of hirsutism; normal total-T, bioavailable-T, and free-T; and AMH <5 ng/dl are not compatible with the diagnosis of PCOS. Prolactin 194 ng/ml is consistent with prolactinoma and explains the amenorrhea. Magnetic resonance imaging demonstrated 6 mm pituitary adenoma. Later, she consented to breast examination, and galactorrhea was present. She responded to cabergoline therapy, galactorrhea stopped, and her menstrual periods resumed.

Patient 4 presented with amenorrhea. Her AMH was >5 ng/dl, suggesting PCO morphology. This case fulfills the clinical criteria for phenotype D of PCOS (amenorrhea plus PCO morphology). Evaluation of patients with phenotype D requires higher level of alertness. This patient is thin; she does not have hirsutism or elevated testosterone. Therefore, hypogonadotropic hypogonadism needs to be considered in the differential diagnosis, and measurement of LH is the key. Low LH confirms the diagnosis of hypogonadotropic hypogonadism, and low estradiol level further supports this diagnosis. Typically, PCOS patients have high LH, and higher LH values are consistent with more severe hyperandrogenemia [13]. However, PCOS women can resort to bulimia for weight control and can present with a mixed picture of PCOS and hypogonadotropic hypogonadism.

Note

- Since PCOS is the most common endocrine disorder affecting young women, other disorders presenting with amenorrhea (prolactinoma, premature ovarian failure, hypogonadotropic hypogonadism, Cushing's disease/syndrome) or hirsutism (adult-onset congenital adrenal hyperplasia, Cushing's disease, idiopathic hirsutism) can be misdiagnosed as PCOS. Therefore, when the history, physical examination, and/or initial laboratory workup with total-T, bioavailable-T, free-T, and/or AMH raise any doubt, other differential diagnoses must be pursued.
- An important point is that oral contraceptives suppress testosterone and raise SHBG and can lower AMH approximately by 30%; therefore, diagnosing PCOS during oral contraceptive treatment can be a challenge.

Importance of Personalized Treatment

Women with PCOS have different clinical presentations, treatment goals, and expectations. In addition, their goals change with time. A young woman who wants treatment for hirsutism at the present may want to get pregnant in the next few years and may need to lose weight and avoid diabetes after the pregnancy and delivery. Therefore, treatments need to be personalized and modified with time.

An important pathology which commonly accompanies PCOS and influences management is insulin resistance. Women with PCOS are more insulin-resistant as compared to their weight-matched counterparts who do not have PCOS [14]. Women with PCOS have increased risks for prediabetes, type 2 diabetes (T2D), gestational diabetes, metabolic syndrome, non-alcoholic fatty liver disease, and obstructive sleep apnea. Obesity, which affects 80% of women with PCOS in the USA, aggravates all these comorbidities. Hence, all women with PCOS should be tested for insulin resistance and dyslipidemia. Insulin resistance precedes glucose intolerance. Prior to appearance of hyperglycemia, normal fasting and postprandial glucose levels are maintained at the expense compensatory hyperinsulinemia [15]. Physical examination and routine laboratory tests can provide invaluable information about insulin resistance: Acanthosis nigricans and/or skin tags in the neck or axilla, waist circumference >35 inches, BMI >31.5 kg/m^2, SHBG <35 nmol/L, and HDL cholesterol <40 mg/dl all support presence of insulin resistance [16]. If insulin levels are measured, they should be tested either at fasting or during oral glucose tolerance test. Random insulin measurements are uninterpretable because they depend on the recent food intake. We found that average fasting insulin levels are 7 μU/ml in insulin-sensitive, 13 μU/ml in moderately resistant, and 24 μU/ml in severely insulin-resistant PCOS women [16].

The HgBA1 levels between 5.7% and 6.4% are defined as prediabetes [17]. We found that HgBA1 >5.7% indicates presence of severe insulin resistance in PCOS [18]. As compared to those with HgBA1< 5.7%, PCOS women with HgBA1 >5.7% were older (35 vs. 31 years) and had higher fasting glucose (100 mg/dl vs. 92 mg/dl), higher triglyceride (125 mg/dl vs. 93 mg/dl), and higher high sensitivity-C reactive protein (hs-CRP) (5 μg/L vs. 2 μg/L). They also had lower insulin sensitivity indices and lower glucose disposal rates as determined by intravenous glucose tolerance test. Hence, we recommend measuring HgBA1 routinely in PCOS.

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Chapter 51
PCOS and Hirsutism

Sidika E. Karakas

Abbreviations

17OHP	17-hydroxyprogesterone;
AMH	Anti-Mullerian hormone
DHEA-S	Dehydroepiandrostenedione sulfate
FSH	Follicle-stimulating hormone
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
IVF	In vitro fertilization
LH	Luteinizing hormone
METS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
SGLT-2	Sodium-glucose cotransporter-2
T	Testosterone
T2D	Type 2 diabetes

A 25-year-old patient with PCOS is complaining of excess hair on her chin that she needs to shave every other day. She also has hair on her abdomen and thighs and around the areolas. She does not have family history of diabetes, acanthosis, or skin tags. She has periods every 6–8 weeks. She is 5′5″ and weighs 164 lbs; her BMI is 27.3 kg/m^2. She is not interested in pregnancy right now. Her main concern is "getting rid of the facial hair." Her laboratories related to PCOS were as follows and other mimicking pathologies were ruled out (Table 51.1).

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Table 51.1 Laboratory test results of case 1

Tests	Reference range	Patient's results
AMH	<5 ng/ml	7.1
Total-T	<55 ng/dl	71
SHBG	30–135 nmol/L	40
Bioavailable-T	2.2–20.6 ng/dl	31.7
Free-T	0.8–7.4 pg/ml	10.2
HgBA1c	<5.7%	5.4

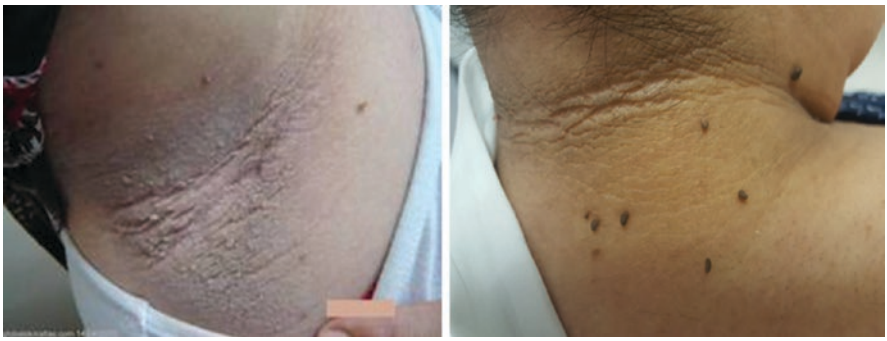

Fig. 51.1 Physical findings of insulin resistance: acanthosis nigricans and skin tags. (Adapted from PCOS: Getting the Right Medical Care. Sidika E. Karakas, MD [1]).

Questions What is the best treatment for her?

1. Spironolactone
2. Metformin
3. Oral contraceptive containing estrogen and progesterone (OCP)
4. Finasteride

How the Diagnosis Was Made The clinical presentation of oligomenorrhea and hirsutism fulfills the criteria for PCOS diagnosis. The laboratory results also confirm PCOS, AMH >5 ng/ml, and she has elevated total-T, bioavailable-T, and free-T concentrations. Her clinical hirsutism is consistent with the laboratory findings of androgen excess. Sex hormone-binding globulin and HgBA1 are normal suggesting that she probably does not have significant insulin resistance. She does not have clinical findings of insulin resistance such as acanthosis nigricans or skin tags either (Fig. 51.1). In addition, she does not have family history of T2D.

Lessons Learned

- *Answer*: The best treatment is oral contraceptives (OCP).
- Her priority is treatment of hirsutism. Oral contraceptives containing both estrogen and progesterone suppress testosterone production in the ovaries and increases SHBG production in the liver; consequently, bioavailable and free tes-

Table 51.2 Laboratory test results of case 1 before and after 3 months of oral contraceptive therapy

Tests	Reference range	Patient's results	
		Before OCP	After OCP
AMH	<5 ng/ml	7.1	–
Total-T	<55 ng/dl	71	36
SHBG	30–135 nmol/L	40	108
Bioavailable -T	2.2–20.6 ng/dl	31.7	7.6
Free-T	0.8–7.4 pg/ml	10.2	2.7
HgBA1c	<5.7%	5.4	–

tosterone levels decrease. Combined OCP are superior to progesterone-only OCP in suppressing testosterone. In addition, OCP provide monthly, predictable periods.

- Hair cycle is approximately 9 months, and therefore, the effects of the therapy may not be observed for at least 6 months. Typically, the treatment lasts minimum of 2 years. It is a good practice to repeat the testosterone panel after 3 months of OCP treatment to assure that testosterone is suppressed. Otherwise, the active pills can be extended to 6 weeks or even to 9 weeks, followed by the placebo during the seventh or tenth week, respectively. This patient had excellent response to OCP (Table 51.2).
- Spironolactone is not recommended as a monotherapy but can be added to OCP if the response is not satisfactory [2].
- Finasteride cannot be prescribed in women who has any risk of pregnancy (even on OCP) because of its feminizing effect on the male fetus.

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Chapter 52
PCOS and Reproduction

Sidika E. Karakas

Abbreviations

17OHP	17-hydroxyprogesterone;
AMH	Anti-Mullerian hormone
DHEA-S	Dehydroepiandrostenedione sulfate
FSH	Follicle-stimulating hormone
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
IVF	In vitro fertilization
LH	Luteinizing hormone
METS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
SGLT-2	Sodium-glucose cotransporter-2
T	Testosterone
T2D	Type 2 diabetes

A 37-year-old patient with PCOS wants to get pregnant. She is 5′ 4″ and weighs 210 lbs; her BMI is 36.0 kg/m^2. Her menstrual cycles vary between 6 and 12 weeks. She has hair on her chin and neck which she waxes weekly. She also has mild acanthosis on her neck and axilla. Her laboratory results are as follows (Table 52.1).

How the Diagnosis Was Made The clinical presentation of oligomenorrhea and hirsutism fulfills the criteria for PCOS diagnosis. In addition, this patient is obese and has clinical finding of insulin resistance (acanthosis nigricans). Even though her total testosterone is normal, this is due to low levels of SHBG, indicating that the

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Table 52.1 Laboratory test results of case 2

Tests	Reference range	Patient's results
AMH	<5 ng/ml	2.1
Total-T	<55 ng/dl	50
SHBG	30–135 nmol/L	28
Bioavailable-T	2.2–20.6 ng/dl	25.2
Free-T	0.8–7.4 pg/ml	8.9
HgBA1c	<5.7%	5.8

bound fraction of testosterone is low. Her bioavailable-T and free-T are high, accounting for the hirsutism. Anti-Mullerian hormone level is <5 ng/ml. This may be due to her age and is not an evidence against the diagnosis of PCOS. Elevated HgBA1 indicates prediabetes. Obesity, acanthosis nigricans, low SHBG, and high HgBA1 indicate presence of significant insulin resistance.

Questions She starts a low-carbohydrate diet and taking metformin. She cannot increase metformin more than 500 mg/day because of gastrointestinal side effects. She loses 12 lbs in 3 months. What is the next best step?

1. Switch metformin to metformin XR and try to increase the dose.
2. Reduce carbohydrates further and ask her to lose another 15 lbs.
3. Increase exercise.
4. Ovulation induction.

Lessons Learned

- *Answer*: The next best step is ovulation induction.
- Even though she is obese and insulin-resistant and has prediabetes and weight loss, exercise and metformin are very appropriate for her health care; her priority is pregnancy. Follicular reserve and quality of the ovarian follicles decline with age. AMH concentration around 0.8 ng/ml is consistent with menopause, and after menopause AMH declines below 0.003 ng/ml. There is evidence that AMH >2.8 ng/ml is associated with higher rates of live birth after in vitro fertilization (IVF) in women older than 35 years [1]. Therefore, this patient has some urgency.
- Both clomiphene and letrozole are used for ovulation induction. Letrozole is the preferred treatment because it leads to higher pregnancy and live birth rates [2].
- Clomiphene blocks estrogen receptors and creates estrogen deficiency at the hypothalamus/pituitary. In response, FSH increases and stimulates the ovarian follicles and induces ovulation. Ovulation leads to higher estradiol levels, but since the estrogen receptors are blocked, the hypothalamus/pituitary cannot sense the feedback, and FSH secretion continues, leading to ovulation from multiple follicles. In addition, estrogen receptors in the endometrium are also blocked; hence, only half of the ovulatory cycles results in implantation and pregnancy. Letrozole treatment also creates estrogen deficiency by blocking aromatase and conversion of testosterone to estradiol in the granulosa cells. This leads to increased FSH secretion and stimulates ovulation, and estradiol levels

rise. The big difference is that, since the estrogen receptors are not blocked, feedback at the hypothalamus/pituitary remains intact and FSH declines. This may cause fewer multiple pregnancies and higher endometrial implantation rates. The commonly used ovulation induction protocol involves administering 2.5 mg/day letrozole between the 3rd to 7th days of the menstrual bleed (natural or induced by progestin withdrawal). Ovulation occurs 5–8 days after the last letrozole pill. If ovulation does not occur, the dose is repeated and then increased to 5 mg/day and then 7.5 mg/day.

- The next step would be specialized treatments such as IVF.

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Chapter 53
PCOS and Insulin Resistance

Sidika E. Karakas

Abbreviations

17OHP	17-hydroxyprogesterone;
AMH	Anti-Mullerian hormone
DHEA-S	Dehydroepiandrostenedione sulfate
FSH	Follicle-stimulating hormone
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
IVF	In vitro fertilization
LH	Luteinizing hormone
METS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
SGLT-2	Sodium-glucose cotransporter-2
T	Testosterone
T2D	Type 2 diabetes

A 27-year-old patient with PCOS wants to have a child before turning 30 years old. She is 5′ 7″ and weighs 180 lbs; her BMI is 28.2 kg/m^2. Her menstrual cycles vary between 6 and 12 weeks. She has hair on her chin and neck which she waxes weekly. She has mild acanthosis on her neck and axilla. Her laboratory results are as follows (Table 53.1).

How the Diagnosis Was Made The clinical presentation of oligomenorrhea and hirsutism fulfills the criteria for PCOS diagnosis. She is overweight and has acan-

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Table 53.1 Laboratory test results of case 3

Tests	Reference range	Patient's results
AMH	<5 ng/ml	6.1
Total-T	<55 ng/dl	50
SHBG	30–135 nmol/L	28
Bioavailable-T	2.2–20.6 ng/dl	25.2
Free-T	0.8–7.4 pg/ml	8.9
HgBA1c	<5.7%	5.6

thosis. AMH >5 ng/ml confirms PCO morphology. Even though her total testosterone is normal, bioavailable-T and free-T are high because SHBG is low. Notably, her HgBA1 is at the upper limit of normal despite her relatively younger age and lack of clinical obesity. Acanthosis nigricans, low SHBG and HgBA1 5.6% raise the suspicion for significant insulin resistance.

Questions She starts a low-carbohydrate diet and metformin. Despite some gastrointestinal disturbances, she can increase metformin to 1000 mg/day. She loses 12 lbs in 3 months. Her periods become more frequent – every 4–6 weeks. What are the next best steps?

1. Switch metformin to metformin XR and try to increase the dose further.
2. Download a menstruation tracker app and monitor periods.
3. Start monitoring for ovulation when periods become every 4 weeks.
4. Start letrozole.
5. 1, 2, and 3.

Lessons Learned

- *Answer: 1, 2, and 3*. Switching to metformin XR and increasing the dose; start tracking the periods; and, when they become regular and monthly, start monitoring for ovulation.
- As you may have noticed, this patient has several similarities with case 2. Both patients have similar menstrual histories, identical signs of hirsutism and insulin resistance, and identical testosterone panels. However, there are also major *personal* differences which alter their managements.
- (1) This patient wants to get pregnant within the next 2 years. (2) She is younger. (3) Her BMI is lower. (4) Her AMH is higher indicating plenty of follicular reserve. (5) She is tolerating and responding to metformin; her periods are becoming regular.
- It is well documented that metformin increases ovulation rates in PCOS. There is argument, however, if metformin should be the first-line treatment for infertility since ovulation induction therapy is more successful [1]. The choice can be based on the level of urgency vs. the risk of multiple pregnancy. In this case, there is no urgency, and therefore, a trial of metformin along with lifestyle

changes to reduce insulin resistance is a good choice. Switching metformin to metformin XR may reduce the gastrointestinal side effects, and once daily dosing may improve compliance.

- Careful documentation of the cycle length is important because regular cycles between 25 and 35 days are likely to be ovulatory. In contrast, shorter or longer cycles are likely to be anovulatory.
- Ovulation can be monitored by measuring blood levels of progesterone during the 3rd week (around days 21–23), and a value >4 ng/ml indicates ovulation. Random progesterone measurements are not helpful or meaningful because serum progesterone is low during the follicular phase of the cycle and increases only after ovulation during the luteal phase. Therefore, progesterone should not be measured during the follicular phase of the cycle. One caveat is that progesterone measurements provide after the fact information, indicating that the ovulation had already occurred. On the other hand, ovulation prediction kits detect the LH surge prior to ovulation and are very helpful in determining the most fertile time of the cycle.

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Chapter 54
PCOS and the Metabolic Syndrome

Sidika E. Karakas

Abbreviations

17OHP	17-hydroxyprogesterone;
AMH	Anti-Mullerian hormone
DHEA-S	Dehydroepiandrostenedione sulfate
FSH	Follicle-stimulating hormone
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
IVF	In vitro fertilization
LH	Luteinizing hormone
METS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
SGLT-2	Sodium-glucose cotransporter-2
T	Testosterone
T2D	Type 2 diabetes

The patient presented in case 2 returns 4 years later. She is 41 years old. She had two children, 1 year apart, with IVF. The younger child is now 5 months old. Both babies were healthy but weighed over 8 lbs at birth. Patient developed gestational diabetes during the second pregnancy. She had to stop nursing the second baby after 6 weeks because of inadequate lactation, and she could not lose the excess weight gained during her pregnancies.

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Table 54.1 Laboratory test results of case 4

Tests	Reference range	Patient's results
AMH	<5 ng/ml	1.1
Total-T	<55 ng/dl	42
SHBG	30–135 nmol/L	21
Bioavailable-T	2.2–20.6 ng/dl	23.1
Free-T	0.8–7.4 pg/ml	7.6
HgBA1c	<5.7%	7.0

She did not have a period since the delivery. She is still waxing the hair on her chin and neck weekly. She thinks that her neck and armpits are getting darker; she is also getting skin tags (Fig. 51.1). She is being treated for vaginal yeast infection.

She is 5′4″ and weighs 242 lbs; her BMI is 41.5 kg/m^2 and BP 154/92 mmHg.

The laboratories show the following (Table 54.1).

How the Diagnosis Was Made The clinical presentation of oligomenorrhea and hirsutism fulfills the criteria for PCOS diagnosis. In addition, she is obese and has clinical findings of insulin resistance (acanthosis nigricans and skin tags). Even though her total testosterone is normal, this is due to low levels of SHBG, indicating that the bound fraction of testosterone is low. Her bioavailable-T and free-T are high, accounting for the hirsutism. Anti-Mullerian hormone decreased from 2.1 to 1.1 ng/ml in the last 4 years, and this is consistent with aging process. HgBA1 7.0% (>6.5%) indicates that she developed T2D. She also has hypertension. Obesity, insulin resistance, and hypertension are parts of the metabolic syndrome (METS). Other components of METS are dyslipidemia (high triglyceride and low HDL cholesterol) and microalbuminuria. The disorders commonly associated with METS include NAFLD and obstructive sleep apnea. She needs to be questioned and tested for these.

Questions She started a low-carbohydrate diet and taking metformin XR 1000 mg/day a month before coming to see you. What is the next best step?

1. Encourage exercise and increase metformin XR to 1500 mg/day.
2. Add a GLP-1 analog.
3. Refer to bariatric surgery.
4. Add a SGLT-2 inhibitor.

Lessons Learned

- *Answer*: The next best step is adding a GLP-1 analog to metformin.
- The goal for this patient is achieving remission of T2D and weight loss. Recent research showed that addition of GLP-1 analog to metformin increased remission rate of early diabetes by from 32% to 64% [1]. Treatment with GLP-1 analog alone achieved 54% remission rate. In obese individuals without PCOS, a GLP-1 analog resulted in approximately 15% weight reduction [2].

- In this case, a potential concern for the use of GLP-1 analog may be chylomicronemia-related risk for pancreatitis. Since she has METS and obesity, she is likely to have hypertriglyceridemia. Therefore, her triglyceride levels should be measured to make sure that she does not have chylomicronemia before starting GLP-1 analog.
- Referral to bariatric surgery is also an option and should be entertained if the GLP-1 analog treatment is not successful. She is a candidate for bariatric surgery since her BMI >40 kg/m^2. She would have been a candidate even if her BMI was >35 kg/m^2 because she has other comorbidities such as T2D and PCOS. Bariatric surgery improves both glucose metabolism and hyperandrogenemia in PCOS [3].
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors can also achieve some weight loss but not as much as GLP-1 analogs can. They are mostly indicated in diabetes patients with kidney disease to delay progression of nephropathy [4] which is not the case in our patient. In addition, SGLT-2 inhibitors can worsen vaginal candidiasis by increasing glycosuria. Since our patient has vaginal candidiasis, SGLT-2 inhibitors are not the best choice.

In conclusion, the practice of PCOS is a perfect example of personalized medicine. Accurate diagnosis and personalized management are crucial in order to help the millions of women who are affected by this common disorder throughout their lives.

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Part XIV
Transgender Medicine

Chapter 55
Introduction to Transgender Medicine

Joshua D. Safer

Transgender and gender nonbinary (TGNB) people have gender identities that are not aligned with their sex recorded at birth (the latter typically determined when external genitalia are visualized). Studies suggest that approximately 0.6% of the adult population of the United States are TGNB [1].

Gender identity refers to people's sense of their own sex. That is, are they male, female, neither, or a combination of both. Gender expression is the term for how people signal gender identity to themselves or to others through appearance, clothing, or actions of various sorts.

Trans, transgender, transsexual, gender nonbinary, gender incongruent, and genderqueer are common adjectives for people who have gender identities that differ either from sex recorded at birth (or from visible genitalia at birth). Trans, transgender, and the acronym TGNB (transgender and gender nonbinary) are all used as umbrella terms for all people for whom external genitalia at birth and gender identity are not aligned.

Cis or cisgender are the common adjectives for people who are not TGNB, that is, for people whose gender identities are aligned with their sex recorded at birth.

People with male gender identity who were identified at birth as female are often called trans men, transgender men, or transmasculine people. People with female gender identity who were identified at birth as male are often called trans women, transgender women, or transfeminine people.

The term gender dysphoria references a mental health diagnosis for the discomfort felt by some TGNB people due to the lack of alignment between their visible anatomy and their gender identity. Not all TGNB people who seek medical interventions to align their bodies with their gender identities suffer dysphoria. However, many payers throughout the world insist on a gender dysphoria designation to cover

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costs of gender-affirming medical care [2]. When the ICD-11 is published, it will include a new diagnostic code labeled gender incongruence that will appear in a new sexual health section [3].

There has been a substantial shift in the model for gender identity etiology [4], with an appreciation that there must be a significant biological component underlying gender identity. Data supporting the biological underpinning to gender identity can be separated into several broad categories in order of the strength of evidence in each category:

1. Attempts to manipulate gender identity by external means have not succeeded [5, 6].
2. TGNB people with identical twins have greater concordance with regard to transgender identity than when they have fraternal twins [7].
3. Increased rates of male gender identity are observed among some individuals with congenital adrenal hyperplasia exposed to excess androgen in utero [8].
4. Individuals with complete androgen insensitivity syndrome have female gender identity [9].

The majority of transgender individuals present to clinicians in late adolescence or adulthood. However, despite the late presentation, many transgender individuals report that their awareness of their gender incongruence began well before puberty.

The data for biological underpinnings to gender identity remain modest. Further, other than a suggestion that there may be some influence from androgens on at least some people, the data shed little light on the mechanisms by which such biology would exert its influence. However, along with greater social awareness, the acceptance of the biological model has provided a basis for the focus on treatment to align the bodies of transgender people with their gender identities rather than to think that the gender identities can be manipulated.

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Chapter 56
Transmasculine Therapy

Mary O. Stevenson and Vin Tangpricha

Objectives

- To describe the medical risks associated with transmasculine therapy, particularly the risk of erythrocytosis
- Review the evaluation and management of erythrocytosis while on transmasculine therapy

Case Presentation

A 67-year-old transgender male patient presented to a new endocrinologist for ongoing management of transmasculine hormone therapy. The patient was started on gender-affirming hormone therapy with intramuscular testosterone therapy approximately 5 years previously by an endocrinologist. The patient's medical history included post-traumatic stress disorder, anxiety disorder, attention deficit disorder, and Wolff-Parkinson-White syndrome. Surgical history included total hysterectomy with bilateral oophorectomy in the 1980s as well as mastectomy in 2017. Current medications included testosterone cypionate 100 mg IM q2week, zolpidem 5 mg qhs, topical lidocaine cream, emtricitabine-tenofovir (for HIV pre-exposure prophylaxis), bupropion XR 100 mg BID, alprazolam 0.25 mg TID prn,

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and amphetamine-dextroamphetamine 10 mg BID. Patient denied tobacco use, alcohol use, or illicit drug use. He did endorse recreational marijuana use.

On physical exam, his vital signs included a blood pressure of 103/71, pulse 104, weight 59.5 kg, and BMI 22.5. His thyroid, pulmonary, cardiac, gastrointestinal, and neurologic exams were all within normal limits. Laboratory evaluation revealed the following values: total testosterone 888 ng/dL (reference range 270–1100 ng/dL), hemoglobin 16.9 gm/dL (12.9–16.1 gm/dL), hematocrit 51.1% (37.7–46.5%), total cholesterol 235 mg/dL (<200 mg/dL), High-density lipoprotein (HDL) cholesterol 40 mg/dL (23–92 mg/dL), Low-density lipoprotein (LDL) cholesterol 153 mg/dL (H) (<99 mg/dL), triglycerides 210 mg/dL (<149 mg/dL), and total bilirubin 2.0 mg/dL (<1.0 mg/dL). Serum creatinine, platelet and the remaining liver function tests were within the normal ranges.

The patient was contacted and asked to hold current testosterone therapy temporarily with a plan to repeat total testosterone levels and blood counts in 2 weeks. The patient returned for lab work after the designated 2 weeks with repeat labs showing a total testosterone 198 ng/dL (270–1100 ng/dL), hemoglobin 17.5 gm/dL (H) (12.9–16.1 gm/dL), and hematocrit 53.0% (37.7–46.5%).

What Are the Known Side Effects of Testosterone Therapy?

As outlined in the most recent Endocrine Society Clinical Practice Guidelines "Endocrine treatment of gender-dysphoric/gender incongruent persons," testosterone therapy is associated with a very high risk of erythrocytosis (defined as a hematocrit >50%), as well as moderate risk of coronary artery disease, cerebrovascular disease, hypertension, and breast or uterine cancer [1]. Testosterone therapy is associated with an increased atherogenic profile of lipids including higher triglyceride and LDL levels and lower HDL levels [1] as well as sleep apnea, hypertension, excessive weight gain, salt retention, and acne [2]. The guidelines suggest that the risk of the adverse outcomes is mitigated by keeping testosterone levels within target range of 400–700 ng/dL [1].

The mechanism of erythropoiesis stimulation and resultant erythrocytosis by testosterone is widely recognized but not clearly understood [2–4]. One dose-response study in cisgender men was undertaken in 2008 to help clarify the relationship [3]. The subjects were divided into two age groups, one group of younger subjects ages 19–35 and one group of older subjects ages 60–75. Participants were given monthly gonadotropin-releasing hormone (GnRH) agonists plus one of five weekly doses of testosterone enanthate (25, 20, 125, 300, or 600 mg IM) for 20 weeks. The study found that hemoglobin and hematocrit increased in linear, dose-dependent manner in both age groups. Hemoglobin and hematocrit levels started to increase within 1 month of initiation of treatment and, in older subjects, peaked at a later and higher level than younger subjects [3]. They did not find a significant relationship between erythropoietin or soluble transferrin receptor levels between the younger and older subjects nor between the dose groups [3].

Transgender men receiving testosterone therapy in the European-based European Network for the Investigation of Gender Incongruence (ENIGI) cohort experienced an increase in hematocrit of about 5% which primarily occurred in the first year [5]. Only 11.5% of the trans men in the cohort developed hematocrit above 50% [5]. In the United States-based Study of Transition, Outcomes and Gender (STRONG) cohort, transgender men experienced a mean increase of hematocrit of 2.5% after initiation of testosterone therapy [6]. Transgender men had a sevenfold and 83-fold increased rate of erythrocytosis (hematocrit >52%) compared to cisgender males and females, respectively [6]. Testosterone ester injections have been reported to have a higher association with erythrocytosis than oral or transdermal formulations [7, 8]. In one study, longer-acting testosterone depots such as testosterone undecanoate was associated with less erythrocytosis than other shorter-acting testosterone esters [5].

Complications from erythrocytosis could include venous thromboembolism (VTE) and increased cardiovascular disease. However, very few adverse events have been reported to occur in transgender men receiving testosterone therapy. There has been one case report of a transgender man who developed thrombosis of a retinal artery leading to scotoma in his left eye [9]. While it is established that testosterone results in increased erythrocytosis, transgender men do not appear to have increased risk of VTE and myocardial infarction (MI), though hematocrit levels were not included as part of this analysis [10].

What Additional Evaluation Should Be Performed?

The patient was contacted by phone after the laboratory evaluation. He denied any symptoms of hyperviscosity, including chest pain, abdominal pain, fatigue, myalgias/muscle weakness, headache, blurred vision, paresthesias, or changes to thinking or mood [11]. To evaluate for common causes of erythrocytosis, including hypoxia [11], he was asked about signs or symptoms of sleep apnea (snoring, daytime somnolence), which he denied, and confirmed that he was not using tobacco or alcohol. He stated that he had been taking the testosterone at the prescribed strength and frequency and denied use of diuretics, another medication known to contribute to erythrocytosis [11]. He knew of no family history of abnormal blood cell counts.

How Should Erythrocytosis Be Managed While on Testosterone Therapy?

Guidelines for testosterone replacement in hypogonadal cisgender men suggest a few strategies to manage erythrocytosis associated with testosterone therapy. One is to withhold testosterone therapy until hematocrit returns to normal range and then resuming testosterone at a lower dose [2]. However, it can take up to 3 months to see

any changes in hematocrit given the red blood cell life span is approximately 3 months. A preferred approach is to lower the testosterone dose without any interruption in testosterone therapy and recheck the hematocrit in 3 months. Another strategy is to use therapeutic phlebotomy to lower hematocrit levels [2, 3]; however, this approach has not demonstrated to change any outcomes related to erythrocytosis in transgender men. In the absence of long-term clinical studies guiding the approach in limiting erythrocytosis, it is likely prudent to follow the recommendations from the Endocrine Society guidelines to maintain hematocrit below 54% while on therapy [1].

Conclusions

As the main component of masculinizing hormone therapy for treatment of gender dysphoria in transgender males, testosterone has a known risk of increasing red blood cell mass. The clinical significance of this is not fully understood, but no long-term studies have shown an increase in VTE or MI in transgender men as compared to cisgender men. The route and dose of testosterone therapy should be individualized with a goal of minimizing erythrocytosis.

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Chapter 57
Perioperative Estrogen Considerations for Transgender Women Undergoing Vaginoplasty

Tamar Reisman and Joshua D. Safer

Objectives

- To briefly understand the data regarding VTE risk and estrogen therapy
- To synthesize the existing literature as it relates to estrogen dosing during the perioperative period for transgender women undergoing vaginoplasty

Case Presentation

A 42-year-old transgender woman presents to her endocrinologist to prepare for upcoming vaginoplasty surgery. She reports that she started self-administering combined oral contraceptive pills on an intermittent basis at age 25. At age 27, she began taking a formal feminizing hormone regimen under the supervision of a physician. Currently, she is taking 2 mg of oral estradiol twice daily and 100 mg of oral spironolactone twice daily.

Her past medical history is significant for childhood asthma, occasional migraines without auras, and hypertension. In addition to the above hormone regimen, the patient takes amlodipine 5 mg daily. Family history is significant for hyperlipidemia in her mother, along with diabetes, hypertension, and hyperlipidemia in her father. Her paternal grandmother had a CVA in her 80s. The patient reports no family history of breast cancer, ovarian cancer, DVT, or PE. Her past surgical history includes breast augmentation obtained at age 38. She is scheduled for vaginoplasty in several months and was instructed by her surgeon to stop taking her hormone regimen 2 weeks prior to surgery.

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Professionally, the patient works as a programmer. She reports that she is a former smoker but quit 2 years ago. She reports social alcohol and marijuana use on weekends. The patient reports no formal exercise regimen; however, she states that she "walks a lot."

Today, the patient is 5′7″ with a weight of 175 lbs, giving her a BMI of 27.8. Physical exam reveals a pleasant woman in no acute distress.

Introduction

Feminizing hormone therapy (HT) typically consists of an estrogen, typically 17-beta estradiol in the form of a tablet, a patch, or an injection, in combination with an adjunct anti-androgen such as spironolactone or a GnRH agonist [1]. Such regimens promote the development of female secondary sex characteristics including breast growth and fat redistribution. Feminizing hormone therapy helps transgender women align their bodies with their gender identity. Overwhelmingly, studies demonstrate that transgender women who initiate hormone therapy have an improvement in their quality of life [2–7]. Worrisomely, estrogen is a known risk factor for venous thromboembolism (VTE), a phenomenon that has been well documented in a number of large-scale studies [1]. Fortunately, a number of concrete steps can be taken to minimize the inherent risk of VTE associated with HT.

Assessing VTE Risk

Our current understanding regarding the risk of VTE in transgender individuals is largely extrapolated from available data in cisgender women. While there is a paucity of studies investigating the risk of VTE in transgender women, there are many studies investigating VTE risk with oral contraceptives and postmenopausal hormone replacement therapy (HRT) in cisgender women.

The first documented cases of VTE in the setting of combined oral contraceptive (COC) use were published in the 1960s when their use became mainstream [8]. Venous thrombosis is the most common vascular complication associated with exogenous estrogen, followed by CVA and then myocardial infarction [2, 3, 8]. The risk of VTE associated with COC is well established. Women using oral contraceptives have estimated risk of 3–9 per 10,000 women-years having embolic events relative to 1–5 per 10,000 women-years in nonusers [9]. The use of oral contraceptive drugs increases the risk of VTE 3.8-fold (95% CI 2.4–6.0) [10].

The risk of VTE is higher in individuals with certain underlying conditions. For example, the incidence of VTE in women with factor V Leiden mutation taking COCs was 29 times higher than women without this mutation [10]. COC's risk of VTE can be additive to other thrombogenic conditions, including smoking tobacco,

history of surgery with prolonged immobilization, systemic lupus erythematosus with phospholipid antibodies, inflammatory bowel disease, and the postpartum period [11].

Choosing an Estrogen

Route of Administration

Route of estrogen administration may impact VTE risk. Oral estrogens appear more thrombogenic than transdermal estrogens. The Estrogen and Thromboembolism Risk (ESTHER) study suggested that oral but not transdermal estradiol increased the risk for VTE in postmenopausal women [12]. Orally administered estrogens may be subject to the first pass effect, which may account for their increased thrombogenicity. Oral estrogens increase the hepatic production of thrombogenic proteins such as von Willebrand factor, factors VII, VIII, and X; prothrombin; and fibrinogen while decreasing the levels of antithrombin and protein S [13–15].

Transdermal estrogen formulations, including patches and topical gels, are associated with the fewest thrombogenic events. In a study of 162 transgender women who were prescribed with transdermal estrogen for average of 4.4 years, no episodes of VTE occurred [16]. This was especially remarkable given the fact that 18 of the study participants were identified as having thrombogenic genetic mutations at the time of hormone therapy initiation.

Transdermal estrogens are not associated with the "first pass effect" and do not mediate an increase in surrogate endpoints for coagulation. Pro-inflammatory cytokines like IL-1, IL-6, IL-8, and TNF-alpha were elevated in 23 transgender women taking Premarin (conjugated equine estrogens (CEE)) over a 6-month span [17]. Meanwhile, transdermal estrogen did not increase cytokine levels or procoagulant factors [17–19].

Alternatively, oral estrogens may be more thrombogenic than transdermal preparations for the simple reason that oral versions tend to provide relatively higher amounts of estrogen. A systematic review conducted in 2019 evaluated postmenopausal hormonal therapy and cardiovascular outcomes. This study, including over 2.5 million women in six clinical trials and 27 prospective observational studies, found that VTE increased with estrogen exposure in a dose-dependent manner [14]. At this time, there are no studies comparing VTE risk among equivalent doses of transdermal and oral estrogens.

The increased VTE risk seen with oral estrogen in controlled trials may be a dose-dependent effect. The available data use nonequivalent doses of oral and transdermal estradiol. The highest transdermal dose studied was 0.1 mg/day; however, it is not unusual for patients to receive doses of 0.2–0.3 mg/day in the clinical setting. The dose-dependent risk of VTE is likely cumulative, and the risk of VTE increases linearly with the duration of hormone therapy. The largest retrospective study

($N = 61$) revealed that 2% of the transfeminine individuals on estrogen therapy in the cohort experienced VTE. The data demonstrated a fourfold increase in risk in women taking estrogen for 8 years compared to those who took estrogen for 2-year duration [3]. However, it is important to note that while the study controlled for smoking history, blood pressure, and history of cardiovascular events, it did not control for important VTE risk factors such as HIV infection, route of estrogen administration, or estrogen dose of the participants. Thus, the study's interpretability is severely compromised.

Type of Estrogen

When comparing different oral estrogens directly, certain types of estrogen are more thrombogenic than others. Ethinyl estradiol, the most common estrogen found in COC pills, is highly linked to VTE. In a study of 966 transgender women followed for a median of 18.5 years, ethinyl estradiol was found to be independently associated with threefold increase in risk of cardiovascular death (including VTE) [5].

By comparison, conjugated equine *estrogens* (CEEs) and 17-beta estradiol appear to be much safer. A cohort of 61 transgender women prescribed with CEEs was not noted to have any venous thromboembolic events, and neither were another group of 23 transgender women taking a 17-beta estradiol regimen [8]. One study did indicate that CEEs are correlated with higher rates of VTE compared to estrogen valerate or ethinyl estradiol [20].

Estrogen Choice Summary

For most young, healthy, transgender women, there is little risk of VTE with HT. One review found the incidence to be 2.3 events per 1000 person-years [21]. Of the patients who develop VTE, most are known to have underlying risk factors. One study indicated that all eleven patients who had thromboembolic events were smokers, underwent recent surgery, and/or suffered from dyslipidemia or hypertension [2]. There is only one published case to date documenting VTE in a patient without known underlying risk factors [22]. For transgender women of advanced age or women with a history of smoking, hypertension, underlying thrombogenic conditions, history of thrombosis, mental illness, HIV infection, malignancies, or hyperlipidemia, the decision to start feminizing HT is more complicated. Ultimately, the patient should be counseled on the risks and benefits of treatment in order to help facilitate decision-making and to help promote favorable health outcomes.

VTE Concern and Perioperative Estrogen

The primary change after vaginoplasty is that absent testes and adjunct antiandrogen agents are no longer necessary. It is possible that estrogen doses may decrease too although that is not always the case.

Because major surgery represents a VTE risk, the biggest question in the perioperative period for transgender women is whether the VTE risk can be mitigated by suspension of estrogens briefly. Recommendations to suspend estrogens for 2–4 weeks are common.

However, the highest risk for VTE associated with COCs is in new users or after prolonged discontinuation [23]. Thus, unnecessary starting and stopping of feminizing HT should likely also be discouraged. At this time, there is no demonstrated benefit to holding HT prior to vaginoplasty or other gender-affirming surgeries. In a retrospective study of 1396 gender-affirming procedures (including 407 primary vaginoplasty operations), there was no observable benefit associated with holding HT perioperatively [24]. In the study, 212 primary vaginoplasty operations were performed without HT held before surgery, and 190 primary vaginoplasty operations were performed with HT held 1 week before surgery. Only one person, a 37-year-old transgender woman, suffered a VTE event, DVT 20 days after vaginoplasty. She was from the group where estrogen therapy was held. All patients received standard postoperative VTE prophylaxis with heparin appropriate to their Caprini score.

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Chapter 58
Feminizing Gender-Affirming Hormone Therapy: Special Considerations for Older Adults

Micol S. Rothman and Sean J. Iwamoto

Objectives

- Outline implications to feminizing gender-affirming hormone therapy (GAHT) with aging.
- Discuss considerations for feminizing GAHT management in adults with older age and increased risk for venous thromboembolism.

Case Presentation

JD, a 57-year-old transgender woman, was referred to endocrinology by her primary care provider with questions about starting feminizing gender-affirming hormone therapy (GAHT). She has always had a sense of "being born in the wrong body" but was physically abused by family members when she revealed this to them as a child, so she kept these feelings to herself. She joined the military and went on to marry a cisgender woman and have two biological children. She has since divorced. Her main goals of hormone therapy are breast development and a more

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feminine appearance, and she is not sure at this time if she would pursue gender-affirming surgery in the future.

JD is under the care of a psychiatrist for depression and post-traumatic stress disorder, (PTSD), and these conditions are well controlled. Her medical history also includes hypertension and type 2 diabetes mellitus, onset of both at age 53 years. She is on the following medications: citalopram, prazosin, lisinopril, hydrochlorothiazide, metformin, and atorvastatin. Her father died of an ischemic stroke at age 70 years, and her mother is alive at age 80 years with a recent hip fracture. She has smoked cigarettes since age 20, and a pack currently lasts 3–4 days. She says she is "trying to cut down." A physical examination is only remarkable for body mass index of 33.7 kg/m^2. Her labs are notable for a hemoglobin A1C of 7.6%, LDL 85 mg/dL, and triglycerides 256 mg/dL. Liver and kidney functions are normal with potassium in the normal range.

Are There Contraindications to Initiating Feminizing GAHT in This Patient?

JD has persistent, well-documented female gender identity; has the capacity to consent for treatment; and is of the age of majority, three of four criteria for initiation of GAHT in adults [1, 2]. Although she has depression and PTSD as well as risk factors for cardiovascular disease, they are reasonably well controlled, which is the fourth criterion for GAHT initiation [1, 2]. The presence of mental health and medical conditions are not absolute contraindications for GAHT but should be optimized as outlined below. Current tobacco smoking is also not an absolute contraindication to initiating or continuing feminizing GAHT, but cessation should be strongly encouraged. Indeed, one group reported that when counseled, 64% of transgender women quit smoking upon initiation of gender-affirming hormone therapy [3]. We would encourage communication among all the healthcare professionals (e.g., primary care provider, psychiatrist, endocrinology) involved in JD's care at the time of GAHT initiation to optimize a team-based approach for her ongoing care.

How Would You Initiate Feminizing GAHT in This Patient?

When considering a regimen for feminizing GAHT, there are several things to discuss with JD: routes and frequency of administration, formulations of estrogens and antiandrogens, availability of medications, efficacy, safety, cost, patient preference, and expectations. Feminizing GAHT typically increases serum estradiol levels and decreases testosterone levels into the typical physiologic cisgender female ranges [1, 4]. While supraphysiologic estrogen dosages can suppress testosterone production through negative feedback of the hypothalamic-pituitary-gonadal axis, the

inclusion of antiandrogen therapy allows for lower estrogen dosages to be used which may decrease the risk of side effects like venous thromboembolism (VTE).

Estrogens

General estrogen-prescribing considerations for younger women are addressed in the previous chapter.

Antiandrogens

The most common antiandrogen medication in the United States is spironolactone, which was identified as such when it was associated with gynecomastia in cisgender men. It is a potassium-sparing diuretic antihypertensive which must be monitored accordingly. In Europe, cyproterone acetate (a progestin) is more common but is associated with hyperprolactinemia and possibly increased VTE risk. Hepatotoxicity and meningiomas are also reported with cyproterone acetate.

Although more expensive, gonadotropin-releasing hormone agonists (GnRHa) are extremely effective at lowering testosterone. In youth and adolescents, GnRHa can also be used to block pubertal changes prior to the initiation of GAHT.

The most effective means to decrease circulating testosterone into the typical female range is with orchiectomy. Both world professional association for transgender health (WPATH) and the Endocrine Society suggest that gender-affirming genital surgeries be deferred until after a year of hormone therapy if hormone therapy is otherwise indicated. JD has not expressed interest in surgery; however, orchiectomy might be consider earlier in older person, particularly if there was a history of a prior VTE.

Other agents of interest to patients include 5-alpha reductase inhibitors (which block testosterone conversion to dihydrotestosterone and are often used for hair loss), bicalutamide (which acts at the level of the androgen receptor to block action but many oppose its use due to concerns of hepatotoxicity), and progestins other than cyproterone acetate (specifically discussed below under breast development).

Case Considerations

With a normal potassium level, spironolactone is a reasonable choice for antiandrogen therapy. If desired for gender affirmation and/or to suppress her testosterone level if unable to do so pharmacologically with estrogen (even with the patch) and antiandrogen, she could be eligible for an orchiectomy after 1 year. It is crucial to provide patients with information about risks, benefits, and alternatives to treatment to allow them to make fully informed decisions about feminizing GAHT.

How Often Should Labs Visits Take Place for Feminizing GAHT?

The Endocrine Society clinical practice guidelines suggest hormone levels be assessed every 3 months for the first year and then once or twice per year as this is a typical dose titrating interval [1]. Potassium should be monitored on spironolactone as well. Lipids should also be assessed periodically, depending on baseline levels and underlying cardiovascular risk as done for the general population.

What Are the Benefits and Expected Changes of Feminizing GAHT?

In younger transgender women, bodily changes typically begin within a few months of initiation of estrogen and androgen blockade. Patients frequently report decrease both in sexual desire and in spontaneous erection as early as 1 month after commencing treatment. Patients may observe breast development, softening skin, decreased body hair, and/or body fat redistribution within the first 3–6 months [1]. The impact on sexual desire may or may not be a desired side effect, and it is important to ask patients about their sexual activity and goals. It can take up to 3 years to see the maximal effects of feminizing GAHT. Feminizing hormone therapy will not induce changes in voice. Speech language pathologists and therapists can assist patients with vocal therapy, and vocal cord surgeries may be an option to facilitate a more feminine voice.

JD identified breast development as one of her key goals. A European study (european network for the investigation of gender incongruence (ENIGI) cohort) of 229 transgender women aged 18–69 (mean age 28) years on estradiol and cyproterone acetate for 1 year found that 48.7% developed less than an AAA bra cup size [5]. Serum estradiol did not predict breast development nor did route of administration, age, body mass index (BMI), or smoking status. It would be important to discuss expectations with JD as she may want to consider breast augmentation in the future if she does not achieve her desired cup size with medical therapy.

What Role Does Progesterone Have in Breast Development and Feminizing GAHT?

Although progesterone does not appear in feminizing GAHT recommendations in WPATH or the Endocrine Society clinical practice guidelines, many patients have questions surrounding its role in breast growth. We lack evidence for benefit from progesterone [6] in transfeminine patients although its use has been advocated for by some [7]. Much of what we know about progesterone's risks and benefits come

from data in cisgender female populations. In cisgender girls, early use of progesterone may lead to premature ductal differentiation and may be suboptimal for breast growth (e.g., Turner syndrome) [8]. Additionally, some types of progesterone may be associated with adverse effects on body weight, lipids, and mood [9]. Medroxyprogesterone acetate was associated with increased risk of cardiovascular disease and breast cancer in postmenopausal women who also received conjugated equine estrogens [10]. Studies exploring progesterone's impact on breast development have not found a difference in breast growth or referrals for breast augmentation surgery when progestins are added to estrogen treatment relative to estrogen alone [6]. In JD's case, we would encourage her to start with estrogen and spironolactone and then reassess goals for breast growth after 1–2 years on this regimen.

How Does Feminizing GAHT Affect Cardiovascular Disease and Ischemic Stroke Risk?

Of special interest to an older patient who already has some cardiac risk factors developing, the relative cardiovascular disease risk for her is important. Whether feminizing GAHT leads to an increased risk of cardiovascular disease and ischemic stroke in transfeminine adults has been the focus of increasing research. While early Dutch cohort analyses revealed higher overall mortality among transfeminine adults compared to the general population, the excess mortality was driven by death from AIDS, illicit drug use, suicide, and ischemic heart disease (standardized mortality ratio 1.64 [95% CI 1.43–1.87]) but not cerebrovascular accidents [11].

More recent studies done in Europe and the United States have shed additional light on cardiovascular disease and ischemic stroke risk. In the updated Dutch cohort study, transgender women had higher standardized incidence ratios for stroke compared to both reference cisgender men and women but only had a higher risk of myocardial infarction compared to reference cisgender women (standardized incidence ratio 2.64 [95% CI 1.81–3.72]), not reference cisgender men (standardized incidence ratio 0.79 [95% CI 0.54–1.11]) [12]. The study of transition, outcomes and gender (STRONG) study also revealed a higher relative risk of ischemic stroke, but not myocardial infarction, in the transfeminine cohort that initiated estrogen during the time period evaluated and had more than 6 years of follow-up when compared to both cisgender men and women [13]. In an example of a growing number of analyses of US Behavioral Risk Factor Surveillance Survey data, one study looking at data from 2014 to 2017 found that transfeminine respondents had a significantly higher adjusted odds of self-reporting a history of myocardial infarction compared to cisgender women (adjusted odds ratio 2.56 [95% CI 1.78–3.68]) but not cisgender men (adjusted odds ratio 1.32 [95% CI 0.92–1.90]) [14].

There are many potential factors that may contribute to the increased risk of cardiovascular disease and ischemic stroke risk among transfeminine adults including known increases in body weight, body mass index, total fat mass, and visceral

fat after initiating feminizing GAHT. A systematic review and meta-analysis revealed increases in triglycerides but no significant change in other lipid parameters after 24 months or more on feminizing GAHT [15]. There does not appear to be higher incidence of type 2 diabetes, hypertension, or hyperlipidemia in transfeminine adults compared to cisgender populations [16]. Other factors that need further study include differences in current smoking, alcohol use, physical activity, and diet. Whether orchiectomy as a gender-affirming surgery has any effect on cardiovascular disease risk has not been studied.

Barriers to access to quality, nondiscriminatory healthcare for transgender and gender-diverse individuals have been well documented. The degree to which such lack of care explains the observed cardiovascular disease risk among transgender women instead of estrogen therapy to which the risk is often attributed is not known.

What Is Known About Bone Health in Older Transfeminine Patients?

Several studies have shown a low baseline BMD in up to 18–22% of transgender women even prior to initiation of GAHT [17, 18]. The etiology is unclear although lower physical activity during accrual of peak bone mass, low vitamin D, and tobacco use may play a role. Exogenous estrogen has been shown to increase bone density in transgender women. A meta-analysis of 13 studies with 392 transgender women reported increased spine BMD at 1 year (0.04 g/cm^2 [95% CI 0.03–0.06]) and 2 years (0.06 g/cm^2 [95% CI 0.04–0.08]) after GAHT although not hip BMD [19]. In a cohort of 102 transgender women from Amsterdam with serial dual-energy X-ray absorptiometry (DXAs) over 10 years, lumbar spine BMD did not show a significant change (+0.006; 95% CI −0.005 to +0.017), but there was a significant increase in z-score. There was a positive association between estradiol levels and BMD, but not with LH or degree of testosterone suppression [20]. However, a recent study demonstrated a fracture risk in transgender women over age 50 years of 4.4% – similar to rates in cisgender women (4.2%) and higher than age-matched cisgender men (2.4%) [21]. Screening recommendations have not been uniform in this area, but the Endocrine Society guidelines suggest consideration of a baseline bone density prior to GAHT initiation and screening DXA for transgender women at age 60 [1]. For JD, based on her risk factors of tobacco use and maternal hip fracture, one could consider obtaining a DXA at this time.

Are There Data on the Safety of Feminizing GAHT Specifically in Older Transfeminine Adults?

In short, the answer is no. However, there are increasing numbers of transgender and gender-diverse cohorts emerging with sizeable older transfeminine populations including the US Veterans Health Administration [22], the Amsterdam Gender

Clinic (about 16% of the transfeminine cohort had reached the age of 60 years or older in 2015) [23], and STRONG (30% of the transfeminine cohort were older than 45 years) [24].

Conclusions

Transfeminine patients may present at any age and deserve patient-centered, well-informed, and affirming healthcare professionals.

Lessons Learned

- Clinicians should obtain baseline and ongoing blood cell count assessments while prescribing testosterone for masculinizing hormone therapy.
- Erythrocytosis is a known complication of testosterone therapy.
- Evaluate for additional secondary causes of erythrocytosis, including smoking and sleep apnea, and discuss management of secondary causes to help mitigate development of erythrocytosis on testosterone therapy.
- There are currently no known long-term consequences of elevated hematocrit levels in transgender men on testosterone therapy; however, further studies are needed to assess this relationship.
- Feminizing GAHT may include estrogen plus antiandrogen, estrogen alone, or antiandrogen alone. Estrogens can come in oral/sublingual, transdermal, or parental formulations. 17-Beta estradiol appears to be very safe when serum estradiol levels are kept in the physiologic female range. Ethinyl estradiol should not be utilized for feminizing GAHT due to its greater risk for VTE than other estrogens.
- While relative risk of VTE among transfeminine adults is consistently higher compared to reference cisgender men and cisgender women, absolute risk remains low.
- When determining risks of VTE, ischemic stroke, and myocardial infarction, pay attention to the demographics of the population being studied (e.g., age, tobacco use, BMI) and the population of comparison (e.g., total general population, reference cisgender men, reference cisgender women).
- Older age is not a contraindication to starting feminizing GAHT. However, lower estrogen doses to mitigate VTE risk may be appropriate. Orchiectomy may facilitate lower estrogen dosing but is typically reserved for patients who have been on stable hormone regimens for a year or more. Initiating or switching to transdermal patch may be the safest route of estrogen administration.

Questions

1. Which of the following medical risks are associated with testosterone therapy for transgender males?

   (a) Thrombocytosis
   (b) Prolactinoma

(c) Erythrocytosis
(d) Decreased GFR
(e) Weight loss
Answer: b

2. Which of the following statements is true regarding testosterone therapy in transgender patients?

(a) Transdermal formulations of testosterone have been reported to have a higher association with erythrocytosis than testosterone ester injections
(b) Complications from erythrocytosis could include venous thromboembolism and increased cardiovascular disease
(c) Hematocrit levels have been found to reach higher levels in younger patients on testosterone therapy as compared to older patients
(d) The risk of adverse outcomes on testosterone therapy is mitigated by keeping testosterone levels within target range of 700–1200 ng/dL
Answer: b

3. A 38-year-old transgender male patient with a past medical history of obesity is currently prescribed with testosterone cypionate 200 mg IM q 2 weeks. His most recent lab work done halfway between testosterone injections shows a testosterone level of 855 ng/dL (270–1110 ng/dL) with a hematocrit level of 51.5% (37.7–46.5%). Which of the following is the next best step in management of his therapy?

(a) Continue testosterone therapy without interruption, but reduce his dose of testosterone cypionate to 150 mg IM q 2 weeks
(b) Discontinue testosterone therapy indefinitely
(c) Change testosterone cypionate to testosterone transdermal patch 5 mg/day
(d) Make no changes to current regimen and repeat labs in 3 months
Answer: a

4. Which of the following are absolute contraindications to initiating or continuing feminizing GAHT?

(a) Depression
(b) Cardiovascular disease
(c) Prior VTE
(d) Current tobacco use
(e) None of the above
Answer: e

5. Which estrogen preparation likely has the lowest risk of VTE for an older transgender woman?

(a) 4 mg oral 17-beta estradiol daily
(b) 5 mg conjugated equine estrogens daily

(c) 150 μg oral ethinyl estradiol daily
(d) 0.2 mg/day transdermal estradiol patch twice weekly
(e) 5 mg estradiol valerate injection weekly
Answer: d

6. Which of the following feminizing hormone regimens is associated with the lowest risk of VTE?:

(a) Oral ethinyl estradiol in a combined oral contraceptive
(b) Oral 17-beta estradiol
(c) Oral conjugated estrogens (aka Premarin)
(d) Injectable estradiol valerate in combination with oral medroxyprogesterone acetate
(e) Transdermal estradiol
Answer: e

7. How should feminizing HT be managed prior to vaginoplasty?

(a) Hold estradiol for 2 weeks prior to surgery
(b) Hold estradiol for 4 weeks prior to surgery
(c) Hold estradiol and spironolactone for 2 weeks prior to surgery and 2 weeks following surgery
(d) The answer depends on the risk factors of the patient. If the patient has a high risk of VTE (like smoking or prior h/o DVT), she should hold estradiol and spironolactone for 2 weeks prior to surgery and 2 weeks after surgery
(e) Continue with HT regimen perioperatively
Answer: e

8. _____ is the most common estrogen type found in COCs.

(a) Conjugated estrogens
(b) Ethinyl estradiol
(c) 17-Beta estradiol
(d) Estriol
(e) Estrone
Answer: b

9. Which of the following is the most commonly reported thromboembolic event associated with estrogens?

(a) CVA
(b) Myocardial infarction
(c) DVT
(d) Superficial thrombophlebitis
(e) C and D
Answer: c

10. Which of the following patient characteristics are associated with increased VTE risk?

    (a) Advanced age
    (b) Underlying thrombophilia (like factor V Leiden)
    (c) History of systemic lupus erythematosus with phospholipid antibodies
    (d) Current tobacco use
    (e) All of the above
    Answer: e

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Part XV
Endocrine Effects in Virus Infections

Chapter 59
Introduction to Endocrine Effects in Virus Infections

Michael A. Via

Infectious agents, especially viruses, may disrupt any of the steps of normal hormone signaling, including hormone production, transport, or the target tissue response. By their nature, virus particles bind to cellular surface proteins, interject their genetic material intracellularly, and usurp the cellular machinery to replicate. Proteins encoded by the viral genome facilitate this process and may block normal cellular function. Viral proteins may also disrupt the host immune function by inhibiting aspects of the cellular or systemic immune response.

Several different mechanisms of endocrine disruption have been described in viral infections. Viruses may infect an endocrine gland directly, inhibiting hormone production. For example, cytomegalovirus infection within adrenal tissues of immunocompromised patients has been commonly described in association with adrenal insufficiency. Similarly, a viral infection within the thyroid is presumed as the inciting event in the development of painful subacute thyroiditis. Viruses may infect target tissues, disrupting their response such as the case of insulin resistance that is observed in both hepatic tissue and adipose tissue during hepatitis C infection. Elevations in hepatic sex hormone-binding globulin release are also observed in hepatitis C infection and may exacerbate hypogonadism in men.

The host immune response also may affect endocrine signaling, such as is classically described in non-thyroidal illness and other aspects of hypothalamic-pituitary dampening during acute infection. Debate continues as to whether this is an adaptive change as is suggested in the case of reduced growth hormone secretion that develops in severe acute illness or potentially pathogenic in the case of decreased

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production of cortisol-binding globulin and enhanced cortisol clearance in severe sepsis.

Treatments of viral infection also have potential to cause endocrine disease. These may include autoimmune-driven endocrine disease seen after interferon therapy or metabolic disruption observed with many of the antiretroviral therapies used in HIV treatment.

This chapter reviews three cases of endocrine disruption commonly associated with virus infection and the suggested clinical approach in each. These include adrenal dysfunction associated with HIV; lipodystrophy associated with HIV; and aspects of type 2 diabetes, hypertension, testosterone activity, and thyroid dysfunction associated with SARS-CoV-2. A high index of suspicion and early intervention yield the best clinical results.

Chapter 60
Endocrinopathies of SARS-CoV-2

Yasmine M. Elamir and Michael A. Via

Objectives

1. To consider issues in disease management for infected patients with diabetes.
2. To highlight the risk of subacute thyroiditis with SARS-CoV-2 infection.
3. To understand the potential role of testosterone signaling in virus propagation.

Case

A 64-year-old male with a past medical history of type 2 diabetes, hypertension, and hypogonadism presents to the emergency department with a 9-day history of dry cough, diarrhea, headache, and fever. The patient's vitals reveal a temperature of 38 °C, blood pressure of 105/70 mm Hg, heart rate of 88 bpm, and O_2 saturation of 97% on room air. PCR testing for SARS-CoV-2 infection was performed and returned positive. An endocrine consultation recommended to hold his empagliflozin 10 mg and also to temporarily hold his testosterone therapy. After monitoring for 3 days, the patient clinically improved and was sent home. He is now referred by his primary care physician to your endocrinology practice 2 days later, 14 days after symptom onset for a follow-up of his diabetes, hypogonadism, and hypertension in addition to new symptoms of a sore throat, anterior neck pain, and

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palpitations. Patient is afebrile, tachycardic to 105 bpm, and O_2 saturation was 99% on room air. Exam reveals a new small goiter that is tender to palpation with slight tremors on outstretched hands bilaterally. Otherwise, his physical exam is within normal limits. The patient denies any family history or personal history of thyroid disorders.

Thyroid function testing revealed a free thyroxine (FT4) level of 3.0 ng/dL (normal 0.8–1.7) and a suppressed thyroid-stimulating hormone (TSH) of <0.01 mU/L (normal 0.4–4.2). Thyrotropin receptor antibody (TRAb) and thyroid peroxidase antibody (TPOAb) were negative. Sedimentation rate was found to be 60 mm/hour, and C-reactive protein was also markedly elevated to 160 mg/L. The patient is given prednisone 40 mg daily with a taper over the next 4 weeks along with propranolol 40 mg every 8 hours for tachycardia. The patient returns 6 weeks later with resolution of his symptoms and complete normalization of his thyroid function testing. He is resumed on empagliflozin for his diabetes and his testosterone therapy that had been held during his original SARS-CoV-2 diagnosis.

Diabetes in COVID-19

Since the initial description and continuing pandemic of SARS-CoV-2 infection, numerous reports demonstrate increased risk in patients with obesity, metabolic syndrome, and diabetes. Both type 1 and type 2 diabetes have been associated with increased severity of COVID-19 infection, including a two- to threefold increase in mortality in either type of diabetes. Moreover, COVID-19 is recognized as a cause for diabetic ketoacidosis (DKA) and commonly causes hyperglycemia that results from systemic inflammation.

SARS-CoV-2 binds and gains cellular entry through angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in numerous cell types including pulmonary endothelium, vascular endothelium, adipose tissue, cardiomyocytes, pancreatic beta cells, the thyroid, the small intestine, and the kidneys. Virus-induced dysfunction of these tissues may lead to new-onset diabetes [1].

Management of Diabetes in Acute COVID-19

Though no high-level evidence exists, prudent care of the patient with diabetes involves careful medication adjustment to maintain euglycemia and minimize potential adverse effects. In the case of patients with type 1 diabetes, insulin doses should be adjusted to meet changing dietary intake. Patients should be aware of the possibility of DKA and have a low threshold to seek emergent care should symptoms or signs of this develop.

Medication management in patients with type 2 diabetes should consider the severity of illness and potential risks. For example, in severe COVID-19, metformin

should be held as dehydration, renal dysfunction, and potential for lactic acidosis may occur.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors demonstrate increased risk of DKA, and numerous cases of DKA, including euglycemic DKA, have been reported in association with COVID-19. Patients should consider cessation of drugs in this class when there is a suspicion of COVID-19, and renal function should be monitored.

Glucagon-like peptide-1 receptor (GLP-1) agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, and insulin may be continued. Some authors suggest that since the virus that causes Middle Eastern Respiratory Syndrome (MERS) is a related coronavirus that uses DPP4 as a cellular receptor, there may be benefit in the use of DPP4 inhibitors in SARS-CoV-2 infection. However, there is presently no data to support this practice, and any benefit may be limited to MERS infection. GLP-1 agonists may be held if poor appetite occurs from illness.

Pioglitazone is considered safe but should be discontinued in patients that develop cardiomyopathy, heart failure, or liver dysfunction. The use of Peroxisome Proliferator-activated receptor gama (PPAR-γ) agonists such as pioglitazone to improve endothelial function, which is affected in both type 2 diabetes and COVID-19, may prove beneficial [2].

Patients with severe COVID-19 at risk for hypoglycemia who are treated with sulfonylureas or meglitinides should discontinue these medications unless hyperglycemia persists.

The Effects of COVID-19 on Thyroid Function

Thyroid function may be affected by SARS-CoV-2. In general, patients with COVID-19 exhibit changes in thyroid function typical of non-thyroidal illness, though possibly to a greater degree. A retrospective study by Chen et al. investigates change in thyroid function among 50 hospitalized patients with laboratory-confirmed COVID-19 without a history of thyroid disease, healthy participants who underwent routine physical exam, and contemporaneous non-COVID-19 pneumonia patients with a similar degree of severity. Thyroid-stimulating hormone (TSH) levels below the normal range were present in 56% (28/50) of the patients with COVID-19. The levels of TSH and serum total triiodothyronine (TT3) of the patients with COVID-19 were significantly lower than those of the healthy control group and non-COVID-19 pneumonia patients. As with many cases of non-thyroidal illness, severity of COVID-19 inversely correlates with TSH and TT3 levels. In this study, the total thyroxine (TT4) level of the patients with COVID-19 was not significantly different from the control group. None of the enrolled patients were given thyroid hormone replacement therapy. After recovery, no significant differences in TSH, TT3, TT4, free triiodothyronine (FT3), and free thyroxine (FT4) levels were found between the COVID-19 and control groups [3].

In contrast to the above study, the THYRCOV study of 287 consecutive hospitalized patients with COVID-19 and no history of thyroid disease demonstrates overt

hyperthyroidism in 20%. Among those who were hyperthyroid, FT4 levels were 1.5-fold to threefold higher than normal range but trended downward over time, achieving normal levels after approximately 7–10 days on average, regardless of therapy with thionamide medication or no therapy [4]. This clinical course may reflect destructive thyroiditis as the underlying pathophysiology. Indeed, many cases of subacute thyroiditis in association with SARS-CoV-2 infection have been reported. The usual treatment measures such as corticosteroid therapy may be considered.

In addition to hyperthyroidism, 5% of patients in the THYRCOV study demonstrated elevated TSH. In this study, both suppression and elevation of TSH levels were associated with increased mortality.

Management of Preexisting Hyperthyroidism

There are several considerations in the treatment of hyperthyroidism that may require intervention in COVID-19. Firstly, uncontrolled hyperthyroidism may be associated with increased severity of COVID-19 and complications. COVID-19 has been reported to induce thyroid storm in susceptible patients. Due to this risk, it is advisable for patients to continue their thyroid treatment if they contract COVID-19. However, neutropenia seen in 9–45% of patents with COVID-19 is indistinguishable from neutropenia resulting from thionamide use. Regardless of the cause, patients with neutropenia should withhold antithyroid drugs and monitor neutrophil count closely. Similarly, conjunctival involvement associated with COVID-19 may appear as thyroid eye disease on physical exam. CT or MRI of the orbits may help to differentiate [5].

Considerations on Androgen Therapy in COVID-19: Type II Transmembrane Serine Protease

Males with SARS-CoV-2 demonstrate increased morbidity and mortality compared to females. Investigation into the cause of this has led to interest in the role of androgen signaling in COVID-19. Transmembrane serine protease (TMPRSS2) is an androgen-regulated protein that is required for cellular entry of SARS-CoV-2. The viral S protein is primed by TMPRSS2 prior to binding with ACE2 receptors. Inhibition of TMPRSS2 activity may decrease the uptake of the virus into the cells [6]. Montopoli et al. report on 9280 patients (4532 males) with SARS-CoV-2 infection from 68 hospitals in Veneto, Italy. Consistent with other publications, males in this study developed more severe complications, were more frequently hospitalized, and had a worse clinical outcome than females. However, men with prostate cancer receiving androgen deprivation therapy (ADT) had a significantly lower risk of SARS-CoV-2 infection compared with men with prostate cancer who did not receive

ADT (OR 4.05; 95% CI 1.55–10.59). This trend also held for prostate cancer patients receiving ADT compared with patients with any other type of cancer (OR 4.86; 95% CI 1.88–12.56) [7].

One effect of ADT is to downregulate TMPRSS2 expression in prostate and in lung tissue, which may be the mechanism responsible for this finding. Though further study is needed, it would be reasonable to withhold testosterone or other androgen therapy in patients who are treated with these agents and develop COVID-19.

Vitamin D

There has been great interest in the use of vitamin D for the prevention and treatment of COVID-19. Vitamin D is a hormonelike vitamin that regulates expression of several hundred known genes and possibly up to 11,000 genes spanning many physiologic functions. Known gene products have roles in the regulation of both innate and adaptive immune function, pulmonary cytokine release, and induction of autophagy as an immune defense, among other functions [8].

Therapeutic effects of vitamin D supplementation have been controversial in recent years. Several large trials have failed to show benefit in the prevention or treatment of type 2 diabetes, cardiovascular disease, and acute infections with vitamin D therapy. However, there is some suggestion that treatment with vitamin D may be beneficial in COVID-19. Both animal models and some human trials demonstrate diminished severity of acute respiratory distress syndrome with vitamin D therapy, though larger studies are ongoing. Vitamin D may also impact vascular endothelial function, which is disrupted in COVID-19. Moreover, there is high overlap in the at-risk population for vitamin D deficiency and those at risk for severe COVID-19. A randomized trial of 75 hospitalized patients with COVID-19 demonstrates significant reduction in the need for ICU admission or mechanical ventilation with calcifediol treatment. In this study, none of the treated patients died, and all were discharged without complications [9]. Other studies investigating the use of vitamin D are ongoing. By the presently available data, it is reasonable to provide vitamin D supplementation to patients with known or at high risk of vitamin D insufficiency. This includes a large part of the population, especially in the fall and winter months.

Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use in Regard to COVID-19 Severity and Infection Rate

There has been speculation as to whether angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB) use can affect infection rates or severity of outcomes in COVID-19. In a retrospective cohort study by Fosbol et al.,

4480 patients diagnosed as having COVID-19 with ACEI/ARB use, compared with no use, showed no difference in mortality (adjusted hazard ratio 0.83 [95% CI 0.67–1.03]). In a case-control study of a cohort of 494,170 patients with hypertension, the use of ACEI/ARB, compared with use of other antihypertensive medications, was not significantly associated with COVID-19 diagnosis (adjusted hazard ratio 1.05 [95% CI 0.80–1.36]) [10]. By this evidence, these medications should be continued during the pandemic and in patients diagnosed with COVID-19.

Questions

1. A 65-year-old female with a past medical history of type 2 diabetes and well-controlled hypertension comes in for a routine follow-up. She takes glargine 10 units daily, linagliptin 5 mg daily, and lisinopril 20 mg daily. Your patient asks you whether she should continue taking her lisinopril in light of the COVID-19 pandemic.

   Do you tell her to:

   A. Continue lisinopril 20 mg daily
   B. Switch lisinopril 20 mg to amlodipine 10 mg
   C. Hold all blood pressure medications
   D. Stop lisinopril 20 mg only if diagnosed with COVID-19

   Answer: (A) Continue lisinopril 20 mg daily

2. A 57-year-old male with a past medical history of diabetes, opioid dependence, and secondary hypogonadism secondary to methadone use calls your practice to let you know he has recently been ill and has contracted COVID-19. Patient has been receiving testosterone replacement therapy via intramuscular injection every 2 weeks. His most recent mid-cycle testosterone levels were at therapeutic range targets, and he demonstrates clinical improvement of previous fatigue and loss of libido.

   Do you:

   A. Continue with current therapy
   B. Reduce testosterone dose by 50%
   C. Increase testosterone dose by 50%
   D. Discontinue testosterone replacement while sick

   Answer: (D) Discontinue testosterone replacement while sick

3. A 62-year-old female with history of hypertension treated with amlodipine and no known history of thyroid disease is admitted to the hospital with acute COVID-19. She is in respiratory distress but is able to maintain oxygen saturation in the 95–97% range in the prone position. She is started on low-molecular-weight heparin. On hospital day 2, telemetry demonstrates sinus tachycardia, with a heart rate of 140–150 s. CT angiogram does not demonstrate pulmonary embolism, but shows bilateral ground glass opacities. Thyroid function tests,

drawn prior to the CT, show TSH of 0.03 mU/L and FT4 of 2.2 ng/dL (normal 0.8–1.7 ng/dL).

What intervention should be made?

A. Stop low-molecular-weight heparin
B. Start methimazole
C. Start corticosteroids
D. Change amlodipine to propranolol

Answer: (C) Start corticosteroids

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Chapter 61
HIV Infection and Lipodystrophy

Tania Al Shamy and Michael A. Via

Objectives

1. Diagnosis of HIV-associated lipodystrophy syndrome (HALS).
2. Identify the metabolic derangements associated with HALS.
3. Medical management of HALS.

Case Presentation

A 60-year-old male patient comes to your clinic for consultation of uncontrolled type 2 diabetes mellitus. He has a past medical history of hyperlipidemia and HIV and has been given highly active antiretroviral therapy (HAART) for the past 30 years. He was diagnosed with type 2 diabetes mellitus 20 years ago and has hypertension.

He reports difficulty managing his diabetes despite close adherence to his prescribed insulin regimen. He checks finger-stick glucose levels three times daily, before meals, which ranges from 200 to 250 ng/dL. He never experiences hypoglycemia. The patient is on a basal-bolus insulin regimen that includes glargine and lispro, with total daily dose of 250 units/24 hours (45% as basal). Other medications

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include rosuvastatin 20 mg, metformin 1 g twice daily, and lisinopril 20 mg daily, as well as dolutegravir, tenofovir alafenamide, and emtricitabine.

Physical Exam

Vital signs: BP 120/80 mmHg, pulse 75, O_2 saturation 99%, and temp 97.5 °F (36.4 °C)

Head, Eyes, Ears, Nose, and Throat (HEENT): normal visual field and extraocular muscles were intact; *loss of facial fat*

Neck: no thyromegaly or cervical lymphadenopathy

Heart: normal rate and rhythm; no audible murmur

Lung: good bilateral air entry; no wheezing

Abdomen: soft, nontender, and *increased abdominal girth and adipose deposition*

Extremities: *loss of subcutaneous fat*; *prominent subcutaneous veins*

Skin: *acanthosis nigricans noted on the back of the neck*

Laboratory Tests

- Glycosylated hemoglobin (HbA1c): 10%
- Serum Sodium: 140 mEq/L
- Serum potassium: 4 mEq/L
- Serum creatinine: 0.9 mg/dL
- Liver function test within normal limits

Based on the history and the clinical picture, in addition to the current comorbidities, what does the patient also have?

Acquired Generalized Lipodystrophy

Review of How the Diagnosis Was Made

Lipodystrophy syndromes are rare heterogenous disorders that are categorized based on the etiology and the distribution of the lost adipose tissues [1]. They are defined as complete or partial loss of adipose tissue, particularly in the face, buttocks, and limbs (lipodystrophy), in combination with an excess of visceral and central adiposity (lipohypertrophy) [2, 3]. The pathophysiology is attributed to the loss of mature functional adipocytes due to signaling errors associated with failure of adipogenesis, adipocyte apoptosis, or a failure to store triglycerides in existing adipocytes because of ineffective lipogenesis or excessive lipolysis [2].

There are four major categories of lipodystrophy that include congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL) [1]. Due in part to the extremely low incidence of congenital lipodystrophy syndromes, many clinicians are unfamiliar with diagnosis and treatment. However, it is crucial to recognize lipodystrophy for optimal management of its metabolic implications and severe comorbidities [1].

The diagnosis of lipodystrophy is made clinically and should be suspected in a patient with partial or generalized lack of adipose tissue. History (age of onset, other clinical features, comorbidities, family history, presence of autoimmune disease) and physical exam (documentation of fat loss by clinical measurements of the limb circumferences and skinfold thickness) serve as the basis for diagnosis [1, 2]. Radiologic studies such as dual energy x-ray absorptiometry and whole-body magnetic resonance imaging may be obtained to support the diagnosis. Signs of insulin resistance and associated hypertriglyceridemia are observed as well as low levels of circulating leptin.

HIV-Associated Lipodystrophy

The use of HAART has significantly reduced morbidity and mortality in HIV-infected individuals. However, long-term therapy has significant risk of metabolic derangements [3]. These complications include HIV-associated lipodystrophy (HALS), insulin resistance, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome, which in return can lead to cardiovascular disease.

HALS is reported among 12–33% of patients with HIV in developed countries [3]. A higher rate of metabolic complications of HAART is observed in middle- and low-income countries, with prevalence of HALS among patients with HIV reported as high as 33% in Africa, 72% in Asia, and 47% in Latin America. This increase is thought to be due to higher rates of malnutrition and to the specific HAART agents utilized [1, 3]. For example, the use of stavudine is highly associated with lipodystrophy, and consequently, the World Health Organization recommends use of alternative agents [3]. However, stavudine is still given as first-line therapy for HIV in low-income countries due to availability and lower cost [3]. Odds ratio for developing lipoatrophy with use of stavudine is reported from 2.8 to 7.4 compared to other antiretroviral regimens [3].

Growth Hormone

Several mechanisms have been identified as etiologic factors for HALS. Of these, impaired growth hormone (GH) secretion may be amenable to replacement therapy [4, 5]. Studies investigating recombinant human growth hormone (rHGH) therapy

in patients with HALS demonstrate reduction in visceral fat by 8.5–11%. However, adverse effects of rHGH therapy for HALS have been observed in clinical trials including peripheral edema, arthralgias, and elevated blood glucose levels. The use of growth hormone-releasing hormone (GHRH) agonists may achieve more physiologic GH release from the anterior pituitary and minimize adverse effects of rHGH therapy in patients with HALS. Consequently, clinical use of tesamorelin, a GHRH analog, has supplanted rHGH [4].

Tesamorelin is approved by the US Food and Drug Association (FDA) for the reduction of abdominal fat in HIV-infected individuals with lipodystrophy, at a dosage of 2 mg subcutaneously daily. Its efficacy was evaluated in two phase 3 trials. In the first study [4], there was significant decrease in waist circumference and visceral adipose tissue (VAT) after 26 weeks of tesamorelin with an absolute reduction of 10% compared to placebo. Triglyceride levels declined by approximately 20% compared to placebo, while total cholesterol decreased by 3%. As expected, IGF-1 levels increased by 109 ng/ml. No change was noted in body mass index, fasting glucose, or fasting insulin levels. The second published study demonstrates a similar 15% reduction in VAT with 26 weeks of treatment that was sustained over an additional 26 weeks of open-label therapy with tesamorelin. A similar rise in IGF-1 by 106 ng/ml was also observed [4].

Based on the above clinical trials, tesamorelin may be considered as a treatment for HALS. Due to the potential for reversal of the effect of tesamorelin on fat redistribution after cessation of therapy, it is recommended to combine the treatment with physical activity program [5].

Leptin

Another potential therapy for HALS is r-metHuLeptin (metreleptin), which is a recombinant human leptin analog. Compared to placebo, the use of r-metHuLeptin reduces body weight and truncal fat and improves insulin resistance in patients with HALS [2]. In one study, a 5.7% relative body weight reduction was observed compared to placebo [6]. Other studies have shown a reduction of up to 32% in VAT, as well as a 55% increase in subcutaneous adipose tissue (SAT) [2].

Additionally, treatment of HALS using r-metHuLeptin demonstrates an increase in HDL levels by 2–4 mg/dL, a reduction of triglycerides by 87 mg/dL, a reduction of LDL cholesterol by 10 mg/dL, and a reduction in fasting insulin levels by 5 IU/ml or 30%. After controlling for the increase on placebo, there was a relative decrease in insulin of 11.9 IU/ml or 71.9% and a relative reduction in insulin resistance by 75% using the homeostasis model assessment of insulin resistance.

The observed improvements in glucose metabolism with r-metHuLeptin suggest a potential advantage of this therapy over GH replacement or tesamorelin in the management of HALS. Presently, this therapy has not been approved by the US FDA for the treatment of HALS, though the above data are compelling.

PPAR-γ Agonists

Thiazolidinediones represent a third class of agents that have shown potential benefit in treating HALS. Peroxisome proliferator-activated receptor-γ (PPAR-γ) activity is downregulated in patients with HIV receiving HAART [7]. PPAR-γ nuclear receptors mediate insulin sensitivity and lipid metabolism and are central in modulating normal adipocyte function. Through PPAR-γ activation, thiazolidinediones increase insulin sensitivity, decrease glucose and fatty acid production, promote adipocyte differentiation, and reduce central adiposity [7]. In a pilot study, rosiglitazone used to treat HALS showed 23% increase in SAT, 21% decrease in VAT, and 59% increase in insulin sensitivity [7].

As patients are given advanced therapies for HIV, the mortality and infectious morbidities have radically decreased. Modern clinical practice includes a focus on the metabolic abnormalities seen with this therapy in patients on long-term HAART treatment. Clinicians must be aware of available therapies including tesamorelin, r-metHuLeptin, and PPAR-γ agonists, as well as their limitations and the continual need for further study.

Lessons Learned

- In patients with insulin resistance, it is crucial to identify lipodystrophy on physical exam, especially given the metabolic comorbidities and cardiovascular outcomes.
- The diagnosis of HALS is made by clinical suspicion; assessment of adipose distribution by imaging or measurement of serum leptin levels can support therapy.
- Consideration for tesamorelin, r-metHuLeptin, or thiazolidinedione therapy should be made. Though no head-to-head trials exist, clinicians must consider risks, benefits, and costs when deciding among these therapies.

Associated Questions: Based on Case Presented

1. Which lab test would you consider in a patient with lipodystrophy that can help with the management?

   A. Urine microalbumin
   B. C-peptide
   C. Leptin
   D. insulin antibodies
   E. Glutamic acid decarboxylase 65 antibody

   Answer: C. Leptin

2. What is the best next step in managing this patient's diabetes given the history of lipodystrophy?

   A. Adding pioglitazone
   B. Discontinue metformin
   C. Switch to U-500 insulin

D. A and C
E. None of the above

Answer: D. A and C

3. Leptin level was found to be low in the above case, what is the next step?
   A. Increase dietary fat intake
   B. Start r-metHuLeptin therapy
   C. Stop pioglitazone
   D. Reduce physical activity

   Answer: B. Start r-metHuLeptin therapy

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Chapter 62
Adrenal Function in HIV Infection

Sara Lubitz

Objectives

- Describe the direct and indirect ways that HIV affects the hypothalamic-pituitary-adrenal axis.
- Recognize the opportunistic infections and malignancies that can infiltrate the hypothalamus/pituitary gland and the adrenal gland in patients with advanced HIV.
- Review the diagnosis and treatment of primary and secondary adrenal insufficiency.
- Discuss the interactions between HIV-related medications and glucocorticoids.

Case Presentation

A 33-year-old male presented to the emergency room with a 3-month history of generalized weakness, fatigue, and dyspnea on exertion. He also reported a nonproductive cough, abdominal pain, and decreased appetite; he thinks he lost about 20-pounds over the last 6 months but does not weigh himself regularly. He had emigrated from Mexico 1 year ago and reports that he was diagnosed with HIV about 3 years prior.

Vital signs were temperature 38.6 °C (100.9 °F), pulse 86/min, respirations 20/min, and blood pressure 98/63 mm Hg. Pulse oximetry on room air shows an oxygen saturation of 96%. On physical examination, he was a thin male with pale-appearing skin and conjunctiva, and crackles auscultated over the right lung field. Laboratory evaluation was significant for creatinine 1.6 mg/dL (0.76–1.27) blood urea nitrogen (BUN) 26 mg/dL (6–20), hyponatremia at 126 mmol/L (134–144),

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hyperkalemia of 5.8 mmol/L (3.5–5.2 mmol/L), glucose 66 mg/dL (65–99), and calcium corrected for albumin of 10.4 mg/dL (8.7–10.2). Hemoglobin was 9.2 g/dL (11.1–15.9) with leukopenia, white blood cells 3.1 × 10E3/μL (3.5–10.7), and lymphopenia absolute lymphocytes 0.4 × 10E3/μL (0.7–3.1). A chest x-ray showed a right-sided pleural effusion, and the electrocardiogram was normal. A cortisol level drawn on the evening of admission was 1 μg/dL (5–23). Morning serum cortisol level was 3 μg/dL (5–23). Two hundred fifty micrograms of synthetic ACTH was administered intravenously, and cortisol levels drawn 30 and 60 minutes later were 3 μg/dL and 4 μg/dL, respectively.

In the emergency room, the patient was treated with supportive therapy including IV hydration and dextrose. Based on the cosyntropin testing results, hydrocortisone was administered at a dose of 100 mg intravenously every 6 hours and then tapered over the next 72 hours to 30 mg daily in divided doses.

Further lab testing revealed a CD4 count of 27 cells/μL and HIV-RNA viral load 98,000 copies/mL. Plasma corticotropin (ACTH) was elevated at 451 pg/mL (7.2–63.3), which was consistent with the diagnosis of primary adrenal insufficiency (AI). A computed tomography scan of the abdomen with intravenous contrast revealed bilaterally enlarged adrenal glands with calcifications (Fig. 62.1). A diagnostic paracentesis was consistent with an exudative effusion with a positive culture for acid-fast bacilli. Adrenal biopsy was not performed because the presentation was consistent with disseminated tuberculosis.

The patient was started on treatment (isoniazid, rifampin, pyrazinamide, and ethambutol) for extrapulmonary tuberculosis. Plans were made to start highly active antiretroviral therapy (HAART) on discharge. The patient will be monitored for interactions between rifampin, protease inhibitors, and glucocorticoids that may affect maintenance doses of hydrocortisone.

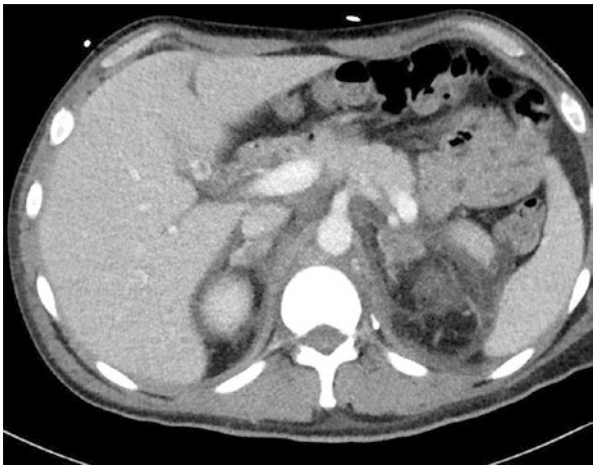

Fig. 62.1 CT scan of the abdomen and pelvis with intravenous contrast showing bilateral adrenal enlargement

How the Diagnosis Was Made

Infection with the human immunodeficiency virus (HIV) type 1 can lead to profound immunosuppression. The innate and T-helper1-directed cellular immunity is particularly affected. A person with HIV infection is considered to have progressed to AIDS when the number of CD4 cells falls below 200 cells/μL or if they develop an opportunistic infection. There is associated endocrine dysfunction, including impairment of the hypothalamic-pituitary-adrenal (HPA) axis. HIV infection affects the HPA axis directly through modulation of the host immune system and indirectly through immunodeficiency-associated opportunistic pathogens and side effects of pharmacotherapy.

Many patients with advanced HIV have anorexia, nausea, weight loss, fever, fatigue, and orthostatic hypotension, which are similar to symptoms in patients with adrenal insufficiency (AI). Due to the high prevalence and significant contribution to morbidity and mortality in this population, all HIV patients with symptoms should be screened for AI.

HIV Infection and Changes to the HPA Axis

Hypothalamic corticotropin-releasing hormone (CRH) stimulates adrenocorticotropic hormone (ACTH) secretion by pituitary corticotroph cells. ACTH stimulates cortisol synthesis and secretion from the adrenal gland. ACTH is secreted in a pulsatile manner and follows a circadian rhythm, reaching peak levels in the early morning and nadirs around midnight. Cortisol exerts negative feedback inhibition on pituitary ACTH and hypothalamic CRH secretion. Pathogens can stimulate the hypothalamus and pituitary directly and indirectly with cytokines and inflammatory mediators secreted from activated immune cells and infected tissues. The stimulated HPA axis increases glucocorticoids in an effort to subside inflammation as a counter-regulatory mechanism to the robust immune response. Glucocorticoids exert their effects on target cells through the glucocorticoid receptor (GR), a nuclear receptor that acts as a ligand-dependent transcription factor, expressed in most tissues and cells.

Subclinical functional abnormalities of the HPA axis are more prevalent than overt AI. Studies have shown elevated levels of basal cortisol and lower dehydroepiandrosterone in HIV patients when compared to healthy controls. Hyporeninemic hypoaldosteronism has also been reported. These alterations in the HPA axis occur most commonly in the context of low weight and advanced degree of illness; the shift in steroid metabolism shunting toward cortisol synthesis may be an adaptive response to stress. The relative hypercortisolemia may also be explained by increases in cortisol-binding globulin. There is direct stimulation of hypothalamic CRH from HIV and cytokines. Cytokines may also directly stimulate adrenal steroidogenesis. Standard-dose ACTH stimulation testing is normal in most patients [1, 2].

Glucocorticoid resistance is also found in some patients with AIDS. This is due to acquired abnormalities of the GR, characterized by increased GR density and decreased GR affinity for the substrate. Proposed mechanisms include IL-2 and IL-4 reduction in glucocorticoid receptor affinity to its ligand and increased expression of GRβ as compared to GRα causing an imbalance of GR antagonists to agonists. There is hyperfunction of the HPA axis, which leads to hypercortisolemia and increased ACTH secretion. In cases of advanced HIV infection, symptoms of AI may be present despite elevated ACTH and cortisol levels, suggesting peripheral glucocorticoid resistance [2, 3].

Adrenal Insufficiency

Primary AI occurs when there is the destruction or dysfunction of the adrenal cortex. Central AI occurs when there is a loss of hypothalamic CRH (tertiary adrenal insufficiency) or pituitary release of ACTH (secondary adrenal insufficiency). The most common cause of central AI is iatrogenic due to suppression of the HPA axis after glucocorticoid administration.

Acute AI is a life-threatening emergency presenting with hypotension or hypovolemic shock. It can occur abruptly or insidiously during times of physical stress in previously undiagnosed patients or those with known AI who fail to properly increase their replacement doses. AI has been reported in 17–50% of patients with AIDS, and there is evidence of adrenal gland involvement reported in 40–70% of patients with AIDS on autopsy studies [1, 2].

Clinical Presentation

Although adrenal crisis is uncommon in HIV patients in the HAART era, mild impairments in adrenal reserve are often seen. Primary AI symptoms do not usually appear until more than 80–90% of the adrenal gland has been destroyed. The clinical diagnosis of AI is complex, as nonspecific complaints such as fatigue and weight loss are common in patients with advanced HIV. The most common presenting features of both primary and secondary AI are fatigue, weight loss, and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. Hyponatremia can occur secondary to inappropriate secretion of ADH resulting from glucocorticoid deficiency and mineralocorticoid deficiency-induced urinary sodium loss. Hypercalcemia occurs due to a combination of reduced calcium excretion and increased calcium input into the extracellular space. Hypoglycemia may also occur but is more common in children. Other signs and symptoms specific to primary AI include skin

hyperpigmentation, postural hypotension, salt craving, and hyperkalemia [4, 5]. It must be noted that some antiretroviral and antimicrobial medications such as zidovudine, tetracyclines, chloroquine, hydroxychloroquine, and phenothiazines can cause hyperpigmentation and mimic features of primary AI.

Laboratory Testing

We are unable to routinely measure CRH, and ACTH measurements are not reliable because of the short plasma half-life, pulsatile secretion, and rigorous specimen handling requirements. Therefore, we rely on serum cortisol testing for the diagnosis of AI. However, due to the circadian changes in cortisol, a random cortisol level is not very useful. The first-line test for diagnosing AI is measuring cortisol levels at 8–9 AM. A cortisol level <3 μg/dL is indicative of AI, and a level >15 μg/dL likely excludes the diagnosis. For morning cortisol levels between 3 and 15 μg/dL, stimulation testing is recommended. The standard-dose test using 250 mcg cosyntropin (synthetic ACTH 1–24) administered intravenously or intramuscularly is suggested. Peak cortisol levels <18.1 μg/dL at 30 or 60 minutes indicate AI. With new cortisol assays using more specific monoclonal antibodies or liquid chromatography with tandem mass spectrometry (LC-MS/MS), lower cutoffs for a normal response to ACTH testing have been proposed. Furthermore, cutoffs for provocative testing are based on total cortisol levels and assume normal cortisol-binding globulin (CBG). Albumin is often used as a surrogate for CBG, and lower cutoffs for normal cortisol response to ACTH testing or the use of free cortisol levels may be considered in patients with low albumin. In HIV patients with advanced disease, one must consider that they may have low CBG when interpreting total cortisol levels. Exogenous glucocorticoids should be held 18–24 hours prior to testing. Measurement of plasma ACTH is recommended to diagnose primary AI. In patients with cortisol deficiency, ACTH >2× the upper limit of the normal range is consistent with primary AI. In addition to hyperkalemia, the simultaneous measurement of plasma renin and aldosterone can diagnose mineralocorticoid deficiency [4, 5].

Imaging

Computer tomography (CT) scan of the adrenals is recommended to identify infectious diseases and malignancies. Bilateral enlargement of the adrenal glands is a feature of granulomatous infections; however, this finding is generally not specific for infiltrative disorders. Bilateral adrenal enlargement may also occur in the setting of chronic ACTH stimulation [4].

Pathogenesis

Adrenalitis and Primary AI Individuals with advanced HIV disease and a CD4 cell count of fewer than 100 cells/μL are at risk for adrenalitis-induced AI by primary adrenal infection or disseminated microbial disease involving the adrenal glands. In autopsy studies that correlate pathology with function of the HPA axis premortem, it is noted that at least 80% of the adrenal gland has to be destroyed before AI occurs. Cytomegalovirus (CMV) is the most commonly found pathogen in autopsy studies. AI secondary to *Mycobacterium tuberculosis* is well described given the adrenal tropism of the bacilli. In the developing world, tuberculosis continues to account for about 20–30% of cases of primary AI. It can disseminate to the adrenal glands through hematogenous or lymphatic spread. Tuberculosis of the adrenals leads to inflammation, necrosis, and eventual destruction of cortical tissue. Adrenalitis can also occur in the setting of other opportunistic infections including *Mycobacterium avium intracellulare*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Pneumocystis jiroveci*, and *Histoplasma capsulatum*. Adrenal function is unlikely to recover despite treatment of the opportunistic infection.

Adrenal dysfunction may occur secondary to adrenal neoplasms found almost exclusively in advanced HIV patients such as Kaposi's sarcoma and non-Hodgkin's lymphoma. Noninfectious etiologies of primary AI in patients with HIV/AIDS include adrenal hemorrhage and autoimmune adrenalitis.

Pituitary Dysfunction and Central AI Pituitary infarction and necrosis can occur in advanced HIV infection. Opportunistic infections such as CMV, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, and neoplasms such as lymphoma can infiltrate the pituitary gland leading to central AI [6].

HIV-Related Pharmacotherapy and the HPA Axis

The introduction of HAART employing combinations of three or more types of antiretroviral drugs, such as nucleoside and non-nucleoside reverse transcriptase inhibitors, viral protease inhibitors, and compounds blocking entry of HIV to CD4+ lymphocytes, suppresses HIV replication and has dramatically improved the clinical course and life expectancy of patients infected with HIV. Since advanced disease is the major risk factor for the development of AI, the prevalence of the condition was significantly higher during the pre-HAART era. However, components of the HAART cocktail can interact with corticosteroids and lead to HPA axis dysfunction, including Cushing's syndrome and central AI.

Protease inhibitors, particularly ritonavir, are potent inhibitors of the cytochrome P450 enzyme CYP3A4, which is necessary for metabolizing glucocorticoids into inactive forms. As a result, levels of glucocorticoids can dramatically increase when

co-administered with CYP3A4 inhibitors and lead to iatrogenic Cushing's syndrome while suppressing endogenous CRH, ACTH, and cortisol. Case reports have highlighted the development of Cushing's syndrome in ritonavir-treated patients that concomitantly receive inhaled, intranasal, and topical steroids [7]. It has been reported that >5% of patients receiving intra-articular steroids while on ritonavir develop sustained HPA axis suppression; recovery after a single injection of triamcinolone may take up to a year. If there is persistent suppression of endogenous cortisol secretion after the cessation of exogenous glucocorticoids, adrenal hormone replacement therapy is needed. Cobicistat is an analog of ritonavir which does not have antiretroviral activity but is a potent inhibitor of the CYP3A4 enzymes and is given in combination with other therapies to boost the levels of medications that are metabolized by the cytochrome P450 system. Cobicistat can similarly reduce the breakdown of exogenous steroids and result in Cushing's syndrome and secondary AI [6].

Medications used for the treatment of opportunistic infections in patients with AIDS are known to affect glucocorticoid metabolism and can lead to AI. Ketoconazole, an antifungal compound, inhibits cortisol synthesis by blocking cholesterol side-chain cleavage complex; 17,20-lyase; 11-beta-hydroxylase; and 17 alpha-hydroxylase enzymes. Rifampin, a tuberculosis treatment, is a strong cytochrome P450 CYP3A4 inducer and may increase cortisol metabolism; in patients with reduced adrenal reserve, it can precipitate AI. Megestrol acetate, used to boost appetite in patients with HIV-associated cachexia, is a synthetic progesterone derivative with glucocorticoid-like actions that causes feedback inhibition of the HPA axis. It can precipitate AI when the medication is withdrawn or in times of stress.

Treatment of HIV-Associated Adrenal Insufficien

Treatment is glucocorticoid replacement, coupled with mineralocorticoid supplementation in cases of primary AI. Patients with severe AI symptoms or adrenal crisis should be treated urgently with intravenous hydrocortisone 100 mg and fluid resuscitation, followed by 200 mg of hydrocortisone in divided doses over the next 24 hours with a quick taper to maintenance doses. Maintenance treatment with hydrocortisone or cortisone acetate 15–30 mg/day in two or three divided oral doses with the highest dose in the morning at awakening is recommended. Prednisolone 3–5 mg/day may be used as an alternative regimen. In patients with primary AI and confirmed aldosterone deficiency, mineralocorticoid replacement with fludrocortisone 0.05–0.1 mg/day with liberal salt intake is recommended [4, 5].

Assessment of adequate glucocorticoid replacement is made clinically by monitoring body weight, postural blood pressure, and energy levels and observing for signs of frank glucocorticoid excess. Assessment of adequate mineralocorticoid replacement in primary AI is made clinically by monitoring for salt craving, postural hypotension, edema, and serum electrolyte measurements. Patients should be

educated about "sick-day rules" and make glucocorticoid adjustments for stressful events [4, 5].

One must be cognizant of the other medications the patient is using, especially medications that affect the cytochrome p450 enzyme CYP3A4 which is required to metabolize glucocorticoids into inactive forms. In a patient on protease inhibitors or azole antifungals, the glucocorticoid response is pronounced due to slowing of the metabolism, and iatrogenic Cushing's syndrome may develop. For example, ritonavir co-administration will affect prednisolone metabolism such that levels are increased by ~30%, and lower doses are recommended to avoid over-replacement. On the other hand, patients taking rifampin or anticonvulsants which induce the cytochrome p450 system need increased doses of maintenance steroids [2, 6].

Lessons Learned

- HIV/AIDS affects the HPA axis directly through modulation of the host immune activity and alteration of biological pathways as well as indirectly through immunodeficiency-associated opportunistic infections and side effects of pharmacotherapeutics.
- HIV infection is usually characterized by higher basal cortisol and lower dehydroepiandrosterone levels than HIV-seronegative individuals. The postulated mechanisms include stress due to HIV infection, increased cytokines resulting in stimulation of the HPA axis, reduction in cortisol catabolism, and glucocorticoid resistance.
- Adrenocortical infiltration tends to occur in advanced disease and usually in the setting of a low CD4 cell count. It is caused by opportunistic infections including Cytomegalovirus and *Mycobacterium tuberculosis* as well as neoplasms such as Kaposi's sarcoma and lymphoma.
- Secondary adrenal insufficiency may also occur due to opportunistic infections and neoplasm infiltration of the pituitary and hypothalamus.
- Adrenal insufficiency presents with fatigue, weight loss, and GI symptoms which are also common nonspecific symptoms in patients with advanced HIV. Given the high morbidity and mortality, all HIV patients with symptoms should be screened for adrenal insufficiency.
- A standard-dose cosyntropin test (250 μg) is the gold standard to establish the diagnosis of adrenal insufficiency.
- Protease inhibitors interact with corticosteroids by inhibiting the CYP3A4 enzymes which can reduce the breakdown of exogenous steroids and result in Cushing's syndrome and secondary adrenal insufficiency.

Questions

1. Which of the following changes to the HPA axis has been described in patients infected with HIV?

   A. Increased dehydroepiandrosterone
   B. Peripheral cortisol resistance
   C. Atrophy of pituitary corticotroph cells
   D. Increased aldosterone

2. Which is the most common opportunistic infection to infiltrate the adrenal gland in a patient with a low CD4 count?

   A. Cytomegalovirus
   B. *Pneumocystis jirovecii*
   C. *Mycobacterium tuberculosis*
   D. *Toxoplasma gondii*

3. Which of the following drug-drug interactions affecting the HPA axis may occur in patients with HIV infection?

   A. Megestrol acetate causing increased metabolism of inhaled budesonide
   B. Rifampin causing decreased metabolism of hydrocortisone
   C. Enfuvirtide causing increased metabolism of prednisolone
   D. Ritonavir causing decreased metabolism of nasal fluticasone propionate

Answers to Questions

1. B
   Glucocorticoid resistance is found in some patients with advanced HIV due to acquired abnormalities of the glucocorticoid receptor. Studies have shown elevated levels of basal cortisol and lower aldosterone and lower dehydroepiandrosterone in HIV patients when compared to healthy controls.
2. A
   Opportunistic infections are the main cause of AI in patients with advanced HIV disease. Cytomegalovirus is the most common organism seen in autopsy studies.
3. D
   The use of potent steroids metabolized by CYP3A4, including fluticasone and budesonide in patients treated with ritonavir, a potent CYP3A4 inhibitor, is not recommended via any route given the potential for iatrogenic Cushing's syndrome and HPA axis suppression. Megestrol acetate causes secondary adrenocortical insufficiency through direct action on the hypothalamus and pituitary gland. Rifampin, a potent inducer of CYP3A4, accelerates the metabolism of glucocorticoids. Enfuvirtide has no clinically important effect on the CYP450 enzymes.

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