ENDOCRINE ESSENTIALS

ENDOCRINE UPDATE FOR GENERAL MEDICINE

Bone and Mineral Homeostasis

Diabetes Mellitus

Cardiovascular Endocrinology

Men's and Women's Health

Thyroid Disorders

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ENDOCRINE UPDATE FOR GENERAL MEDICINE

Bradley D. Anawalt, MD
Editor

THE ENDOCRINE SOCIETY®

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Accreditation Statement
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Learning Objectives
The educational content of this volume is provided in a case-based format, with questions designed to assess competence in the diagnoses and management of endocrine disorders. While the topics vary, covering multiple aspects of endocrinology, the learning objectives apply to problem solving for a variety of endocrine disorders. Upon completion of this enduring activity, participants should be able to:

- List common causes or risk factors for diabetes, endocrine, and metabolic disorders and choose appropriate strategies of therapy
- Identify and differentiate endocrine cases that can be treated in a primary care setting and those that are in need of referral to an endocrinologist for treatment
- Recognize factors important in the evaluation and diagnosis of common endocrine disorders and formulate a treatment plan in a primary care setting

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This continuing medical education activity should be of substantial interest to endocrinologists, internists and family practitioners who care for patients with endocrine disorders.

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PREFACE

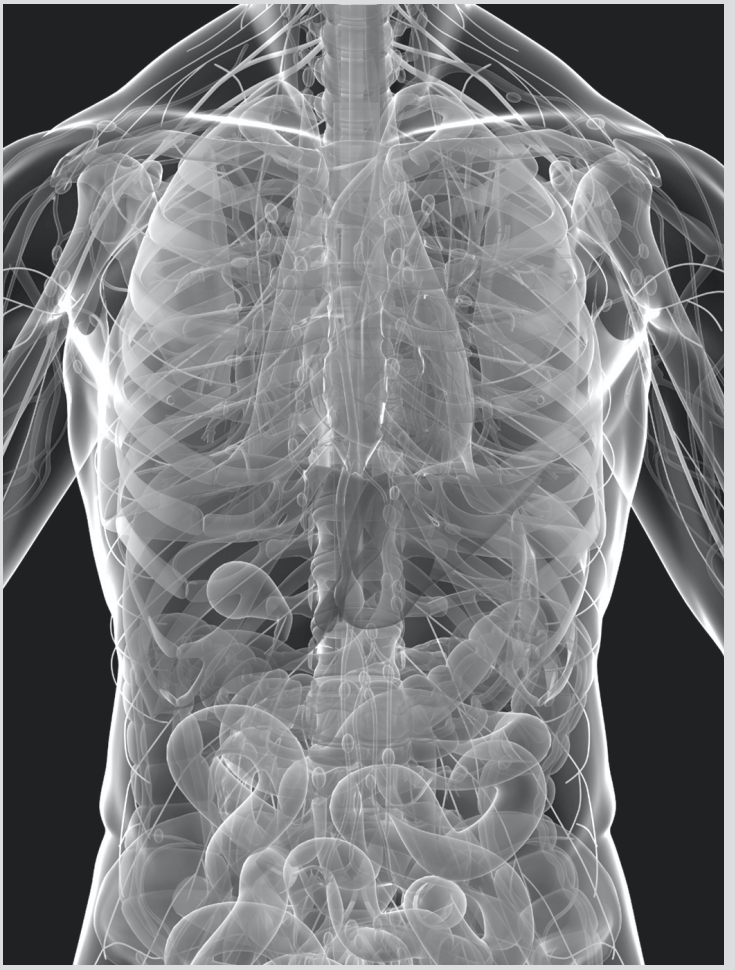
I am pleased to present this second volume of *Endocrine Essentials*, a work that reviews the recent clinical research on some of the most common clinical endocrinology topics that primary care clinicians, endocrinologists and other clinicians grapple with in the clinic. These topics include osteoporosis, calcium disorders, diabetes management, subclinical thyroid dysfunction, lipid disorders and selected areas in men's and women's health.

Each chapter is based on a talk given at the Endocrine Society's Annual Scientific Meeting in 2010 or 2011. The chapter synthesizes the most recent clinical research into practical approaches to the management of common endocrinology disorders. The chapters contain a succinct review of a topic and case-based questions and answers. Each chapter also includes a multiple choice question written in the format of questions used in the American Board of Internal Medicine exam. The content of each chapter will be useful for busy clinicians who want a rational, evidence-based approach to the clinical dilemmas that they face in the clinic and for those clinicians preparing for board examinations in internal medicine or endocrinology.

I hope that you enjoy reading this book and applying the principles in it to the care of your patients!

Bradley D. Anawalt, MD
Clinical Science Chair, ENDO 2011

BONE AND MINERAL HOMEOSTASIS



1 Vitamin D:

When and How to Use

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Vitamin D deficiency is common, but there is great controversy about what defines optimal vitamin D levels. Vitamin D stores are generally assessed by measuring the levels of its metabolite, 25-hydroxyvitamin D (25-OHD) in the blood. The need for adequate vitamin D to prevent and treat rickets in children and osteomalacia in adults is well known. Levels of 25-OHD above 10 ng/ml suffice for this purpose. However, higher levels of 25-OHD are required to prevent/treat osteoporosis and to prevent falls and fractures, especially in the elderly. Although there is some controversy over the level required to optimize the beneficial actions of vitamin D on the musculoskeletal system, an expert panel constituted by the Institutes of Medicine (IOM) has recently concluded that 25-OHD levels above 20 ng/ml suffice. However, many experts dispute this conclusion and recommend higher levels (30 ng/ml) to optimize skeletal health, to prevent fractures in older patients, and perhaps to confer other extraskeletal benefits.

BARRIERS TO OPTIMAL PRACTICE

- The diagnosis of vitamin D deficiency is subtle. Keep a high index of suspicion in patients with malabsorption, osteopenia, and osteoporosis; with drugs that can affect metabolism, such as dilantin; and with lifestyle factors, including limited sunlight exposure and avoidance of dairy products.
- Long-term compliance with a drug that has no obvious, immediate, perceived benefit to the patient is difficult.
- Variability in test results between labs has improved, but clinicians need to be aware that the problem persists.
- Vitamin D2 metabolites are more rapidly cleared from the blood than vitamin D3 metabolites. Vitamin D2 should be taken at least weekly.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Know the metabolism and biologic activity of vitamin D and its metabolites
- Know the difference between vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) and the appropriate use of each therapeutically
- Understand the basis for the IOM recommendations for vitamin D supplementation

- Understand the limits of the evidence for the nonskeletal actions of vitamin D

Review of strategies for diagnosis and management of vitamin D deficiency. Vitamin D3 is produced in the skin. This requires ultraviolet radiation (UVB, wavelength 280–320) to break the B ring of 7-dehyrocholesterol in the skin to form pre-D3 and subsequently D3. One cannot become vitamin D toxic from too much sun, but excess UVB does cause other skin problems. Skin pigment limits the UVB effectiveness (dark skin makes less vitamin D for a given dose of UVB). Likewise, the angle of the sun determines intensity of UVB. Farther from the equator, there is less time during the year that the UVB intensity is sufficient to induce vitamin D production. Vitamin D2 comes from plants and fungi. It differs in the side chain, so that it binds the vitamin D binding protein less well and is more rapidly cleared from blood than vitamin D3 and its metabolites.

Vitamin D affects a large number of physiologic processes. They include: *Skeletal health*: A number of studies have been conducted to determine whether vitamin D supplementation prevents fractures. Bischoff-Ferrari et al.[1] recently published a meta-analysis of randomized controlled trials (RCT) examining the efficacy of vitamin D supplementation on fracture prevention with or without supplementary calcium in subjects over 65 years old. These studies included non-vertebral fractures (12 RCTs, 42,279 subjects) or hip fractures (8 RCT, 40,886 subjects). Studies using 400 IU vitamin D or less did not show benefit, whereas those studies using more that 400 IU vitamin D showed a significant reduction (approximately 20%) in fractures. Part of the reduction may come from increased bone mineral density in the individuals receiving vitamin D supplements, but part of the benefit may also come from an improvement in neuromuscular function and a decreased risk of falling.

Hormone secretion: 1,25(OH)2D regulates the production and secretion of a number of hormones, many of which regulate renal production of 1,25(OH)2D. Vitamin D deficiency has been linked to a variety of diseases resulting from either over- or under-secretion of such hormones, providing a physiologic basis for the importance of this regulation.

- *Parathyroid hormone (PTH)*. 1,25(OH)2D inhibits the synthesis and secretion of PTH and prevents the proliferation of the parathyroid gland[2]. 1,25(OH)2D also upregulates the calcium-sensing receptor, which, by sensitizing the parathyroid gland to calcium inhibition, provides an additional means by which 1,25(OH)2D regulates PTH production and secretion. Hyperparathyroidism is a feature of vitamin D deficiency and contributes to bone loss; thus, PTH levels are a useful marker to follow when vitamin D supplementation is initiated to correct vitamin D deficiency. Vitamin D and its metabolites, on the other hand, are useful in treating causes of secondary hyperparathyroidism, such as renal failure or vitamin D deficiency due to malabsorption.
- *Insulin.*1,25(OH)2D stimulates insulin secretion, presumably by regulating

calcium flux, although the mechanism is not well defined. Pittas et al. [3] recently published a meta-analysis of studies demonstrating a link between vitamin D deficiency and type 2 diabetes mellitus. Vitamin D is not a proven therapy for diabetes.

- *Fibroblast Growth Factor 23 (FGF23)*. FGF23 is produced primarily by bone, in particular by osteoblasts and osteocytes. 1,25(OH)2D stimulates FGF23 production [4]. A number of diseases are caused by overproduction or underproduction of FGF23, leading to abnormalities in vitamin D metabolism and phosphate handling. At this point, the role of FGF23 in vitamin D deficiency has not been determined, but elevated FGF23 levels may contribute to the osteomalacia frequently observed in chronic kidney disease.
- *Renin*. The juxtaglomerular cells of the kidney produce renin, a protease that converts angiotensinogen to angiotensin I that is subsequently converted to angiotensin II, a major regulator of aldosterone production and vascular tone. Mice lacking the ability to produce or respond to 1,25(OH)2D (CYP27B1 null, VDR null, respectively) have increased renin production, leading to increased angiotensin II, hypertension, and cardiac hypertrophy[5]. The negative regulation of renin/angiotensin by 1,25(OH)2D may explain the inverse correlation between hypertension and heart disease with 25-OHD levels observed in epidemiologic studies.

Regulation of immune function: The potential role for vitamin D and its active metabolite 1,25(OH)2D in modulating the immune response rests on the observations that VDR are found in activated dendritic cells, macrophages, and lymphocytes; that these cells produce 1,25(OH)2D (i.e., express CYP27B1); and that 1,25(OH)2D regulates the proliferation and function of these cells [6]. Two forms of immunity exist, each regulated by 1,25(OH)2D.

- *Adaptive immunity*. The adaptive immune response involves the ability of T and B lymphocytes to produce cytokines and immunoglobulins, respectively, to specifically combat the source of the antigen presented to them by cells such as macrophages and dendritic cells. Vitamin D exerts an overall inhibitory action on the adaptive immune system. This may be useful in the management of autoimmune diseases [7] and transplanted organs [8], as has been shown in animal studies and some epidemiologic studies with type 1 diabetes mellitus and multiple sclerosis.
- *Innate immunity*. The innate immune response is the first line of defense against invading pathogens. The response involves the activation of toll-like receptors (TLRs) in polymorphonuclear cells (PMNs), monocytes, and macrophages as well as in a number of epithelial cells, including those of the epidermis, gingiva, intestine, vagina, bladder, and lungs [9]. TLRs are transmembrane pathogen-recognition receptors that interact with specific membrane patterns (PAMP) shed by infectious agents that trigger the innate immune response in the host [10]. Activation of TLRs leads to the induction of antimicrobial peptides and reactive oxygen species, which kill the organism. Among those antimicrobial peptides is cathelicidin [11].

The expression of this antimicrobial peptide is induced by 1,25(OH)2D in both myeloid and epithelial cells, cells that also express CYP27B1 and so are capable of producing 1,25(OH)2D needed for this induction. It is through this mechanism that vitamin D may be essential for resistance to a number of infections, including tuberculosis [12].

Regulation of proliferation and differentiation: The proliferation and differentiation of many different cell types are controlled at least to some degree by vitamin D and its metabolites. Therefore, the role of vitamin D in the prevention and/or treatment of conditions where such regulation goes awry has received considerable attention. Much of the interest has focused on cancer prevention and treatment. 1,25(OH)2D has been evaluated for its potential anticancer activity in animal and cell studies for several decades. The list of malignant cells that express VDR is now quite extensive. However, data from prospective trials with vitamin D and its metabolites for the prevention/treatment of cancer are limited. A prospective 5-year trial with 1100 IU vitamin D and 1400–1500 mg calcium showed a 77% reduction in cancers (multiple types) after excluding the initial year of study [13]. In this study, vitamin D supplementation raised the 25-OHD levels from a mean of 28.8 ng/ml to 38.4 ng/ml, with no changes in the placebo or calcium-only arms of the study. However, this was a relatively small study in which cancer prevention was not the primary outcome variable. Trials with 1,25(OH)2D and its analogs for the treatment of cancer have been disappointing and limited by hypercalciuria. One such study involving 250 patients with prostate cancer using 45g 1,25(OH)2D weekly in combination with docetaxel demonstrated a nonsignificant decline in PSA, although survival was significantly improved (HR 0.67) [14].

THERAPEUTIC CONSIDERATIONS

What is vitamin D sufficiency? Serum 25-OHD levels provide a useful surrogate for assessing vitamin D status, as the conversion of vitamin D to 25-OHD is less well controlled (i.e., primarily substrate dependent) than the subsequent conversion of 25-OHD to 1,25(OH)2D. 1,25(OH)2D levels, unlike 25-OHD levels, are well maintained until the extremes of vitamin D deficiency because of the secondary hyperparathyroidism, and so do not provide a useful index for assessing vitamin D deficiency, at least in the initial stages. Historically, vitamin D sufficiency was defined as the level of 25-OHD sufficient to prevent rickets in children and osteomalacia in adults. Levels of 25-OHD below 10 ng/ml (or 25 nM) are associated with a high prevalence of rickets or osteomalacia. Although there is currently no consensus for the optimal levels, the recent recommendations from the IOM state that levels of 25-OHD above 20 ng/ml are sufficient [15]. Although that recommendation is based primarily on prospective clinical trials regarding skeletal health, other experts point out that this level may be too low for the nonskeletal actions of vitamin D [16].

Vitamin D treatment strategies. Adequate sunlight exposure is the most cost-effective means of obtaining vitamin D. Whole-body exposure to enough UVB

radiation or sunlight to provide a mild reddening of the skin (minimal erythema unit) has been calculated to provide the equivalent of 10,000 IU vitamin D3. Duration of exposure depends on skin pigmentation and intensity of the sunlight. A 0.5 minimal erythema dose of sunlight (i.e., half the dose required to produce a slight reddening of the skin) or UVB radiation to the arms and legs, which can be achieved in 5–10 min on a bright summer day in a fair-skinned individual in Boston, has been calculated to be the equivalent of 3000 IU vitamin D3. However, concerns regarding the association between sunlight and skin cancer and/or photoaging have limited this approach, perhaps to the extreme, although it remains a viable option for those unable or unwilling to benefit from oral supplementation. Current recommendations from the IOM for daily vitamin D supplementation include 400 IU for infants, 600 IU for children and adults 1–70 years, and 800 IU for adults older than 70 [15].Upper limits range from 1000 IU in infants to 4000 IU in older children and adults. These are recommendations for the general population and would not apply to those with malabsorption of vitamin D or alterations in its metabolism.

A number of studies have demonstrated that for every 100 IU vitamin D3 supplementation administered on a daily basis for four or more months, 25-OHD levels rise by 0.5—1 ng/ml. Thus, to increase a patient's 25-OHD level from 10 ng/ml to 20 ng/ml, the supplementation would need to be 1000–2000 IU per day. 700–800 IU appears to be the lower limit of vitamin D supplementation required to prevent fractures and falls in the elderly, but the levels of vitamin D required to confer the other potential benefits of vitamin D are not established. We also know very little about the optimal age-specific 25-OHD levels. Unfortified food contains little vitamin D, with the exception of wild salmon and other fish products, such as cod liver oil. Milk and other fortified beverages typically contain 100 IU/8 oz serving. The 25-OHD level after a single 50,000 IU dose of D2 returns to baseline by 2 wks, whereas a comparable dose of D3 results in elevated 25-OHD levels for over 1 month. However, when given on a daily basis, 25-OHD levels are equally well maintained with either form of vitamin D. Therefore, if vitamin D2 is used, it needs to be given at least weekly. Toxicity due to vitamin D supplementation has not been observed at doses less than 10,000 IU per day, although such doses are seldom required except in situations in which the vitamin D is poorly absorbed (malabsorption syndromes). Toxicity manifests as hypercalcemia and hypercalciuria, leading to renal failure as a result of nephrocalcinosis and nephrolithiasis and neurologic symptoms, including coma.

CONCLUSIONS

- Suspect vitamin D deficiency in individuals with a history of limited sunlight exposure, limited ingestion of dairy products and other vitamin D–fortified foods, unexplained bone loss, malabsorption.
- Serum 25-OHD level is the best measurement for assessing vitamin D sufficiency.
- The IOM recommends that all individuals should have a 25-OHD level of 20 ng/ml or more, but levels above 50—60 ng/ml may be problematic.
- 600 IU of vitamin D daily should suffice for most ambulatory individuals

up to the age of 70, 800 IU for those older than 70 years, and 400 IU for infants. Avoid dosages over 4000 IU per day. 600 IU might not suffice for dark-skinned subjects. These recommendations are based in part on levels known to reduce the risk of fractures.
- Nonskeletal actions of vitamin D are less well studied and may have different vitamin D requirements.
- If vitamin D2 is used instead of vitamin D3, the dosing should be at least weekly.

CASE 1

A 60-year-old white man enters your office with a complaint of low back pain. His primary physician ordered a lateral spine radiograph that showed diffuse osteopenia\degenerative changes primarily in the lumbar spine, and mild compression fractures in T6 and L1. DEXA measurements confirmed osteopenia (T score –2.0) of the spine and hip. The back pain is not severe, but it is starting to interfere with routine activities around the house. There is no history of trauma to the back. The patient gives a 40-pack-year history of cigarette smoking, but quit 5 years ago. He drinks 1 or 2 cocktails on weekends, but was a heavier drinker during his 5 years in the service. He gives no history for malabsorption but avoids dairy products because they give him gas. He is sedentary and does not spend much time outside. Your initial physical examination finds a mildly overweight male in no acute distress but with some stiffness and pain on flexion of the back. He has no neurologic abnormalities on exam.

1. ***What lab tests should be ordered?***
   A. This patient has several risk factors for osteoporosis and vitamin D deficiency. Both the history of heavy smoking and drinking in the past could lead to bone loss and osteoporosis. You also should consider the possibility of lung cancer and prostate cancer with metastases to the spine. The patient might have lactase deficiency leading to the avoidance of dairy products, which are the main source of dietary calcium and vitamin D. So the workup should include a screening chest x-ray, a PSA, serum testosterone, calcium, phosphorus and 25-OHD level, and a 24-hour urine calcium with creatinine (to assess completeness of collection).
2. ***The serum calcium and phosphorus come back at 9.1 mg/dl (normal 8.8–10.2) and 2.9 mg/dl (normal 3.5–5.0), respectively. 25-OHD comes back as 15 ng/ml. Twenty-four-hour urine calcium is 95 mg, with creatinine of 1600 mg. Chest x-ray is essentially clear. The PSA is 4 mg/dl, testosterone 350 ng/dl (normal 300–1000). What additional information do we need? What is the approach to treatment?***
   A. These values are consistent with vitamin D deficiency, which leads to a low normal calcium and phosphate, low 25-OHD, and low urine calcium, a reflection of the reduced intestinal calcium absorption. At this point, supplementation with 1500 IU vitamin D each day plus 1000 mg calcium would be expected to bring his serum 25-OHD level to about 30 ng/ml

(my preferred target), although 600–800 IU should raise the level above 20 ng/ml. You should consider prescribing a bisphosphonate for his osteoporosis (assuming that the compression fractures are not due to another cause). Refer to an endocrinologist if the patient's bone density does not improve.

CASE 2

A 75-year-old white woman comes to your office with the diagnosis of normocalcemic primary hyperparathyroidism. You obtain a history of a 3-inch loss of height over the past 20 years and a recent rib fracture after falling against the dining room table. The patient had a mild stroke a few years ago, and although she has fully recovered, she developed a seizure disorder for which she takes dilantin. The patient lives alone and doesn't get out much because of "arthritis" and some gait imbalance for which she uses a walker around the house. She cooks for herself, but her appetite is poor. Physical examination shows kyphosis and tenderness to fist percussion over the thoracic spine, with some pain on compression of the ribs. Mild symmetric weakness is noted in the proximal musculature. You order a DEXA, and a T score of –3.0 was noted in the lumbar spine. You send off a PTH and serum calcium: the PTH is 120 pg/ml (upper limits of normal 65 pg/ml) but the serum calcium is 9.4 mg/dl (normal 8.8–10.2).

1. ***What further tests do you want?***
   A. The history and DEXA values are consistent with either osteoporosis or osteomalacia. The poor appetite, lack of sunlight, and dilantin treatment all suggest osteomalacia due to vitamin D deficiency. Dilantin accelerates the metabolism of vitamin D metabolites, making an already marginal patient with respect to vitamin D intake/production more susceptible to deficiency. The elevation in PTH with a normal calcium level is likely in this patient to be due to severe vitamin D deficiency. A serum phosphate, urine calcium/creatinine, and 25-OHD will most likely confirm this diagnosis.
2. ***How should this patient be treated?***
   A. This patient may need more than the standard amount of vitamin D supplement because of the dilantin therapy. I would treat her with 8 wks of 50,000 IU per week of vitamin D2 (ergocalciferol) then switch to a daily supplement of vitamin D based on the 25-OHD level obtained pretreatment using the rule of thumb of 100 IU for every 1 ng/ml below target value, which, as stated above, for my patients is 30 ng/ml. Because of the dilantin therapy, the 100 IU/1 ng/ml rule may be too conservative. This should be supplemented with 1 g calcium as citrate. The osteoporosis should be treated with a bisphosphonate that can be started at the same time as the vitamin D. Consider consultation with an endocrinologist for this complex patient, particularly if treatment with vitamin D fails to raise her 25-OHD and reduce her PTH.

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2 Risk Assessment for Osteoporotic Fracture

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is recognized as a major public health problem in developed countries. The prevalence of the disease, as judged by bone mineral density (BMD) measurements, increases markedly with age. Approximately 3–6% of women in the developed world have osteoporosis at the age of 50 years, and this proportion rises steeply with age to reach 50–75% of those age 90 years. In women age 50 years, the remaining lifetime risk of experiencing a major osteoporotic fracture exceeds 30–40% in developed countries. In men, the prevalence increases from 0.5%–1% at 50 years of age to 15–28% at 90 years. Thus, the clinical significance of osteoporosis lies in the resulting osteoporotic fractures, the incidence of which rises markedly with age [1]. It is critical for primary care providers to accurately identify patients at higher risk of osteoporotic fracture.

BARRIERS TO OPTIMAL PRACTICE

- The triggers that should make us think of osteoporosis are missed. For example, physicians and their patients may link vertebral and hip fractures to osteoporosis, but many other types of fractures that may indicate a high risk for osteoporotic fracture are assumed to be unrelated to osteoporosis.
- There may be limited access to diagnostic testing, particularly dual x-ray absorptiometry (DXA).
- Many clinicians look after patients who suffer from diseases that are associated with osteoporosis, but the clinicians often are not familiar with fracture risk assessment.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Identify historical and physical examination findings that are critical in the assessment of osteoporotic fracture risk.
- Recognize the utility and importance of using radiographic studies to assist in determination of fracture risk.
- Use clinical risk factors without bone mineral density data to estimate future fracture risk and to stratify need for therapy.

- Appreciate the contribution of specific risk factors (i.e., previous fractures and glucocorticoid use) to estimation of future fracture risk and decisions to use pharmacologic anti-fracture therapy.

CASE 1

A 75-year-old female Caucasian is seen for her routine yearly physical exam. The patient is in generally good health except for a history of hypertension, controlled by an ACE inhibitor. She also has a history of chronic anxiety and osteoarthritis of the lumbar spine. She does not smoke or drink alcohol. She took estrogen for only a short time after menopause. She has a history of lactose intolerance and does not consume dairy products but does take calcium carbonate 600 mg twice daily with 400 IU of vitamin D. She has no known history of fractures, no history of major trauma. There is no known family history of osteoporosis or hip fracture.

On physical exam her height is 63 inches, which is 2 inches lower than her adult maximum. Her weight is 120 lbs. Exam is remarkable for mild thoracic kyphosis. Rib to pelvis distance is reduced at 1 fingerbreadth bilaterally, and her wall to occiput distance is 3 fingerbreadths. Laboratory tests, including complete blood count, complete metabolic panel, TSH, 25-hydroxyvitamin vitamin D and urinalysis, are within normal limits. A DXA bone mineral density (BMD) is obtained and reveals a lumbar spine T score of –1.9 and a femoral neck T score of –2.0.

Key points

Osteoporosis is defined as a history of low-trauma fracture or BMD T score of <–2.5. .This patient does not have osteoporosis. However, many patients at risk of fracture have osteopenia rather than osteoporosis. The FRAX score can be used to evaluate the 10-year risk of fracture in such subjects.

Epidemiologic studies indicate that at least half the population burden of osteoporosis-related fractures affects persons with osteopenia (low bone density), who comprise a much larger segment of the population than those with osteoporosis [2].

The public health burden of fractures will fail to decrease unless the subset of patients with low bone density who are at increased risk for fracture are identified and treated. Risk stratification for medically appropriate and cost-effective treatment is facilitated by the World Health Organization (WHO) FRAX algorithm, which uses clinical risk factors, bone mineral density, and country-specific fracture and mortality data to quantify a patient's 10-year probability of a hip or major osteoporotic fracture. The FRAX algorithm uses the following risk factors: femoral neck (but not lumbar spine) bone mineral density, prior fractures, parental hip fracture history, age, gender, body mass index, ethnicity, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis. FRAX was developed by the WHO to be applicable to both postmenopausal women and men age 40 to 90 years; the National Osteoporosis Foundation Clinician's Guide focuses on its utility in postmenopausal women and men age >50 years. It is validated for untreated patients only. The current National Osteoporosis Foundation Guide recommends treating patients with

FRAX 10-year risk scores of greater than or equal to 3% for hip fracture and/or 20% for major osteoporotic fracture (hip, clinical spine, distal forearm and proximal humerus combined), to reduce their fracture risk [3]. Additional risk factors, such as frequent falls, not represented in FRAX, warrant individual clinical judgment. FRAX has the potential to demystify fracture risk assessment in primary care for patients with low bone density, directing clinical fracture prevention strategies to those who can benefit most [4].

1. ***What clinical findings for this patient are helpful in the determination of future fracture risk?***
   A. History of low-trauma fracture and risk factors for osteoporosis (including those used in the FRAX algorithm) are important clues to determine future risk. In addition, the clinical history and physical examination may provide evidence for vertebral fracture. The symptoms of vertebral fracture (back pain, height loss, change in appearance of back) are not specific to osteoporosis but can be considered triggers for spinal radiography, particularly historical height loss of more than 4 cm, especially in an older woman [5]. The physical examination is generally insensitive and nonspecific for osteoporosis, but detection of kyphosis by measurement of wall to occiput (>5 cm) or rib to pelvis distance (<2 fingerbreadths) might be useful [6]. Any historical risk factors for osteoporosis or signs or symptoms of vertebral represent triggers to use the FRAX algorithm to calculate the patient's osteoporotic fracture risk in the next 10 years.

2. ***What is this patient's risk for fracture in the next 10 years?***
   A. The FRAX algorithm (http://www.shef.ac.uk/FRAX/tool.jsp) indicates that her 10-year risk of hip fracture is 2.9% and 10-year risk of major osteoporotic fracture is 11%.

3. ***What other clinical data are available to more accurately assess fracture risk for this patient, and how are these data used to best determine the need for pharmacologic treatment?***
   A. A previous lateral chest x-ray obtained four weeks earlier for a persistent cough is unremarkable except for a ìthoracic compression fracture.î

Comment
It is common for radiologists to miss fractures on lateral chest or spinal radiographs, or for them to use terminology that doesn't clearly identify vertebrae as fractured [7].

Comment
The FRAX algorithm now indicates that her 10-year risk of hip fracture is 4.1% and 10-year risk of major osteoporotic fracture is 16%. The inclusion of previous vertebral fracture in the FRAX score results in a risk of fracture that suggests that the patient would benefit from pharmacotherapy.

CASE 2

A 60-year-old man presents for evaluation and possible treatment. He has a history of Crohn's disease for over 20 years, for which he has been glucocorticoid dependent. He has also undergone bilateral hip replacement for avascular necrosis of the femoral heads. He complains of chronic low back pain and has lost 3 inches of height from his historical maximum. His current medications include prednisone 15 mg per day, infliximab 350 mg every 8 weeks, and calcium 600 mg with 400 IU vitamin D twice daily. There is no family history of osteoporosis or hip fracture. He does not smoke or imbibe alcohol.

On physical examination he is in mild discomfort due to low back pain. He is 170 cm tall (66.9 inches), which is 5 cm or 2 inches below his adult maximum, and he weighs 70 kg (154 pounds). Examination is notable for no thoracic kyphosis although his lumbar lordotic curve is flattened. Rib to pelvis distance is one fingerbreadth bilaterally. The remainder of the exam is unremarkable. Laboratory studies are unremarkable, including a 25-OHD level of 30 ng/ml and a normal 24-hour urine calcium. DXA bone density shows lumbar spine T score of –0.8, but there are obvious degenerative changes. Proximal radius T score is normal at –0.5. Hip DXA cannot be performed due to his hip prostheses. Thoracolumbar radiographs reveal compression fractures at L1 and L3 and significant degenerative disc and facet joint disease.

1. ***What is this patient's risk for fracture in the next 10 years?***
   A. According the FRAX algorithm, this patient's 10-year fracture risk is at least 4.9% at the hip and 17% for overall major osteoporotic fracture. Note that the FRAX allows for femoral neck T score input, but no other bone site T score.

      In the absence of available femoral neck BMD data, inclusion of secondary risk factors for osteoporosis (malabsorption in Crohn's disease) contributes significantly within FRAX to estimation of fracture risk.

      In addition, recent data suggest that FRAX estimates of fracture risk may be adjusted based on dose of glucocorticoids that the patient receives [9].

      Prevalence of vertebral fractures in patients with IBD may be as high as 25% and is higher in males [10].

2. ***Is it appropriate to offer this patient a pharmacologic anti-fracture therapy?***
   A. Yes! Independent of FRAX estimation of fracture risk, previous vertebral fractures robustly predict a higher risk of future vertebral and nonvertebral fractures [11].

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3 Drug Therapies for Osteoporosis:

When, Which & How Long to Use?

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is a systemic skeletal disorder leading to decreased bone mineral density and a propensity for fracture. The disease affects millions and is a source of significant morbidity and mortality in both men and women. Fracture-related costs have skyrocketed in recent years and projections suggest an increase as the population ages.

BARRIERS TO OPTIMAL PRACTICE

Recent advances in the understanding of bone biology have improved the therapeutic options for osteoporosis treatment and prevention. Increased therapeutic options have led to challenging clinical questions: Whom should I treat? For what duration? Which therapy is optimal for which patient? Is this therapy safe? If so, for how long? Evidence-based answers to these questions are available for many osteoporosis therapies. For others, specifically the most widely used agents, the bisphosphonates, many unanswered questions regarding drug safety and optimal duration of therapy exist.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Discuss optimal opportunities for discontinuation of osteoporosis medications.
- Discuss the advantages and disadvantages of bisphosphonates.
- Develop clinical strategies for patients failing first-line therapy.

This session focuses on aspects of skeletal health for which evidence-based data are insufficient to allow informed, confident clinical decision making. Through the use of clinical case scenarios, the existing evidence to support a care plan is discussed; the facilitator's opinion is offered.

CASE 1

A 53-year-old perimenopausal white female (menopause age 51) has a screening bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) scan. This reveals a BMD 2 standard deviations below a young ethnically matched female population (T-score = -2.0) at the lumbar spine (LS) and a T-score = -1.8 at the femoral neck (FN). She has no personal or family history of fracture, does not

smoke and has no secondary causes of osteoporosis by history. She is 5'8" tall and weighs 130 pounds.

1. ***Does this patient need treatment for her skeleton?***
   A. This patient has low bone density. No known health consequences beyond fracture risk have been reported for this condition. Our decisions regarding therapeutic intervention should be guided by our attempts to reduce fractures. To answer the question about whether to treat her low bone density, we must determine her risk of fracture.

2. ***Is this patient at high risk for fracture?***
   A. A significant body of evidence supports the correlation between BMD and fracture risk. Every standard deviation reduction in a patient's T-score is associated with an approximate doubling of fracture risk. Age is also a significant risk factor for fracture. At any BMD measurement, older age increases fracture risk. Our patient has an approximate 4-fold increased risk of fracture compared to other 53-year-old white women (relative risk) but her overall risk of fracture is still low (absolute risk) because of her age. The National Osteoporosis Risk Assessment (NORA) trial followed 200,160 post-menopausal North American women for self-reported fracture incidence over a 12-month span. Each participant received BMD measurement from a peripheral device. Approximately 53% of the NORA participants were 50-64 years old. About a third of this cohort had low BMD (T-score < -1.0). Though the absolute number of fractures was greater in the over 65-year-old cohort (two times higher), the younger cohort suffered a considerable number of fractures (about a third of the vertebral fractures reported and about 20% of the hip fractures). In the Fracture Intervention Trial (FIT), alendronate usage was associated with a significant decreased risk of vertebral fractures in the sub-population of women aged 55-80 with BMD T-scores between (-1.6 and -2.5). The greatest benefit from treatment was seen in those women with prior vertebral fractures; in those without an incident fracture, treatment benefit was less evident.

      It is unclear on an individual b asis whether intervention to reduce fracture in a patient with low bone density (T-score >-2.5) is necessary or cost-effective. The Fracture Risk Assessment (FRAX) tool is a WHO-derived algorithm that uses clinical data and BMD scores to generate an individual's 10-year probability of hip fracture or major osteoporotic fracture. FRAX can assist clinicians by identifying individuals without osteoporosis at high risk for fracture for whom treatment might be beneficial. According to the most recently revised National Osteoporosis Foundation guidelines, anyone over age 50 with a FRAX-derived 10-year probability of hip fracture >3% or major osteoporosis fracture risk of >20% should be considered for an FDA-approved therapy for osteoporosis.

      Getting back to our patient, her FRAX risk assessment would place her at a 0.6% risk of hip fracture and a 5.6% risk for major

osteoporotic fracture over 10 years. The benefits of pharmacotherapy to reduce fractures would not clearly outweigh the risks and costs of pharmacotherapy. Clinicians must understand the limitations of the FRAX tool and realize that these guidelines are not strict rules of engagement but a platform to prompt clinical decision making. Individual assessment regarding osteoporosis therapy must be performed and many factors must inform our therapeutic decisions for individuals below and above the FRAX fracture thresholds.

1. ***What about therapy to prevent further bone mineral loss in this patient?***

A. The loss of estrogen in the perimenopausal period is associated with a significant decrease in BMD. An argument to treat peri-menopausal women to reduce bone mineral loss and prevent fracture is commonly made. Estrogen, raloxifene, and bisphosphonates have all shown to reduce peri-menopausal bone loss and are approved drugs for this purpose. Which therapy to use is a matter of debate. Postmenopausal estrogen therapy has been associated with an increased risk of cardiovascular and thromboembolic events as well as an increased risk of breast cancer when used in combination with progesterone. However, this risk seems greatest in older women and in those initiating therapy further from menopausal onset. Raloxifene is associated with thromboembolic events and increased climacteric symptoms, but does not seem to increase the incidence of cardiovascular events and modestly reduces the risk of breast cancer in high-risk women. More significantly, the bone mineral-sparing effects of estrogen and raloxifene only last as long as these agents are being used; once discontinued, bone mineral loss similar to that seen in the perimenopausal period would be expected. Evidence suggests that fracture rates increase to those of non-treated women within five years of estrogen discontinuation. Therefore, use of these agents for bone mineral preservation would warrant extended use and the attendant risks might outweigh benefit. Bisphosphonates have been shown to preserve and increase BMD when used in younger perimenopausal women. Treatment with alendronate for two years in this cohort was associated with a persistent decrease in bone turnover markers and a diminished rate of BMD loss for 4 years. Concerns over the long-term effects of bisphosphonate use (see next case) would proscribe use of these agents for osteoporosis prevention beyond a two-year period in my opinion.

My personal recommendations for this patient would be to consider non-pharmacologic approaches to reduce fracture risk, specifically, exercise, balance training, appropriate calcium and vitamin D supplementation, and avoidance of smoking and excessive alcohol. Though none of these modalities has been shown to prevent perimenopausal bone loss, they can reduce fracture risk. A repeat BMD assessment by DXA in 2 years would be appropriate to evaluate individuals at risk for rapid bone loss in whom therapy might be indicated.

CASE 2

A 72-year-old female has received alendronate therapy for 7 years; a screening DXA scan revealing osteoporosis prompted treatment. She has never sustained a fracture or loss of height, but she believes her mother had osteoporosis (kyphosis). She is an educated consumer and is concerned about the recent headlines regarding bisphosphonate therapy. A repeat DXA reveals a LS BMD T-score of -2.3 and a FN T-score -2.0, she's had a BMD increase from baseline of 7% and 4%, respectively.

1. ***Should she be continued on bisphosphonate therapy? What are therisks of continuation?***

   A. The bisphosphonate agents are the most widely used class of drugs for the treatment of osteoporosis. These agents are known to concentrate in bone and to disrupt osteoclast action and survival, resulting in an anti-resorptive effect. Drug development has resulted in agents with varying degrees of potency and has allowed for different delivery modalities (oral, intravenous) and dosing frequency (daily, weekly, monthly, annually) for the individual formulations. The bisphosphonates have proven efficacy to reduce osteoporotic fractures to varying degrees depending on the formulation used and the skeletal site studied. Many of these agents are FDA-approved for use in the treatment and prevention of post-menopausal osteoporosis, male osteoporosis and glucocorticoid-induced osteoporosis. Head to head trials comparing the efficacy of the different bisphosphonate therapies have not been performed.

   Clinical trials with bisphosphonates have typically lasted 2-3 years, but the skeletal half-life of these compounds is very long. Concern whether these agents might cause aggressive suppression of bone remodeling, leading to skeletal fragility with extended use, has led to much confusion and consternation for the clinician and the patient. Increased reports of an association between bisphosphonate use and the development of osteonecrosis of the jaw (ONJ) led to a joint committee report to define ONJ as ìexposed necrotic bone in the maxillofacial region, not healing after 6-8 weeks, in patients with no history of craniofacial radiation.î Very few cases of ONJ seem to be related to bisphosphonate exposure and the vast majority of bisphosphonate-associated ONJ is seen with higher intravenous doses. Risk factors for ONJ development include recent dental extraction, cancer, concomitant chemotherapy, and higher dose of bisphosphonates. The estimated incidence of bisphosphonate-induced ONJ varies per study but is estimated to be 1 in 10,000 to 1 in 160,000 for individuals receiving typical doses for osteoporosis treatment. Given the comparative risk of osteoporotic fracture, the use of bisphosphonates for osteoporosis should not be modified by concerns about ONJ.

   Bisphosphonates have been implicated in increased risk of subtrochanteric and diaphyseal fractures, so-called atypical fractures, via excessive suppression of bone resorption. In a retrospective analysis of three major bisphosphonate trials in 14,195 postmenopausal women,

no increased incidence of atypical fractures in the cohort receiving bisphosphonates was seen. However, few subjects in this analysis were exposed to bisphosphonate therapy for longer than 4 years. In a retrospective case control study of a large Canadian health registry, the use of bisphosphonates was associated with an increased risk of atypical fractures and duration of bisphosphonate exposure increased this risk. The overall risk of atypical fracture was small (0.35%) and paled in comparison to the reduction in typical osteoporosis fractures associated with bisphosphonate use in the same group (34% reduced fracture rate).

2. ***What is the risk of bisphosphonate discontinuation?***
   A. The Fracture Intervention Trial Long-term Extension (FLEX) trial randomized participants who had already received alendronate for five years to either continue alendronate or placebo, in a double-blind fashion, for another five years. The rates of nonvertebral and morphometric vertebral fractures were the same between the two groups at ten years but the incidence of clinically detectable vertebral fractures was decreased by continued alendronate use. In the cohort of women with T-scores < -2.5, continued alendronate use was associated with a significant reduction in non-vertebral fractures. According to the FLEX results, some patients receive prolonged anti-fracture benefit for at least 5 years after alendronate discontinuation. Conversely, high-risk patients might benefit from alendronate continuation for ten years before considering a *drug holiday* (discontinuation for 1-2 years or more). Similar outcomes have been described following risedronate discontinuation after 3 years of use. In most patients, the benefit of bisphosphonate-induced fracture protection outweighs the risk of long-term exposure. However, given the dearth of long-term safety data, clinicians must continually reassess bisphosphonate safety and efficacy individually. A judicious approach might include:
      - Stopping bisphosphonate therapy in those without astrong initial indication. (such as the patient in Case 1)
      - Offering patients achieving BMD T-scores > -2.5 and no history of fracture a drug holiday after 5 years. Bisphosphonates or alternative agents are re-instituted if BMD begins to decline, bone biomarkers suggest increased turnover, or fracture occurs.
      - Offering patients with BMD <-2.5 or a history of fracture a drug holiday after ten years of bisphosphonate use. Alternative agents might be necessary during the bisphosphonate-free interval for those at severe fracture risk.

CASE 3

A 73-year-old male with known COPD and vertebral fracture suffers a second vertebral fracture during the third compliant year of risedronate use.

What are options for therapy in this patient?

A. Unfortunately, bisphosphonates only reduce osteoporotic fractures by 50-70%, and many individuals will suffer a fracture despite appropriate use. The initial plan for ìbisphosphonate failureî is to identify and correct secondary factors predisposing to fracture and to assure compliance with calcium, vitamin D and proper bisphosphonate administration. If patients have difficulties adhering to oral bisphosphonate dosing instructions, switching to an intravenous formulation (zoledronic acid) may be effective. If proper dosing and adherence to the bisphosphonate is determined, and secondary causes of osteoporosis are ruled out, switching to an alternative drug, with a different mechanism of action, is appropriate.

Teriparatide (PTH 1-34) activates the PTH receptor and retains all the biologic properties of the full (PTH 1-84) polypeptide. Intermittent skeletal exposure to teriparatide stimulates osteoblastic bone formation; the only available anabolic agent for osteoporosis. In the Fracture Prevention Trial, teriparatide administered to a group of 1637 postmenopausal women with a prior osteoporotic vertebral fracture was associated with a significant increase in BMD, and a 65% and 53% reduction in vertebral and non-vertebral fracture rates, respectively. Too few hip fractures were observed in this study to measure efficacy. Teriparatide has shown similar gains in BMD in men with osteoporosis, although no large trials regarding fracture efficacy in males have been conducted. The use of this drug has proven efficacy to reduce glucocorticoid-induced osteoporosis. Teriparatide is administered as a once daily subcutaneous 20-microgram dose. In teratogenicity trials, teriparatide use in rats (at significantly higher than equivalent human doses) resulted in an increased risk of osteosarcoma. Concerns about osteosarcoma development have resulted in FDA recommendations to limit the lifetime exposure to teriparatide to two years in humans. Due to the cost, subcutaneous administration, and unknown long-term effects of teriparatide, it is often used as a second-line agent. Potential candidates for use include the following groups: men and women with severe osteoporosis (T-score < -3.5, or < -2.5 with a fracture), those with osteoporosis unable to tolerate other agents, and those failing other therapies, that is, suffering fractures or loss of BMD despite documented compliance.

Denosumab is a human antibody to RANKL shown to interfere with RANK/RANKL binding and to reduce osteoclastic bone resorption. Administration of denosumab (60 mg SQ every 6 months) was associated with a significant increase in BMD among a group of 7868 postmenopausal women with osteoporosis. In the same study, denosumab reduced the incidence of vertebral fractures by 68%, hip fractures by 42%, and other non-vertebral fractures by 24% compared to placebo. Denosumab has been shown effective in postmenopausal women previously treated with bisphosphonates, maintaining or improving BMD following bisphosphonate discontinuation. It has been shown to prevent osteoporosis and vertebral fracture in men with

prostate cancer receiving androgen deprivation therapy. Denosumab is administered as a bi-annual subcutaneous injection of 60 milligrams. In clinical trials, denosumab use was well tolerated. It is a potent anti-resorptive agent but its actions seem to be short-lived, requiring continued use for continued skeletal benefit. Use during clinical trials and post-trial extension periods with a duration of six years revealed continued anti-resorptive effect and did not result in osteonecrosis of the jaw, atypical fractures or delayed fracture healing. The long-term adverse effects of denosumab beyond six years of use are unknown. The FDA has approved denosumab for the treatment of postmenopausal osteoporosis.

DRUG SUMMARY

The FDA-approved therapies for the treatment or prevention of osteoporosis aresummarized below. (LS = spine; Op = osteoporosis, GiOP = glucocorticoid osteoporosis)

DRUG: *Estrogen*
Dosing: Multiple oral and transdermal preparations
BMD Effect: Increase 3-4% LS, 1-2% hip
Fracture efficacy: Approximate 30% reduction in hip and vertebral fractures
Indication: Postmenopausal osteoporosis prevention and treatment
Duration of use for skeletal benefit: Lifelong
Adverse effects/concerns: Cardiovascular events, thromboembolism, breast cancer

DRUG: *Raloxifene*
Dosing: 60 mg poqd
BMD Effect: 2-3% increase at LS and hip
Fracture efficacy: 34% reduction in vertebral fractures
Indication: Postmenopausal osteoporosis treatment and prevention
Duration of use for skeletal benefit: Lifelong
Adverse effects/concerns: Thromboembolic, climacteric symptoms

DRUG: *Calcitonin*
Dosing: 200 IU daily intra-nasal spray
BMD Effect: 1.2% increase
Fracture efficacy: 33% reduction in vertebral fractures
Indication: Postmenopausal osteoporosis, possible analgesic effect
Duration of use for skeletal benefit: Life-long, tachyphylaxis may occur
Adverse effects/concerns: Inconsistent dosing effect and high drop-out rate in clinical trials.

DRUG: *Teriparatide (PTH 1-34)*
Dosing: 20 mcg SQ daily (transdermal and intra-nasal preps in production)
BMD Effect: Increase 9% LS, 3% FN
Fracture efficacy: 65% reduction vertebral, 53% reduction non-vertebral

Indication: Severe osteoporosis, men and women, glucocorticoids
Duration of use for skeletal benefit: 2 years
Adverse effects/concerns: Hypercalcemia, hypercalciuria, site reactions, cramping, hyperuricemia, concern about teratogenicity

DRUG: *Denosumab*
Dosing: 60 mg SQ every 6 months
BMD Effect: Increase 9.2% LS, 4% total hip
Fracture efficacy: Reduction: 68% vertebral, 42% hip, 24% non-vertebral
Indication: Treatment of postmenopausal osteoporosis
Duration of use for skeletal benefit: Lifelong
Adverse effects/concerns: Hypocalcemia, cellulitis, upper respiratory infections, limited long-term safety data

DRUG: *Alendronate*
Dosing: 10 mg po daily, 70 mg po weekly
BMD Effect: Increase 6% LS, 4% hip
Fracture efficacy: Decrease 50% vertebral, 30% hip, 30% non-vertebral
Indication: Prevention and treatment of postmenopausal Op, male Op, GiOp
Duration of use for skeletal benefit: 3-10 years
Adverse effects/concerns: Hypocalcemia, acute phase reaction, esophagitis, osteonecrosis of the jaw, atypical fractures (see text)

DRUG: *Risedronate*
Dosing: 5 mg po daily, 35 mg po weekly
BMD Effect: Increase 5% LS, 3% hip
Fracture efficacy: Decrease 40% vertebral, 30% hip and non-vertebral
Indication: Prevention and treatment of postmenopausal Op, male Op, GiOp
Duration of use for skeletal benefit: 3-10 years
Adverse effects/concerns: Hypocalcemia, acute phase reaction, esophagitis, osteonecrosis of the jaw, atypical fractures (see text)

DRUG: *Ibandronate*
Dosing: 2.5 mg poqd, 150 mg po q monthly
BMD Effect: Increase 5% LS and 4% hip
Fracture efficacy: Decrease 50% vertebral
Indication: Prevention and treatment of postmenopausal osteoporosis
Duration of use for skeletal benefit: 3-10 years
Adverse effects/concerns: Hypocalcemia, acute phase reaction, esophagitis, osteonecrosis of the jaw, atypical fractures (see text)

DRUG: Zoledronic acid
Dosing: 5 mg IV annually
BMD Effect: Increase 7% vertebral, 6% hip
Fracture efficacy: Decrease 70% vertebral, 40% hip, 25% non-vertebral

Indication: Prevention and treatment of postmenopausal Op, male Op, GiOp
Duration of use for skeletal benefit: 3-10 years
Adverse effects/concerns: Hypocalcemia, acute phase reaction, esophagitis, osteonecrosis of the jaw, atypical fractures (see text), atrial fibrillation

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4 Gauging Response to Osteoporosis Therapy

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Patients, health care providers, and third party payers want reassurance that treatment is effective. This can be difficult to ascertain, especially for chronic conditions like osteoporosis that involve multiple risk factors, some of which, like aging, are ongoing, and progression is clinically silent until a fracture occurs. Response to therapy has been defined for large groups in research studies, but statistical response and individual response in clinical practice are not the same.

BARRIERS TO OPTIMAL PRACTICE

Methods to evaluate response to osteoporosis therapies either are well validated but slow, or are faster but are affected by large variation within individuals and between laboratories and lack well-tested outcomes. Stable bone density after treatment indicates at least some success, because bone density normally is lost with age and illness. However, patients continue to feel vulnerable and want better evidence of progress. Even if response to therapy has been established, the optimal intervals for retesting in individual patients are uncertain.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Recognize the controversies regarding follow-up assessment once osteoporosis therapy has been initiated
- Describe the strengths and limitations of the methods for evaluating treatment response in individual patients
- Recognize the considerations and uncertainties regarding intervals for monitoring after initiating therapy, once stable response to therapy has been achieved, and after therapy is stopped

MEASURING RESPONSE TO OSTEOPOROSIS THERAPY

1. ***Is measuring the response to osteoporosis therapy always necessary?***
   A. No, according to authors of an analysis of the inter-individual and intra-individual response to alendronate therapy vs. placebo in postmenopausal women with low bone density who were enrolled in the Fracture Intervention Trial (FIT) between 1992 and1993.[1] They found a clinically adequate hip bone density increase of ≥ 0.019 g/cm^2 over 3

years in 97.5% of women in the bisphosphonate-treated group. Intra-individual variation was much more pronounced than inter-individual variation.

Yes, according to responders to the above, because participants in clinical trials are more likely to be compliant, be more interested in good lifestyles, be healthy, and be on fewer medications than patients in the "real world." [2,3] Even if most patients respond as expected, it is important to identify those who do not because of non-compliance with medication, incorrect dosing, malabsorption, and other secondary causes of bone loss that have not been addressed, as well as true non-responders. Bisphosphonates are not equal [4]; whether there are significant differences in fracture outcome is uncertain. Consistency of response to generic bisphosphonates has not been tested. No one has evaluated the outcome of non-bisphosphonate therapies in the same way.

Both groups agree that non-compliance is best assessed and addressed by discussion with individual patients. There are no good data to indicate that measuring response to therapy improves persistence with treatment.

Ongoing assessment is desirable for those whose situations change—for example, patients starting glucocorticoid or hormone suppression therapy, patients changing or stopping therapy, or patients who are immobilized.

2. ***What should be measured?***

A. The principal tools for gauging the response to pharmacotherapy for osteoporosis are central bone mineral densitometry (by DXA) and serum and urinary markers of bone turnover (*Table 4-1*).

Serial measurements showing an increase in central (hip and spine) bone density by DXA provide a surrogate indicator of fracture protection. Peripheral bone density measurements are not recommended for follow-up. Either they are not sufficiently sensitive or changes have not been validated by correlation with fracture risk.

During bone remodeling and repair at bone-forming units in adults with bone loss, osteoclast activity exceeds the coupled osteoblast activity that follows. Measurements of bone turnover indicating reduction in osteoclast and osteoblast activity show excellent correlation with reduction in fracture risk in clinical trials of anti-resorptive therapies. Their application for individual patients is less certain. (The only anabolic therapy, hPTH[1-34] or teriparatide, increases markers of both osteoclast and osteoblast activity.)

Many bone turnover markers have been used. Markers of bone resorption (osteoclast activity) are products of type 1 collagen breakdown: urinary cross-linked N-telopeptides (U-NTX), serum cross-linked C-telopeptides (CTX), and urinary pyridinoline and deoxypyridinoline. Bone formation (osteoblast activity) markers include serum bone-specific alkaline phosphatase, procollagen type 1 propeptides (PINP if from the N-terminal end and PICP if from the C-terminal end), and osteocalcin.[5,6,7]

Table 4.1. Bone mineral density vs. bone turnover markers for monitoring osteoporosis therapy

Measurement	Bone Mineral Density (DXA)	Bone Turnover Markers
Acceptance	Widely accepted method	Not formally endorsed by any group but "may be helpful" per National Osteoporosis Foundation (NOF), North American Menopause Society (NAMS), American Association of Clinical Endocrinologists (AACE)
Availability	Widely available in USA, less so elsewhere	Less widely available
Insurance coverage	Yes, every 2 years. More often if compelling circumstances	Variable
Database	Large database for Caucasians; smaller but available for other groups. Wide age range. Data for men	Reference intervals for healthy, premenopausal women in UK, France, Belgium and USA.8 Need data for other groups
Measurement precision	Good	Highly lab dependent.9 Newer methods may be better but need external quality assurance programs. May need repeated measurements.10
Day-to-day variation	No	20–50%
Diurnal variation	No	20% +
Diet-dependent	No	Fasting values preferred for CTX
Site-specific	Spine, hip	No. Reflects total body turnover
Desirable range	Stable or increased level correlated with lower fracture risk	Lower half of premenstrual range? Not validated clinically
Time to reflect significant change, compliance, or treatment effect	1–2 years	3–6 months

3. ***At what intervals should measurements be made?***
   A. Bone density response to intervention is slow compared to response of bone turnover markers. Reassessment of bone density is recommended at 1–2 year intervals after initiating therapy. In clinical practice, monitoring after that usually is done at 2-year intervals as long as therapy remains unchanged and the patient's clinical situation is stable. There are no data to indicate how long this should continue.

      Response to bisphosphonate therapy can be prolonged. In a small trial, a single dose of intravenous zoledronic acid resulted in changes in bone density and bone turnover markers that persisted up to 3 years.[11] Either measurement might be done annually to determine when to administer another dose.

      Loss of bone can occur rapidly in exceptional situations, including initiation of high-dose glucocorticoid therapy, or hormone suppression therapy, or immobilization. Changes in bone turnover markers are apparent within weeks.

4. ***At what intervals should monitoring be done if therapy is stopped?***
   A. The optimal duration of therapy is unknown. Risk for osteonecrosis of the jaw or atypical subtrochanteric femoral shaft fractures is associated

with increased dose or duration of bisphosphonate therapy, although causality has not been proven and the mechanism(s) is(are) uncertain. Both events are rare with the bisphosphonate doses used for treatment of osteoporosis, but there also is concern about possible consequences of prolonged or increased suppression of bone repair. This is especially true with the more potent bisphosphonates and denosumab, respectively.[11, 12]

Gain or stability of bone density and changes in bone turnover markers are lost within 1–2 years after discontinuation of all therapies except the bisphosphonates, which accumulate in bone. Bone density returned to baseline in 5 years in postmenopausal women who stopped taking alendronate after 5 years of treatment. The incidence of clinical vertebral fractures was reduced in the group that remained on bisphosphonate therapy.[13]

Task forces assembled by the American Society of Bone and Mineral Research have addressed . whether bisphosphonate therapy should be stopped for a "drug holiday."[14, 15] It is unclear whether stopping bisphosphonate therapy reduces risk of osteonecrosis of the jaw, but it may reduce the risk for atypical femoral fractures. [15,16] The task force evaluating femoral shaft fractures suggested that if bisphosphonate therapy is continued after 5 years because of ongoing moderate or high risk for fractures, patients should be evaluated annually with clinical assessment, including examination of the jaw, and measurement of bone density.15 The task force also suggested that if bisphosphonate therapy is stopped for a "drug holiday" in patients without recent fractures whose DXA T scores are greater than –2.5 after the initial course of therapy, follow-up should include clinical assessment, bone turnover markers, and bone density measurements. They did not specify appropriate intervals.[15]

Patients treated with bisphosphonates who develop groin or thigh pain should have immediate radiographic evaluations of both femurs to look for cortex changes that precede atypical femoral fractures. If the results are equivocal or negative but suspicion is high, MRI or radionuclide scintigraphy should be performed.[15]

There are no studies to indicate when or whether bisphosphonate or other therapy should be restarted.

CONCLUSIONS

Measurement of response to osteoporosis therapy is desirable to identify possible true non-responders, non-compliance, errors in dosing or administration or malabsorption, unsuspected secondary causes of bone loss or consequences or rapidly changing clinical circumstances.

Response to initial osteoporosis therapy can be done by measurement of central bone mineral density by DXA after 1–2 years (well-validated, site-specific, widely available [in USA] but slow response over months to years).

Response to therapy can be measured by bone turnover markers of osteoclast and osteoblast activity (highly laboratory-dependent, acceptable response not

evidence-based, not site-specific, daily and diurnal variation, but rapid response within weeks to months)

In clinical practice, ongoing response to therapy usually is monitored at 2-year intervals until stability is established. How long such monitoring should continue in clinically stable patients is not established.
Monitoring should be more frequent in situations of rapid bone loss, such as glucocorticoid therapy or hormone suppression therapy or immobilization.

Bone density and bone turnover markers return to baseline within 1–2 years after stopping all therapies except for bisphosphonates, which accumulate in bone. If bisphosphonate therapy is stopped, loss of bone density is slower.
The optimal duration of therapy is unknown. Follow-up by clinical assessment and bone density and bone turnover markers is recommended annually for patients remaining on bisphosphonates after 5 years; the same monitoring is recommended if therapy is stopped for a "drug holiday," but the optimal intervals are not known.

CASES FOR CONSIDERATION

Assume that lifestyle factors and calcium and vitamin D needs have been addressed.

CASE 1

A 55-year-old woman with spine T score of –2.0 and no fractures has been treated for 5 years with alendronate. What would you do? How would you follow her?

A. This woman meets the criteria for a "drug holiday." She is clinically stable with no recent fractures and a T score after treatment of >–2.5. If she is at least 5–6 years beyond menopause, then most of the especially rapid bone loss in the early years after menopause would be behind her. Based on the FLEX trial, we know that her risk for clinical vertebral fractures would be less if she remained on the bisphosphonate, [13] but this must be balanced with the increased (albeit low) risk for osteonecrosis of the jaw or an atypical femoral fracture associated with bisphosphonate use. We know that bone is lost more slowly after withdrawal of a bisphosphonate than other osteoporosis therapies.

We suggest stopping the bisphosphonate, clinical assessment of fracture risk annually, measuring bone turnover markers now and annually and a DXA scan in 2 years (at 1 year if there is a significant increase in bone turnover markers at that time).

CASE 2

A 70-year-old woman with three spine fractures was treated with zoledronic acid one year ago. She has a new radial fracture. What would you measure? What would you do?

A. No osteoporosis therapy abolishes fracture risk completely, and bone density changes at the radius with treatments usually are small. Zoledronic acid is one of the most potent anti-resorptive therapies and changes in both bone turnover markers and bone mineral density often are sustained after even a single dose.11 In the HORIZON trial,

nonvertebral fractures were reduced 25% over 3 years of treatment with zoledronic acid.[17]

We do not know how much trauma was associated with this patient's radial fracture; we will assume a fall from a standing height. We know that individuals who have had one fragility fracture are at high risk for another.

We suggest obtaining a DXA scan to assess her current bone density baseline, especially at the hip, and obtaining bone turnover markers. If these are suppressed well into the lower half of the premenopausal range, it is likely that the zoledronic acid is working as expected. If not, she could be given a second dose. Denosumab causes more complete inhibition of osteoclast activity, but the combined effects of residual bisphosphonate plus denosumab could result in profound suppression of bone turnover and repair.[12] The addition of teriparatide, which has anabolic activity at the spine and hip, also could be considered. Bone turnover markers could be obtained again in 6 months. Bone turnover markers and follow-up DXA should be obtained in 1 year.

CASE 3

A 50-year-old woman was started on estrogen and progestin replacement shortly after menopause at age 40. Ibandronate was added when she was 48. Now she has right femur pain. Her DXA scan reveals a spine T score of –2.3 and a hip T score of –1.7. What would you do?

A. She has been on a bisphosphonate for a relatively short time, but she should have radiographs of both femurs immediately. Individuals who develop atypical femoral shaft fractures often report a prodrome of thigh or groin pain. If the radiographs are negative but suspicion remains high, she should have either an MRI including both femurs or a radionuclide study to look for cortical thickening. There is evidence that stopping bisphosphonate therapy reduces the risk of atypical femoral fractures.[15,16] We definitely would recommend this if any suspicion remains after her imaging studies.

She has been on estrogen for 10 years, and she will have to decide whether the benefits outweigh the risk of prolonged estrogen replacement. The effects of estrogen on bone turnover and bone density will be lost within 1–2 years if she stops estrogen therapy. The effect of ibandronate will be lost more slowly.

At this time her bone density is not in the osteoporosis range. She has not had any fractures and is younger than the usual hip fracture age range. A "drug holiday" would be appropriate for her. If she stops one or both of her treatments, we recommend clinical assessment and a follow-up DXA in 1 year. If she remains on both of her treatments, we recommend clinical reassessment annually and a follow-up DXA in 2 years. If both estrogen and a bisphosphonate are contraindicated but she needs treatment, raloxifene might be a good choice for her.

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5 New Options for Vertebral Fracture

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Vertebral fractures are widely held to be the most common osteoporotic fractures, yet they account for only ~4% of all clinical fracture presentations to Accident & Emergency &Trauma Centers. As many as two-thirds of vertebral fractures are never diagnosed.[1,2]

Whether clinically silent[3,4] (asymptomatic 'morphometric' or 'radiographic' vertebral fracture) or symptomatic[5,6] ('clinical vertebral fracture'), vertebral fractures are associated with excess mortality. Mortality increases with the severity and number of vertebral fractures[1,7] and is particularly high in patients who are hospitalized for vertebral fractures.[8] Although vertebral fractures can be asymptomatic, they can be associated with considerable pain and disability.[9] Post-vertebral fracture morbidity also includes a subsequent 2–3-fold increase in fracture risk at spine and all other skeletal sites.[10] Secondary fractures often occur rapidly; 16–26% of patients with vertebral fractures sustain at least one further fracture within 2 years of the initial vertebral fracture if they do not receive specific fracture prevention therapy.[11,12]

Most patients with vertebral fractures are not adequately evaluated or treated. This deficient management is partially explained by patient factors (50% of vertebral fractures are asymptomatic or the patient may not seek evaluation for fracture-induced pain). Vertebral fractures are often not diagnosed because spine imaging that reveals vertebral fractures is unrecognized, unreported, or reported with vague terminology, such as "collapse," "height loss," or "wedging."[12,14]

BARRIERS TO OPTIMAL PRACTICES

- Failure to identify and to diagnose vertebral fractures
- Failure to respond when vertebral fractures are identified
- Uncritical use of treatments for fracture secondary prevention
- Increased use of invasive interventions that have not been proven to be effective

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Identify mechanisms to increase the rate of diagnosing vertebral fractures
- Understand when to consider uncommon causes of vertebral fractures
- Identify the drug therapies that are most effective for prevention of

vertebral fractures
- Assess the role of percutaneous vertebral augmentation procedures (vertebroplasty and balloon kyphoplasty)

1. ***What criteria define the presence of a vertebral fracture?***
   A. Central to the definition of vertebral fracture is loss of vertebral body height (whether of posterior, or mid or anterior vertebral height). Three grades of vertebral fracture are recognized: grade 1 = 20–25% height loss, grade 2 = 25–40% height loss, and grade 3 = more than 40% loss. Loss of endplate integrity is important, because the presence of intact endplates makes a vertebral fracture unlikely *(Figure 5-1)*.

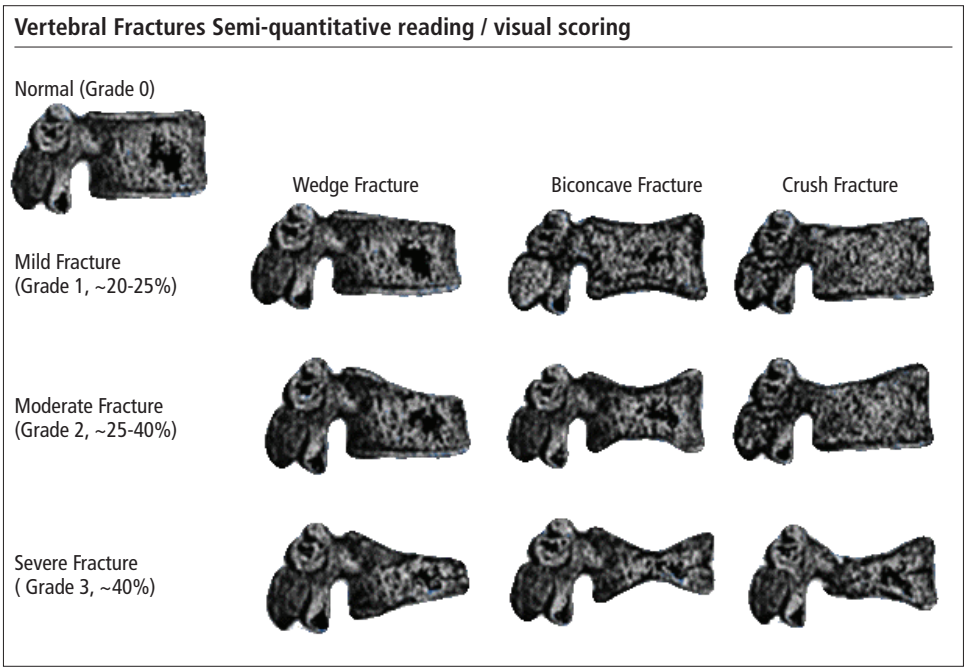

Figure 5.1. The semi-quantitative visual approach to diagnose vertebral fractures[15]

2. ***Are grade 1 vertebral fractures important?***
   A. Prevalent and incident grade 1 vertebral fractures are associated with a doubling of subsequent vertebral and non-vertebral fracture incidence.[16] While more severe grades of prevalent and incident fractures (at least of grade 2 severity) carry even greater implication for future fracture risk, grade 1 fractures are clinically relevant.

3. ***What can be done to increase identification of patients with vertebral fractures?***
   A. The opportunities lie a) in carefully reviewing the "scout" vertebral x-ray that is a component of dual x-ray absorptiometry (DXA) and b)

in collaborating with radiologists to clearly report vertebral fractures in patients who undergo spine imaging (X-rays, MRI, CT, etc.) and to link patients with radiographic fractures to a pathway of care that leads to appropriate evaluation and treatment.

Factors associated with increased vertebral fracture risk are recognized (such as age and height loss), but, even when used in combination in algorithms, clinical risk factors are of limited utility in predicting the presence of vertebral fractures in practice.[17] While recognizing that vertebral fracture assessment by DXA is not licensed as a diagnostic imaging modality, the 30-second low-dose lateral spine X-ray scout image of the DXA allows assessment for vertebral fractures from around the sixth thoracic to the fifth lumbar vertebra. We incorporate this assessment into all DXA scan interpretations.

It is essential to collaborate with local radiologists to ensure that 'fracture' is explicitly mentioned in reports. But that is only part of the solution, because even when fractures are mentioned, this may not trigger action by the referring clinician.[12,14] In our center, we run a Fracture Liaison Service (FLS) that provides routine post-fracture assessment to all women and men age 50+ who present with low-trauma fractures.[18] For the last 4 years, our FLS has liaised with our radiology departments to ensure that all patients who are reported to have a vertebral fracture undergo appropriate assessment, including DXA.

4. ***Is DXA necessary when spine imaging shows a vertebral fracture?***
   A. The prevalence of vertebral fractures increases with age, but ~11% of men and ~7% of women age 50–54 have at least one vertebral fracture.[19] Whether the fractures are a consequence of low bone mineral density (BMD) is uncertain, especially in men. Furthermore, whether fractures arise due to early trauma or due to childhood diseases such as leukemia, vertebral fractures occurring in early life will persist radiographically through adulthood. Identification of vertebral fracture on spine imaging does not necessarily imply that the fracture has occurred recently. Further assessment, including DXA, may be appropriate to ascertain the need for treatment.

CASE

DM is a 26-year-old male with Asperger's syndrome who presented with a 4-month history of severe lumbar back pain that started after coughing. The pain was beginning to interfere with his work as a museum attendant. Plain-film X-ray interpretation suggested that the bone was "unusually osteopenic," with grade 1 wedge fractures at lumbar vertebrae 1, 2 and 3.

There is no past medical history of note and he was not on any prescription medication.

Investigations: Complete blood count, sedimentation rate, serum calcium, phosphate, alkaline phosphatase, 25-OH vitamin D, PTH, testosterone, FSH,

LH, serum and urine electropheresis were all normal.
DXA: Lumbar spine T score = –6.5, femoral neck T score = –2.6.

1. ***What other investigations should be considered in a patient like this one, a young person with multiple vertebral fractures?***
   A. Tests to exclude Cushing's syndrome are indicated in this young man with advanced osteoporosis. In a series of 80 patients with Cushing's syndrome (mixed pituitary, adrenal and ectopic ACTH etiology),76% were shown to have at least one vertebral fracture, and 52% had two or more.[22] About 52% were asymptomatic. In the setting of a secondary care osteoporosis clinic, 10.8% of patients with osteoporosis and vertebral fractures had abnormalities in cortisol dynamic tests (such as low-dose dexamethasone suppression test, cortisol diurnal rhythm or 24-hr urinary cortisol).[23]

      Investigations confirmed that the patient had Cushing's disease, with a pituitary adenoma that was cured subsequently by transsphenoidal hypophysectomy.

2. ***In typical patients with vertebral fractures, is FRAX useful in determining treatment?***
   A. FRAX[24] only accounts for a single fracture. When multiple vertebral fractures are present, FRAX will seriously underestimate fracture risk. Also, the BMD parameter that contributes to the FRAX fracture risk calculation is the absolute BMD at the femoral neck; spine BMD is often lower than the femoral BMD, especially in the context of vertebral fractures. FRAX is of limited value in patients with one or more vertebral fractures.

FDA Approved Medications

	Prevention in F	Treatment PMO	Treatment M with O	O in M&F + Steroids
Alendronate O				Rx if O + steroid
Risedronate O				Prevention & Rx
Ibandronate O, iv				
Zoledronic acid iv				Prevention & RX
Calcitonin in, sc				
HRT O				
Raloxifene O				
Teriparatide SC				Rx if high risk fractures on steroids
Denosumab SC				

Figure 5.2. FDA-approved medications for osteoporosisand for prevention of fractures
F = female and M = male; PMO = postmenopausal osteoporosis; O = osteoporosis

Table 5.1. Absolute fracture rates (vertebral and non-vertebral) reported in placebo arms of key clinical trials in women with postmenopausal osteoporosis and absolute fracture risk reductions achieved with drug treatments that aim to reduce fracture risk.

Rx	Ref.	Absolute number of fractures in PBO group per 1000 women per treatment-year				Absolute number of fractures prevented per 1000 women per treatment-year			
		Vertebral fractures		Non-vertebral fractures		Vertebral fractures		Non-vertebral fractures	
		Radio-graphic	Clinical	All sites	Hip	Radiographic	Clinical	All sites	Hip
ALN	30	48	17	49	7	23	9	9	3
RIS	31	46		21		17		7	
RAL	32	71		35		22		0	
1-34PTH	33	82		32		54		11	
IBAN	34	25		18		12		9	
ZOL	35	34	7	34	8	24	5	10	3

ALN = alendronate (oral) RIS = risedronate (oral) RAL = raloxifene (oral)
IBAN = ibandronate (oral) 1-34PTH= teriparatide (sc) ZOL = zoledronic acid (IV)

3. ***What treatments should be considered for prevention of secondary fractures in patients with vertebral fractures?***
   A. When vertebral fractures are identified, there are evidence-based treatment options for prevention of secondary fractures, and some are capable of preventing secondary fractures not only in the spine but also at non-vertebral sites. *Table 5-1* summarizes the absolute fracture risk reduction (vertebral and non-vertebral fractures) that has been reported for some of the main treatment options from clinical trials involving women with postmenopausal osteoporosis. The table also includes the absolute fracture rates reported in the placebo (PBO) arms of these trials—emphasizing that these studies included patients with different absolute fracture risks.

4. ***In the case of DM (see case history above), in addition to treating the Cushing's disease, is treatment indicated for the prevention of secondary fractures?***
   A. Surgical cure of Cushing's disease will significantly improve BMD, with expected increases in spine BMD of typically 20–30%. The severity of this patient's osteoporosis and the magnitude of fracture risk justify consideration of additional treatment options. Oral alendronate or risedronate, iv zoledronic acid, or sc teriparatide are all reasonable options (*Table 5-2*). Teriparatide might be slightly preferable given the potential additional gains in BMD, but the choice ultimately will be determined by patient preference *(Figure 5-2)*.

5. ***Do percutaneous vertebral augmentation procedures such as vertebroplasty (VP) or balloon kyphoplasty (BKP) have a role in pain management of patients with vertebral fracture?***

A. In 2009 there were two well-conducted, multicenter, randomized sham/simulated procedure-controlled RCTs of vertebroplasty (VP)[25,26]; these trials included 78 and 131 patients, respectively, with one to three painful vertebral fractures of at least grade 1 severity. Outcome measures during post-procedure follow-up included indices of pain and of function, disability, and quality of life at 1 or 3 months. Neither trial showed any objective benefit in any outcome measure compared with sham procedure. In 2009 there was also a randomized trial of balloon kyphoplasty (BKP) versus conventional non-surgical management.[27] Three hundred patients with 1 to 3 new painful vertebral fractures were randomized to BKP or conventional pain management within 3 months of the fracture(s). BKP was superior to conventional pain management during the first 6 months, but the outcomes (pain, loss of function and disability) did not differ after 12 months. It is unclear how the outcome of this study would have differed had a sham-procedure group been included.

While the numbers and follow-up intervals are small, none of these trials reported an increase in vertebral fracture incidence following these procedures.

Risks associated with VP include cement leakage (40%), pulmonary embolism (1.8%), spinal cord compression (0.5%), and radiculopathy (2.5%); the complications of BKP include cement leakage (8%), pulmonary embolism (0.3%), and radiculopathy (0.3%).[28,29]

Table 5.2. Summary of clinical trials of effective drugs for corticosteroid-induced osteoporosis.

Studied Rx	N Age Range (av) Duration	Starting or On steroids	% change LS BMD	Incidence of Morphometric VFx
ALN v PBO[1]	477 (1:1:1) 17-83 (54) yr 12mo	S O	+2.9% v -0.4% p≤0.02	RR 0.6(0.1-4.4) NS
ROS v PBO[2]	290 (1:1:1) 18-85 (59) yr 12mo	O	+2.9% v -0.4% p≤0.02	70% decrease p=0.04
ROS v PBO[3]	518 (1:1:1) 18-85 (59) yr 12mo	S O	+1.9% v -1.0% p≤0.001	70% decrease p=0.01
PTH v ALN[4]	428 (1:1) 22-89 (57) yr 18mo	O	+7.2% v +3.4% p≤0.001	0.6% v 6.1% p=0.004
ZOL v RIS[5]	833 (1:1) 18-85 (53) yr 12mo	O S	+1.36(0.67 to 2.05) +1.96(1.04 to 2.88)	NS

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CONCLUSIONS

Vertebral fractures are under-recognized, underdiagnosed and under-treated. New approaches are required to increase the identification of patients with vertebral fractures in order that they can benefit from treatment with drugs with proven efficacy for preventing secondary fractures at spine and non-vertebral sites.

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6 Investigation & Management of Hypocalcemia

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Hypocalcemia is common in hospitalized patients and can be a source of excess morbidity. Hypocalcemia is less common among outpatients, but it can be a cause of poorly defined neuromuscular complaints and fatigue.

BARRIERS TO OPTIMAL PRACTICE.

Clinicians caring for patients with hypocalcemia must be able to evaluate parathyroid and vitamin D status and understand how to interpret laboratory tests that reflect disordered mineral metabolism.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Recognize the causes of hypocalcemia and develop a diagnostic plan
- Effectively manage acute and chronic hypocalcemia

INTRODUCTION

In general, hypocalcemia is due either to reduced secretion (or action) of parathyroid hormone (PTH) or, more commonly, to defective supply or activation of vitamin D. Maintenance of normal circulating concentrations of calcium requires the intricate interplay of parathyroid, renal, gastrointestinal, and skeletal factors. Calcium and phosphorus levels are regulated primarily by parathyroid hormone (PTH) and vitamin D, and also by factors like parathyroid hormone-related protein (PTHrp), fibroblast growth factor-23 (FGF23), and the phosphate regulating endopeptidase gene (PHEX). Vitamin D promotes intestinal absorption of calcium and, to a lesser extent, phosphorus. Vitamin D also increases renal tubular reabsorption of calcium and has a permissive role in the phosphaturic effect of PTH. In a vitamin D–sufficient state, intestinal calcium absorption is typically up to 30%, but during periods of active growth, calcium absorption can reach 60–80%. In a vitamin D–deficient state, intestinal calcium absorption is only about 10–15%.

PTH secretion is regulated through the interaction of extracellular calcium with specific calcium-sensing receptors (CASRs) that are expressed on the plasma membrane of the parathyroid cell. In turn, PTH regulates mineral homeostasis and skeletal integrity through its actions on specialized target cells in bone and kidney that express the PTH/parathyroid hormone-related peptide (PTHrP) or type 1 PTH receptor. PTH increases bone resorption and

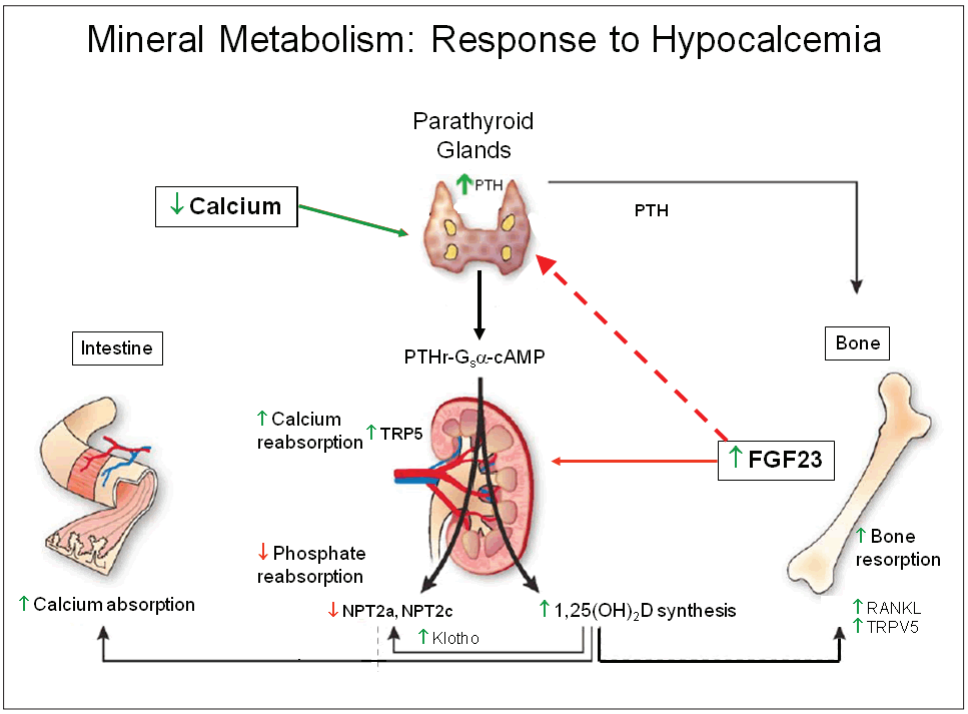

Figure 6-1. Mineral metabolism: the response to hypocalcemia. As extracellular ionized calcium level drops, calcium-sensing receptors on parathyroid cells decrease signaling, thereby leading to increased release (acutely) and increased production (chronically) of parathyroid hormone (PTH). PTH binds to specific receptors on osteoblasts, activating adenylcyclase, which leads to release of RANK ligand (RANKL). RANKL is a potent activator of osteoclast differentiation and function. Osteoclast-dependent bone remodeling ensues, and in the presence of calcitriol (1,25-OHD), calcium and phosphorus are released from skeletal stores. PTH also acts on cells in the renal proximal tubule to reduce expression of the sodium-phosphate co-transporters NPT2a and NPT2b, leading to decreased tubular resorption of phosphorus; activation of TRPV5 calcium transporters in the distal nephron increases calcium reabsorption. In addition, PTH activates CYP27b, the renal P450 hydroxylase enzyme that converts 25-OHD produced in the liver to 1,25-OHD (calcitriol), the most active vitamin D metabolite. Calcitriol acts on nuclear receptors in the kidney to stimulate renal production of klotho, which increases the expression and function of the epithelial calcium channel TRPV5 and therefore enhances calcium reabsorption in the distal tubule. PTH also activates TRPV5. Calcitriol also activates cells located in the upper intestine to increase active absorption of calcium via TRPV5 and TRPV6 calcium transporters. Calcitriol also increases production of FGF23 in osteocytes, and FGF23 acts through a hybrid receptor consisting of FGFR1 and klotho in the kidney to reduce expression of NPT2a and NPT2b and to decrease expression of CYP27b, thereby participating in a negative feedback loop that regulates production of calcitriol. FGF23 also increases production of CYP24, a 24-hydroxylase that degrades calcitriol and 25-OHD, and may inhibit secretion of PTH. The integrated actions of PTH and calcitriol on bone, kidney, and intestine result in increasing the serum calcium back to a normal level while avoiding hyperphosphatemia.

renal calcium resorption, and decreases renal phosphate reabsorption. PTH also induces expression and activity of the renal 1-hydroxylase enzyme that converts 25-hydroxyvitamin D (25-OHD) to 1,25-dihydroxyvitamin D (1,25-OHD), thereby increasing intestinal absorption of calcium and phosphate as well as osteoclastic bone resorption.

MEASURING THE PROBLEM

Approximately 99% of total body calcium is in the skeleton in the form of hydroxyapatite, leaving only 1% of the total body calcium within extracellular fluids and soft tissues. Calcium is distributed among three interconvertible fractions in the circulation. Approximately 45–50% of total serum calcium is in the ionized form at normal serum protein concentrations and represents the biologically active component of the total serum calcium concentration. Another 8–10% is complexed to organic and inorganic acids (e.g., citrate, sulfate, and phosphate); together, the ionized and complexed calcium fractions represent the diffusible portion of circulating calcium. Approximately 40% of serum calcium is protein-bound, primarily to albumin (80%) but also to globulins (20%). Although conventional measurement of serum calcium implies determination of the total serum calcium concentration, more physiologically relevant information is obtained by measurement of the ionized calcium concentration. From a practical point of view, measurement of total serum calcium concentration provides a reasonable estimate of the ionized calcium concentration, but several caveats are worth noting. For example, decreased concentration of serum albumin, the major calcium binding protein in the circulation, is the most common cause of hypocalcemia in hospitalized patients.

Plasma levels of ionized calcium can be measured in most clinical chemistry laboratories using now-standardized techniques. However, when it is not possible, or practical, to determine the ionized calcium concentration directly, a "corrected" total calcium concentration can be derived using one of several proposed algorithms that are based on albumin or total protein concentrations. None of these correction factors is absolutely accurate, but they often provide useful estimates of the true concentration of calcium in serum. One widely used algorithm estimates that total serum calcium declines by approximately 0.8 mg/dl for each 1 g/dl decrease in albumin concentration, without a change in ionized calcium.

CAUSES OF HYPOCALCEMIA

1. Neonatal hypocalcemia.

Early-onset neonatal hypocalcemia is evident within the first 4 days of life and most likely represents an exaggeration of the normal physiologic calcium nadir that occurs at 24 to 48 hours of life. This is due to either an inadequate release of PTH, decreased response to PTH by the kidney, or an exaggerated calcitonin release. Common associations with neonatal hypocalcemia include prematurity, low birth weight, hypoglycemia, maternal diabetes mellitus, and respiratory distress syndrome. A more severe form of transient neonatal hypoparathyroidism and tetany occurs in infants who were exposed to maternal hypercalcemia in utero. Late-onset hypocalcemia occurs on postnatal days 5 through 10 and is due to relative immaturity of parathyroid glands and/or resistance of renal tubules to PTH action. Because the kidneys do not excrete phosphate, hyperphosphatemia ensues and induces hypocalcemia. Late-onset hypocalcemia most typically occurs in newborns who are fed humanized cow's milk–based formulas, which have much higher concentrations of phosphorus than breast milk. Serum levels

of PTH are typically inappropriately low, but sometimes can be very high and consistent with transient pseudohypoparathyroidism.

2. Hypoparathyroidism.
Hypoparathyroidism must be considered when hypocalcemia persists beyond 4 weeks of life. Severe congenital hypoparathyroidism is most commonly due to agenesis or dysgenesis of the parathyroid glands. The velocardiofacial/conotruncal anomaly/DiGeorge sequence (DGS) is caused by an embryonic field defect that impairs the development of the third and fourth branchial pouches and the fourth pharyngeal arch. The clinical features of the DGS are highly variable between individuals; some have subtle findings, whereas others are severely affected. The most common cause of DGS is hemizygosity on chromosome 22q11, which occurs in 1 out to 2500 to 4000 live births. A large, contiguous gene deletion can be identified by fluorescent in situ hybridization (FISH) of peripheral blood cells in 75 to 90% of patients with DGS. DGS with loss of genetic material on chromosome 22q11 is often referred to by the acronym CATCH-22, which describes the presence of Cardiac anomalies, Abnormal facies, Thymic aplasia, Cleft palate, Hypocalcemia and 22q11 deletion in affected patients. Hypoparathyroidism may be transient and resolve during childhood, only to recur during stress or illness. Occasional patients with DGS are not diagnosed until late adulthood.

The DGS critical region includes the TBX1 gene, which encodes a transcription factor that is expressed in pharyngeal arches and pouches, and small mutations in this gene have been described in some patients with DGS who are negative for the large 22q11 deletion. DGS can also be caused by large deletions at 10p13 (DGSII). This region includes the GATA3 gene that accounts for the hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome. DGSII can also be identified by FISH analysis, and both DGSI and DGSII can be diagnosed by SNP microarray analysis. In addition to genetic defects, DGS can also occur in infants who were exposed in utero to retinoic acid, ethanol, or maternal diabetes.

Hypoparathyroidism can occur as a feature of several other complex developmental syndromes, including the autosomal recessive Kenny-Caffey syndrome (which is characterized by short stature, osteosclerosis, basal ganglion calcifications, and ophthalmic defects) and the allelic Sanjad-Sakati syndrome (growth and mental retardation), both due to mutations in the TBCE gene. Barakat syndrome, also termed the HDR syndrome (hypoparathyroidism, deafness, and renal defects), is due to autosomal dominant mutation of the GATA3 gene on chromosome 10p13.

Isolated hypoparathyroidism can occur as a result of dominant inhibitor or homozygous inactivating mutations of the GCM2 gene, which is required for development of the parathyroid glands. Impaired secretion of PTH can arise as a consequence of dominant or recessive mutations of the PTH gene. A milder form of hypoparathyroidism occurs in patients who have dominant activating mutations in the CASR gene that encodes the calcium-sensing receptor. This form of hypoparathyroidism is termed autosomal dominant hypocalcemia. Affected infants have parathyroid glands, but secretion of PTH is reduced

significantly due to a gain-of-function mutation that increases sensitivity of the calcium-sensing receptor to extracellular calcium. The activated calcium sensing receptor not only reduces PTH secretion, but also increases renal excretion of calcium and magnesium, and thus causes hypocalcemia with hypercalciuria. Some older patients can develop essentially the same syndrome due to the presence of antibodies that bind and activate the calcium-sensing receptor.

Destruction of parathyroid gland tissue is another cause of hypoparathyroidism and can occur secondary to an autoimmune process. Autoimmune polyglandular syndrome type I (APS-1) consists of the triad of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis, which can be familial or occur sporadically, and is typically due to homozygous inactivating mutations of the AIRE gene, which is highly expressed in the thymus. Patients with APS-1 develop a variety of autoantibodies that destroy endocrine tissues, including the parathyroid glands. Hypoparathyroidism can also occur as a consequence of surgical procedures that involve the parathyroid, thyroid, or other structures in the neck, but this risk has been minimized with awareness of the parathyroid gland's location prior to and during surgery. Infiltration of the parathyroid tissue with metals, such as copper (Wilson disease) or iron (secondary to genetic or acquired hemochromatosis), can also result in impaired function of parathyroid tissue.

Hypomagnesemia can cause either decresed secretion of PTH or PTH resistance.

3. Pseudohypoparathyroidism (PHP).

The hallmark of PHP type 1 is renal resistance to PTH. PTH resistance is manifested by a blunted nephrogenous cAMP response to PTH. In subjects with PHP type 1, PTH resistance is caused by a deficiency of the alpha subunit of Gs (Gs), the signaling protein that couples PTH1R to stimulation of adenylyl cyclase. Molecular and biochemical studies have provided a basis for distinguishing between two forms of PHP type 1: patients with generalized deficiency of Gs, due to mutations within exons 1-13 of the GNAS gene, are classified as PHP type 1a (OMIM 103580), whereas patients with more restricted deficiency of Gs due to mutations that affect imprinting of GNAS, are classified as PHP type 1b (OMIM 603233). PHP 1a and PHP 1b also differ in the pattern of hormone resistance and in the expression of additional somatic features. Generalized resistance to hormones that require Gs for coupling of their heptahelical receptors to activation of adenylyl cyclase is more common in patients with PHP type 1a than in patients with PHP type 1b. Patients with PHP type 1a, with haploinsufficiency of GNAS, typically manifest a constellation of skeletal anomalies that are collectively termed Albright hereditary osteodystrophy (AHO), and which include short stature, round faces, brachydactyly, dental defects, and heterotopic ossification of the skin and subcutaneous tissues. Additional features had been associated with AHO, such as obesity and sensory-neural abnormalities, but these defects appear limited to patients with PHP type 1a who have maternal GNAS mutations that cause abnormal Gs signaling in the central nervous system. Patients who manifest AHO and have normal hormonal responsiveness due to inactivating mutations on the paternal GNAS allele are considered to have the

genetically related disorder pseudoPHP. Short stature and brachydactyly may be due in part to premature fusion of epiphyses in tubular and long bones, which implies a requirement of two functional copies of GNAS for normal growth plate maturation. Occasional patients with PHP type 1b develop brachydactyly as well as mild resistance to TSH, suggesting that the imprinting defect may have more generalized consequences. Most patients with inherited PHP type 1b have mutations in STX16 or NESP55 that impair normal methylation patterns on the maternal allele, converting it into a paternal epigenotype. Some patients with sporadic PHP type 1b have paternal uniparental isodisomy, or a maternal defect that fails to erase a paternal imprint, and thus have two GNAS alleles with paternal imprints.

4. Vitamin D Deficiency.
Vitamin D insufficiency and deficiency are common, and may occur in at least 50% of the population.Recent studies from the National Center for Health Statistics show that about one third of Americans are not getting enough vitamin D, which explains why so many in the US are at risk for low vitamin D levels. Of course, the recent Institute of Medicine report that revised the lower limit of normal for serum 25-OHD to 20 ng/ml will affect these statistics. Many experts continue to believe experimental and observational data that support the premise that 32 ng/ml represents the lower limit of physiological normal, particularly when analyzing the inflection point for optimization of serum PTH concentrations. In conditions of vitamin D deficiency (e.g. serum 25-OHD less than 32 ng/ml), PTH levels begin to increase, presumably due to reduced serum levels of ionized calcium. Increased PTH secretion has the following effects: 1) increased calcium reabsorption in renal tubules, 2) increased 1-hydroxylase activity causing increased 1,25(OH)2 vitamin D synthesis, and 3) increased osteoblastic synthesis of RANKL, which stimulates differentiation of pre-osteoclasts to osteoclasts, inhibits osteoclast apoptosis, and therefore stimulates bone resorption. Increased PTH also causes loss of phosphorus in the urine. Decreased levels of calcium and phosphorus, and decreased calcium-phosphorus product, result in decreased bone mineralization. Failure or delay of calcification of osteoid leads to osteomalacia. In children who have unfused epiphyses, the lack of mineralization and deficiency of phosphorus disrupt normal organization of the growth plates and lead to rickets, with consequent bone deformity.

Rarely, neonatal vitamin D deficiency can also manifest as hypocalcemia after the first few days of life, when intestinal absorption of calcium begins to rely on vitamin D–dependent transport. Maternal vitamin D deficiency is typically associated with this condition.

What is an appropriate serum level of vitamin D?

A. 25-OH D is the major circulating form of vitamin D, and the serum concentration of 25-OH D is reflective of total body vitamin D status. The half-life of 25-OH D is about 2–3 weeks, much longer than that of the active metabolite, 1,25-OHD, which has a serum half-life of only

4 hours. There is physiological and epidemiological evidence that an optimal serum level of serum 25-OH D is higher than the serum 25-OH D concentration of 50 nmol/L (20 ng/ml) that has been proposed by the Institute of Medicine as "sufficient." Although a serum level of 20 ng/ml is adequate to prevent osteomalacia or rickets, several studies suggest that concentrations of at least 75 or 80 nmol/L (30–32 ng/ml) are necessary for optimal intestinal absorption of calcium and avoidance of secondary hyperparathyroidism. Based on studies of mineral metabolism in adults, the following serum levels of 25-OHD have been suggested as criteria for vitamin D status:
<12.5 nmol/L (5 ng/ml): severe vitamin D deficiency
<50 nmol/L (20 ng/ml): vitamin D deficiency
50–80 nmol/L (20–31 ng/ml): vitamin D sufficiency
80–200 nmol/L (32–80 ng/ml): optimal vitamin D status
>250 nmol/L (100 ng/ml): vitamin D excess
>375 nmol/L (150 ng/ml): vitamin D intoxication

STRATEGIES FOR DIAGNOSIS

The clinician should suspect hypoparathyroidism when hypocalcemia occurs in the presence of low or normal serum concentrations of PTH. By contrast, patients with hypocalcemia and elevated serum levels of PTH have secondary hyperparathyroidism, and are likely to have vitamin D deficiency or (less commonly) pseudohypoparathyroidism. It is important to recognize that it is inappropriate for the serum PTH level to be "normal" in the presence of hypocalcemia, and this relationship implies abnormal parathyroid function. Decreased parathyroid "reserve" is present in many patients with DGS who "outgrow" clinical hypoparathyroidism, but who may experience transient hypocalcemia when calcium demands are high (e.g., rapid growth). Similarly, patients with thalassemia who have had multiple blood transfusions can develop parathyroid insufficiency due to deposition of iron in the parathyroid glands and will be at risk of symptomatic hypocalcemia during periods of stress or illness. An important biochemical concomitant of hypoparathyroidism is hyperphosphatemia, which occurs as a consequence of deficient PTH-dependent renal excretion of phosphorus. The serum concentration of PTH provides a useful clue to distinguish hypoparathyroidism from pseudohypoparathyroidism, a condition characterized by target tissue resistance to PTH and high rather than low PTH concentrations.

Patients with hypoparathyroidism will have normal levels of serum alkaline phosphatase and 25-OHD, but serum concentrations of 1,25-OHD will be low because of the lack of PTH-induced conversion of 25-OHD to the fully activated form, 1,25-OHD. Serum magnesium levels should always be checked.

These findings are in contrast to those found in patients with nutritional vitamin D deficiency rickets, where elevated serum levels of PTH activate bone resorption and depress renal tubular reabsorption of phosphate, with consequent hypophosphatemia. Although serum concentrations of 25-OHD are typically low, serum concentrations of 1,25-OHD may be low, normal, or

even elevated. The serum level of bone-derived alkaline phosphatase is usually elevated in proportion to the mineralization defect that results from the low serum levels of phosphate and calcium.

CASE 1

A 70-year-old man presented with a smooth mass in his right buccal mucosa and cervical adenopathy. He was diagnosed with undifferentiated carcinoma of the salivary gland with metastases to cervical lymph nodes and extensive sclerotic bony metastases. He was treated with palliative radiation to the right side of his face and neck. Seven months later, he presented with fatigue, muscle cramps, paresthesias, blurry vision, and ataxia. He has no history of nephrolithiasis.

Laboratories: Total calcium 6.5 mg/dl (normal 8.8–10.4), Albumin 3.8 g/dl (normal 3.5–5.0) Phosphate 2.8 mg/dl (normal 3.5–5.0), Mg 1.8 mg/dl (normal 1.5–2.5), Alkaline phosphatase 985 U/L (normal 20–120), 25-OHD 14 ng/ml, Intact PTH 252 pg/ml (normal 10–65), 1,25-OHD 154 pg/ml (normal 16–56).

CASE 2

A 14-year-old boy has a history of several months of episodic weakness and diarrhea. He also has chronic abdominal pain and muscle cramps and has been losing weight.

His past medical history is unremarkable; he was healthy previously. His family medical history is negative for endocrinopathies. Physical examination is remarkable for height at 85% percentile, but weight at 25% percentile, sallow color, Tanner 4 pubertal development, and a positive Chvostek's sign.

Total calcium 7.4 mg/dl (normal 8.8–10.4), Albumin 3.6 g/dl (normal 3.5–5.0), Phosphate 28.4 mg/dl (normal 3.5–5.0), Alkaline phosphatase 97 U/L (normal 20–120), 25-OHD 35 ng/ml, Intact PTH 6 pg/ml (normal 10–65), 1,25-OHD 154 pg/ml (normal 16–56), Spot urine calcium/creatinine ratio 0.21 (high; suggesting >200 mg Ca in urine per 24 hours)

Additional studies: Creatinine. 1.1 mg/dl (normal 0.7–1.2),Hemoglobin 10.4 g/dl (normal 12.0–15.0),Normal anti-tissue tranglutaminase antibodies

Gene testing: Normal CASR gene

AIRE gene: homozygous for the common British mutation 964del13

ANSWERS

The major differential diagnoses in the first case are vitamin D deficiency, idiopathic hypercalciuria, pseudohypoparathyroidism, and the much less common diagnosis of osteoblastic hypocalcemia. In this patient with hypocalcemia and hyperparathyroidism, the mechanism of hypocalcemia is one of the following: a) inadequate absorption of calcium in the gut that is most commonly due to vitamin D deficiency or lack of vitamin D effect (pseudohypoparathyroidism); b) "renal leakage" of calcium due to idiopathic hypercalciuria; or c) markedly increased osteoblastic activity due to tumor. The patient's hypocalcemia and compensatory hyperparathyroidism are out

of proportion to the low levels of 25-OHD and should prompt the clinician to suspect another cause. Pseudohypoparathyroidism is associated with hyperphosphatemia because of the resistance to PTH effect; this patient has a low serum phosphate that virtually excludes pseudohypoparathyroidism. Idiopathic hypercalciuria seldom causes significant hypocalcemia, and it is often associated with nephrolithiasis, which this patient does not have. Osteoblastic hypocalcemia should be considered in this patient with multiple sclerotic bony metastases because the increased osteoblastic activity in the areas of sclerotic bone may cause hypocalcemia and compensatory hyperparathyroidism by markedly increasing calcium uptake. In osteoblastic hypocalcemia, compensatory secondary hyperparathyroidism results in a low serum phosphate, decreased 25-OHD levels due to increased conversion of 25-OHD to 1,25(OH)2, and low urinary calcium levels. Measurement of urine calcium would distinguish idiopathic hypercalciuria from osteoblastic hypocalcemia.

This patient with osteoblastic hypocalcemia was successfully treated with palliative chemotherapy and radiotherapy to his bone metastases plus a combination of intravenous calcium gluconate to manage his acute, symptomatic hypocalcemia, plus oral calcium carbonate, vitamin D, and calcitriol. Acute, symptomatic hypocalcemia is an indication for intravenous calcium, but chronic hypocalcemia in the absence of symptoms and signs of tetany should not be treated with intravenous calcium.

This 14-year-old boy likely has autoimmune hypoparathyroidism. Hypocalcemia plus hyperphosphatemia suggest inadequate PTH secretion or effect. Low PTH levels confirm the diagnosis of hypoparathyroidism; even a normal PTH level would be inappropriate and would suggest the diagnosis of hypoparathyroidism. Hypo- and hypermagnesemia must be excluded as a cause of hypoparathyroidism. Other etiologies for acquired hypoparathyroidism include neck surgery (with infarction of the parathyroid glands), neck radiation, congenital lack of parathyroid gland development, and very rarely parathyroid gland infiltration with iron, copper, or tumor. The subacute presentation at age 14 years excludes congenital hypoparathyroidism. In this patient with no history of neck surgery or radiation, autoimmune hypoparathyroidism is the likely etiology. The relative hypercalciuria in this patient suggests production of antibodies that activate the CASR on parathyroid and kidney cells, thereby replicating autosomal dominant hypocalcemia due to activating mutations of CASR geme. In most patients with polyglandular autoimmune endocrine deficiency type 1, the parathyroid antibodies are cytotoxic.AIRE gene mutations are associated with autimmune hypoparathyroidism and polyglandular autoimmune endocrine deficiency syndrome type 1: hypoparathyroidism, mucocutaneous hypoparathyroidism, adrenal insufficiency, and skin abnormalities (vitiligo and alopecia). Occasionally, these patients with polyglandular autoimmune endocrine deficiency syndrome type 1 also present with primary gonadal failure, thyroiditis, and/or type 1 diabetes mellitus. Other features of this autoimmune endocrinopathy syndrome that may account for some of this patient's symptoms include hepatitis, pernicious anemia, and malabsorption. Most patients with this autoimmune syndrome present in childhood, but some or all of the

endocrinopathies may present in early adulthood. Management of hypocalcemia is similar to Case 1. Interestingly, many of these patients "outgrow" their hypoparathyroidism although they have decreased parathyroid reserve as adults and may develop acute hypocalcemia during major illnesses.

Acute neuromuscular spasm or seizures are treated urgently with intravenous administration of 10% calcium gluconate solution, 0.5 ml/kg up to a maximum 10 ml over 15 minutes. This may be repeated if spasms are not controlled after the first bolus. After controlling the hypocalcemia-induced spasms, a continuous infusion of 500 mg calcium gluconate/kg/24 hours should be started in neonates. A continuous infusion of 1 to 3 mg of elemental calcium per kg/hour should be started for infants and older children. Because too rapid an infusion of calcium can induce bradycardia, all patients should be monitored by electrocardiogram. Serum magnesium levels may indicate a need for supplemental magnesium administration, which may subsequently normalize parathyroid secretion, especially in neonates or premature infants.

Because PTH deficiency is associated with impaired synthesis of 1,25-OHD, long-term treatment of hypoparathyroidism requires administration of calcitriol, 50 to 90 nanograms/kg/day in 2 to 3 divided doses. Supplemental calcium (requirements vary with age) should be given with meals to provide a constant source of calcium and to reduce gastrointestinal absorption of phosphorus. Under some circumstances it may be reasonable to consider daily injections of recombinant human PTH instead of treatment with calcitriol. Patients with hypoparathyroidism have increased urinary calcium excretion in relation to serum calcium and are therefore prone to hypercalciuria, and this is particularly true for patients with activating mutations of the CASR gene. Serum and urinary calcium levels should be monitored regularly, and those patients with hypercalciuria (greater than 4 mg/kg/24 hours calcium), who are at greatest risk of nephrocalcinosis and nephrolithiasis, should have renal ultrasound examinations annually.

Suggested Reading

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7 Normocalcemic Hyperparathyroidism

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Primary hyperparathyroidism is a common disorder, and the great majority of patients are discovered because of evaluation for hypercalcemia. However, serum parathyroid hormone (PTH) may be measured in a number of other clinical settings. Probably the most common situation in which PTH would be measured would be in the evaluation of a patient with osteoporosis. The clinician occasionally will encounter patients with completely normal serum calcium levels but elevated serum levels of PTH. It is important to determine why the patient has an elevated PTH, because it may be the first sign of primary hyperparathyroidism. Such patients might have some of the sequelae of hyperparathyroidism or may develop them later. Therefore, separating mild primary hyperparathyroidism from other causes of normocalcemic hyperparathyroidism is important.

BARRIERS TO OPTIMAL PRACTICE

Clinicians need to know which tests constitute a reasonable evaluation of the patient who may have normocalcemic hyperparathyroidism. In addition, primary care clinicians may need guidance in deciding how to follow patients with this disorder and which patients may have indications for parathyroidectomy.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- List potential causes of elevated PTH levels with normal serum calcium concentrations
- Outline an evaluation of patients with such findings
- Determine a long-term follow-up plan for patients with normocalcemic hyperparathyroidism

STRATEGIES FOR DIAGNOSIS AND MANAGEMENT OF NORMOCALCEMIC HYPERPARATHYROIDISM

In the bad old days, primary hyperparathyroidism presented often as severe cases of "stones, moans, bones, or groans." With the advent of routine chemistry testing, most cases were identified as relatively asymptomatic hypercalcemia, although the classic symptoms would lead to an earlier diagnosis than in the past, when serum calcium testing was not so readily available. The ability to

measure parathyroid hormone (PTH) accurately improved our diagnostic abilities in patients with hypercalcemia. However, PTH has been measured in other settings. Despite no definitive evidence that PTH is a cost-effective test in patients presenting with a fragility fracture or after bone mineral density testing by dual energy x-ray absorptiometry (DXA), many patients will have PTH measurements performed as part of their osteoporosis evaluation. Some experts use the PTH measurement to help determine if the patient's 25-hydroxyvitamin D (25-OHD) level is adequate, because they have more faith in the PTH assay than the vitamin D assay. The thinking is that, if the PTH is elevated with even a mildly low 25-OHD level, it would be important to replace vitamin D before retesting PTH and before starting osteoporosis therapy. Some patients with a fragility fracture or with osteoporosis diagnosed by DXA will have an elevated PTH level despite a normal serum calcium level and normal 25-OHD level. Some of these patients will have early primary hyperparathyroidism (normocalcemic primary hyperparathyroidism).

As is illustrated in the cases below, there are disorders other than early or mild primary hyperparathyroidism that present with normocalcemic hyperparathyroidism, and distinguishing the cause of normocalcemic hyperparathyroidism is important for prognosis and treatment. Probably the most common cause of normocalcemic hyperparathyroidism is a low serum 25-OHD concentration. However, as demonstrated by debate about the Institute of Medicine (IOM) report on calcium and vitamin D, there is controversy about the definition of a normal serum 25-OHD level. The IOM concluded that a serum level of 20 ng/ml (50 nmol/L) was sufficient for bone health of the general population. Because of potential problems with the 25-OHD assays and differing individual threshold needs for vitamin D, many osteoporosis experts believe that 30 ng/ml (75 nmol/L) would be a better target for patients with osteoporosis. In one histomorphometric study, all evidence of osteomalacia was eliminated only if the patients had vitamin D levels above 30 ng/ml. Thus, for the patient with osteoporosis by DXA or after a fragility fracture, it would be reasonable to check the PTH level only after the 25-OHD level has reached 30 ng/ml.

After vitamin D has been replenished, what else should the clinician think about in the patient with osteoporosis (either by DXA or fragility fracture) with a normal serum calcium and elevated PTH level? If the patient has a history of calcium-containing kidney stones, an idiopathic hypercalciuric disorder is a possible explanation for normocalcemic hyperparathyroidism. Idiopathic hypercalciuric disorders are more common in men, whereas normocalcemic primary hyperparathyroidism has been reported mostly in women. Nonetheless, it is important to distinguish between a hypercalciuric disorder and normocalcemic primary hyperparathyroidism. In studies of normocalcemic primary hyperparathyroidism, most patients do not have hypercalciuria, but some patients have hypercalciuria, although not more than 350 mg/24 hours.

There are two different types of idiopathic hypercalciuria. Idiopathic hypercalciuria due to increased gut absorption of calcium results in suppressed PTH levels and should not be confused with normocalcemic primary hyperparathyroidism. On the other hand, in idiopathic hypercalciuria due to

a "renal leak of calcium," patients have normal serum calcium levels and often have elevated serum PTH levels. Although there are not rigorous studies to prove it, probably the only way to determine whether a given patient has a renal leak of calcium or primary hyperparathyroidism is to follow the patient. If the serum calcium increases, then the underlying problem resides in the parathyroid glands.

Celiac disease is among the causes of osteoporosis and is being diagnosed more often today, even in patients with few or no gastrointestinal symptoms. Many patients will have low vitamin 25-OHD or urinary calcium level, but some will have a normal serum and urine calcium and elevated PTH. Because celiac disease is more frequent than previously thought (maybe as high as 1 in 250 people in certain studies), it is a diagnosis that should be considered in osteoporotic patients who appear not to have many risk factors for osteoporosis. The preferred serological tests for celiac disease are IgA anti-tissue transglutaminase and IgA anti-endomysium antibodies. A small bowel biopsy is necessary to confirm the diagnosis.

Of the other potential causes of elevated PTH with normal serum calcium, secondary hyperparathyroidism from chronic kidney disease is by far the most common. Indeed, the diagnosis of normocalcemic hyperparathyroidism requires normal renal function.

Mild or normocalcemic primary hyperparathyroidism has been best characterized by the group at Columbia University. In their review of cases, patients with decreased renal function, liver disease, hypercalciuria of greater than 350 mg in 24 hours, and use of thiazides or lithium were excluded by definition. About 3/4 of the patients were discovered in the process of evaluating low bone density. A few were referred because of a recent fragility fracture or kidney stones. About 10% had a PTH elevation found as part of evaluation for other complaints. The average age of the patients was 58, and 95% were female. The mean serum calcium (9.4 mg/dl), serum phosphate (3.3 mg/dl), 25-OHD (33 ng/ml) and 24-hour urinary calcium (193 mg) were within normal limits, whereas the mean PTH was 93.5 pg/ml (normal 10–65). DXA tests were in the osteoporotic range in the spine (34%), femoral neck (38%) and distal 1/3 radius (28%). The mean T scores for these three regions of interest were–2.0, –1.8, and –1.7, respectively. More than half of the patients had osteoporosis in at least one region of interest.

The patients were followed for an average of 3 years, during which about 1/5 became hypercalcemic. These women tended to have higher serum and urinary calcium levels at baseline. A small number of patients developed a kidney stone or suffered a fracture. Significant bone loss was found in at least 10% of the patients followed. For those who underwent parathyroidectomy, the histologic findings were similar to those of typical hyperparathyroidism, but the number is too small to make any conclusions about adenoma versus hyperplasia in normocalcemic primary hyperparathyroidism. The Columbia group concluded that, while some patients with normocalcemic hyperparathyroidism may be asymptomatic, the clinical findings of osteoporosis and development of hypercalcemia suggest that identifying this population may have benefit. However, the cost-effectiveness of screening large numbers of asymptomatic

patients by measurement of PTH has not been established and is unlikely.

Based on the information above and studies of laboratory evaluation of patients with osteoporosis, a reasonable (if not proven cost-effective) diagnostic plan can be constructed for patients who present with fracture or low bone density without clear risk factors or explanation. Serum calcium (plus albumin to correct the serum calcium), creatinine (and/or estimated glomerular filtration rate), and 25-OHD plus 24-hour urine calcium are important. After vitamin D is replenished, serum PTH can be considered in such patients. Those with elevated PTH levels will need longitudinal follow-up of serum calcium and clinical surveillance for the manifestations of hyperparathyroidism. Those with normal PTH levels might need antibody measurements for celiac disease. Other secondary causes of osteoporosis will usually have clues in the history and physical examination. The clinician can then decide which additional laboratory tests are needed.

CASE 1

A 62-year-old woman is referred because of declining bone density despite alendronate treatment. Her general history and physical examination are unremarkable. She takes a calcium/vitamin D supplement (600 mg/200 IU) twice a day. By DXA, her spine T score is –2.5, total hip –2.2, and femoral neck –2.7. Her serum calcium is 9.6, phosphate 3.5, albumin 3.7, creatinine 0.7, and PTH 78 pg/ml (normal 10–65). Before referral she had a negative parathyroid scan and some small thyroid nodules on ultrasound exam.

She was referred to a surgeon, who found similar blood test results.

1. ***What test would you order next?***
   A. 25-hydroxyvitamin D

2. ***The level comes back 12 ng/ml. The lab says the normal value is 32 ng/ml. How do you interpret this number, especially in light of the Institute of Medicine report?***
   A. For the population's bone health, 20 ng/ml is considered adequate. A case can be made to aim for a higher level in patients with known osteoporosis.

3. ***Does this patient have normocalcemic primary hyperparathyroidism?***
   A. No. It is likely that the patient has secondary hyperparathyroidism due to vitamin D deficiency. In any case, the first thing to do will be to increase the patient's vitamin D intake and bring the serum 25-OHD up to about 30 ng/ml. At that point, the serum PTH will likely normalize.

CASE 2

A 55-year-old woman is referred for a very low bone density by DXA: her T scores are spine –3.6, total hip –2.2, and femoral neck –2.2. She has no history of fracture or renal stones, no gastrointestinal symptoms, and no other medical problems. She eats a normal diet. Her mother suffered a forearm fracture; a child has type 1

diabetes mellitus. On exam she is 5 feet 1 inch tall and weighs 98 lbs. Otherwise the exam is normal.

Lab exam reveals normal results except an elevated PTH: serum calcium 9.1, phosphate 4.3, albumin 4.4, creatinine 0.5, hemoglobin 12, PTH 113.2, 25-OHD 44 ng/ml, 24-hour urine calcium 163 mg.

1. ***Is there anything else worth checking before making the diagnosis of normocalcemic primary hyperparathyroidism?***
   A. Yes. The patient should be checked for celiac disease because it can be relatively asymptomatic. Her tests were positive and were confirmed by a biopsy.

2. ***How often is celiac disease found among osteoporotic women?***
   A. In one study, 3.4% of osteoporotic women had celiac disease, whereas in the control group, the prevalence was 0.2%.

3. ***When should you suspect celiac disease?***
   A. Be alert for this disorder in patients who seem to have no explanation for relatively early osteoporosis or fracture. Celiac disease is more common than previously thought.

      Most patients with celiac disease have low serum 25-OHD levels; this patient was unusual.

CASE 3

A 72-year-old man was in a screening study for osteoporosis in men, although he was known to have COPD and prostate cancer. His spine T score was –2.1, total hip –2.6, femoral neck –2.8, and forearm –2.3. On history he had a traumatic rib fracture and was on omeprazole for peptic ulcer disease, but he had not received androgen deprivation therapy. He had no history of kidney stones. Lab tests revealed: serum calcium 10.1, phosphate 3.3, albumin 4.2, 25-OHD 37.1 ng/ml, PTH 70. His urine calcium to creatinine ratio was mildly elevated.

1. ***Does this patient have normocalcemic hyperparathyroidism?***
   A. Probably yes. It would be important to determine if he had significant hypercalciuria because idiopathic hypercalciuria due to a renal leak of calcium can cause both low bone mass and mild secondary hyperparathyroidism. Hypercalciuria due to increased gut absorption of calcium will suppress serum PTH levels. It will be important to follow the patient over time.

2. ***What are his likely serum calcium levels over the next few years?***
   A. It is likely that his serum calcium will remain normal, but there may be an occasional serum calcium level in the high range. It is also possible that he will change into hypercalcemic primary hyperparathyroidism, with more striking elevation of the serum calcium. The chance of this happening in 3 years is about 1 in 5. Thus, longitudinal evaluation will be

necessary. This patient was treated with alendronate and his serum calcium levels were followed.

3. ***Is this a typical patient with normocalcemic hyperparathyroidism?***
   A. No. Most are women, presenting at an average age of 58. Most are being evaluated for osteoporosis because of a fracture or have had a screening DXA. This brings up the question of which patients, or at least women, with osteoporosis should have a PTH level measured after vitamin D is replenished.

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8 Medical Options for Primary Hyperparathyroidism

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SIGNIFICANCE OF THE PROBLEM

Primary hyperparathyroidism (PHPT) remains a very common endocrine disorder that most often presents as an asymptomatic disease. The disease is characterized by hypercalcemia associated with a non-suppressed parathyroid hormone level (PTH) and has been reported to affect up to 0.3% of the general population. There is no controversy that surgery is the treatment of choice for those with symptomatic disease and for those with asymptomatic disease who meet the current surgical criteria. However, there is a cohort of patients who either do not meet surgical criteria, are too ill to undergo surgery, or who refuse surgery and therefore require long-term medical management. The Third International Workshop on Primary Hyperparathyroidism that took place in 2008 published recommendations for diagnosis, monitoring, and surgical and medical management of patients with PHPT. This review uses the recommendations of this workshop as the basis for discussion.

BARRIERS TO OPTIMAL PRACTICE

The lack of symptoms in most patients with PHPT makes patients less likely to follow recommendations for either surgical or medical management. The coexistence of vitamin D deficiency and PHPT can make the diagnosis unclear at times and is often an indication for an endocrine consultation. In addition, successful parathyroidectomy is best performed by an experienced endocrine surgeon, who might not be available in all medical centers.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Discuss the 2008 guidelines for parathyroid surgery in asymptomatic PHPT
- List the 2008 management guidelines for patients with asymptomatic PHPT who do not undergo parathyroid surgery
- Describe the effectiveness of the antiresorptive agents in preventing the skeletal complications of PHPT
- Describe the role of cinacalcet for normalizing PTH and serum calcium and preventing the skeletal complications of PHPT

CASE 1

A 65-year-old Caucasian woman presents for evaluation of hypercalcemia. Her primary care physician has noted that her serum calcium has been in the 10.6–10.9 mg/dl range (normal 8.5–10.5) over the past several years. He has not been

overly concerned because her PTH has been in the normal range of 53–64 pg/ml (10–65 pg/ml). She has no history of renal calculi, no bone pain, and no history of malignancy or fracture. Her only medications are calcium carbonate 500 mg with 400 IU of vitamin D once daily, a MVI and ibuprofen prn. There is no family history of hypercalcemia and nothing to suggest that she is at risk for MEN syndrome.

Further evaluation includes the following:

- *Serum calcium*—10.8 mg/dl (normal 8.5–10.5), Albumin = 4.0 g/dl (normal 3.5–5.0)
- *Serum phosphate*—2.8 mg/dl (normal 3.5–5.0), Creatinine = 0.9 mg/dl (normal 0.5–1.3)
- *PTH—78 pg/ml* (normal 10–65 pg/ml)
- *25-hydroxyvitamin D*—31 ng/ml (normal 10–45 ng/ml)
- *24-hour urine calcium*—275 mg (normal <250)
- *DXA: Lumbar spine T score*— –2.3; Total hip T score = –1.9; Forearm T score = –2.0

You tell the patient that she has asymptomatic PHPT because she has reproducibly mild hypercalcemia with an inappropriately normal (non-suppressed) to increased PTH level. The patient's high urine calcium rules out familial hypocalciuric hypercalcemia (FHH) as a cause of her hypercalcemia. At this point you recommend treatment.

1. ***Does this patient meet surgical criteria for asymptomatic PHPT?***
   A. The 2008 guidelines for surgery in asymptomatic PHPT include the following:
      - Serum calcium >1.0 mg/dl (0.25 mmol/liter) above upper limit of normal
      - 24-hour urine calcium: not a criterion [although some physicians still regard 24-hr U Ca > 400 mg/dl (10 mmol/dl) as an indication for surgery]
      - Creatinine clearance (calculated) < 60 ml/min
      - BMD T score ≤ –2.5 at any site and/or previous fracture fragility (Z score for premenopausal women and men <50 yr)
      - Age <50 yr

Based on these guidelines, this patient does not meet surgical criteria. It is important to remember that these are general guidelines and that each patient should be considered individually because there are some patients who will benefit from parathyroidectomy even though they do not strictly meet the criteria for surgery. Vitamin D insufficiency is as common in patients with PHPT as it is in the general population and may be associated with higher PTH levels, larger tumors, and accelerated bone turnover. Therefore, routine measurements of 25-hydroxyvitamin D levels are recommended. There is no consistent definition of vitamin D deficiency in the literature, but replacement of vitamin D

to at least 20 ng/dl is indicated before making any medical or surgical decisions for the management of PHPT. In the past, there have been some concerns that aggressive replacement of vitamin D would worsen the disease. There is recent evidence that suggests that vitamin D can be replaced without worsening hypercalcemia. In general, PHPT patients require at least as much vitamin D as those who do not have the disease, and calcium-restricted diets, as were proposed in the past, are harmful. However, the optimal dose and safe upper limit for vitamin D replacement in PHPT have not been established. All patients on vitamin D replacement, and particularly those with PHPT, should have close monitoring of serum calcium. Additionally, it is prudent to monitor urinary calcium excretion during vitamin D replacement in PHPT patients who are high at baseline. There are no data available on the effects of long-term vitamin D replacement in PHPT. Significant or refractory vitamin D deficiency and PHPT would be an indication for a referral to an endocrinologist.

In addition, renal imaging is recommended if kidney stones are suspected. Ultrasound is the first-line recommendation, followed by CT if indicated. It is also recommended that a 24-hour urinary calcium be obtained at as a part of the initial evaluation to help in ruling out familial hypocalciuric hypercalcemia (FHH) as a cause of mild hypercalcemia.

2. ***If surgery is not recommended, with what and how frequently will you monitor this patient?***
   A. The 2008 guidelines for management of patients with asymptomatic PHPT* who do not undergo parathyroid surgery are as follows:
      - Serum calcium: Annually
      - 24-hour urinary calcium: Not recommended
      - Serum creatinine: Annually
      - Bone densitometry: Every 1–2 yr (3 sites)
      - Abdominal X-ray/USG Not recommended

      (*These guidelines only apply to patients who remain asymptomatic and do not apply to patients who develop new symptoms or clinical evidence of disease progression.)

The patient is relieved that she does not meet surgical criteria but you are both concerned about her low bone density and would like to prevent further bone loss in the future.

3. ***How effective are the antiresorptive agents in preventing bone loss in patients with PHPT?***
   A. Although large placebo-controlled trials have not been done to determine the role of bisphosphonates for the prevention of bone loss in PHPT, there are a number of small studies that show them to be effective in PHPT. There have been several very small studies done with clodronate, pamidronate, and risedronate, but alendronate is the bisphosphonate that has been evaluated most extensively. These studies

consistently show that alendronate suppresses markers of bone turnover and increases BMD in the hip (4.0–4.8%) and lumbar spine (3.8–8.6%) with no change in the forearm when given to men and women over 1–2 years. Some, but not all, of the studies report an early transient decrease in serum calcium and increase in PTH with bisphosphonate therapy. This inconsistent effect may have be attributable to low vitamin D levels that were not consistently measured in the studies. It is hypothesized that the bisphosphonate-induced fall in bone resorption results in the fall in serum calcium in the face of vitamin D deficiency. This may further stimulate PTH production. However, there does not appear to be a sustained bisphosphonate effect on serum calcium, PTH, or urinary calcium. Fracture outcomes have not been evaluated.

Estrogen is another antiresorptive agent effective in the treatment of postmenopausal osteoporosis. Because PHPT is most common in postmenopausal women, it is not surprising that hormone therapy (HRT) has been studied in PHPT. Early studies with conjugated equine estrogens, ethinyl estradiol, and norethisterone lowered total serum calcium without a change in PTH in small groups of postmenopausal women with PHPT. Subsequent studies report similar changes in total calcium with no change in ionized calcium or PTH, indicating that the fall in total calcium is likely due to the HRT effects on the fraction of protein and anion-bound calcium and possible hemodilution. HRT reduces markers of bone turnover in PHPT, and one study has demonstrated a positive effect on bone density (lumbar spine +6.6%, hip +3.4%, forearm +5.4%) compared to placebo. Other studies comparing HRT to surgery show that the magnitude of HRT effects on bone is similar to those that occur after parathyroidectomy.

Raloxifene, a selective estrogen receptor modulator (SERM), has been studied in two small trials in postmenopausal women with PHPT. Similar to HRT, raloxifene resulted in a small decrease in serum calcium with no effect on PTH. Ionized calcium was not measured. Although there was a decline in markers of bone turnover, the magnitude was much smaller than that observed in response to HRT. There have not been any controlled trials measuring the effect of raloxifene on bone density in women with PHPT.

Given the ongoing concerns with HRT in postmenopausal women, the bisphosphonates are the first-line therapy to treat the skeletal complications in patients with PHPT who do not undergo surgery. They would be appropriate in the patient in Case 1. It is important to remember that the site of greatest bone loss in PHPT is often the forearm. This site should be included when obtaining a DXA in patients with PHPT.

CASE 2

An 83-year-old male is referred for evaluation of PHPT. The patient has a history of hypercalcemia for at least 4 years and has been previously evaluated and diagnosed with PHPT.

Recent labs:

- *Serum calcium*—11.9 mg/dl (normal 8.5–10.5), Albumin = 4.7 g/dl (normal 3.5–5.0)
- *Serum phosphate*—3.7 mg/dl (normal 3.5–5.0), Creatinine = 0.6 mg/dl (normal 0.5–1.3)
- *PTH*—95 pg/ml (normal 10–65 pg/ml)
- *25-Hydroxyvitamin D*—48 ng/ml (normal 10–45 ng/ml)
- *24-Hour urinary calcium*—275 mg (normal <250)
- *DXA: Lumbar spine T score*— –3.9; Total hip T score = –1.8; Forearm T score = –3.6

This represents a significant decline (10%) compared to his previous scan 2 years ago.

He denies a history of renal calculi. He has no known adult fractures but he has lost 2 ½ inches in height. He has been on alendronate 70 mg/week and calcium carbonate 1500 mg/day for the past year.

Medications: alendronate, calcium carbonate, atenolol, tamsulosin, and glucosamine.

PMH: The patient has recently been evaluated for diarrhea and weight loss and has been placed on a gluten-free diet. He has a history of benign prostatic hyperplasia. He complains of fatigue and back pain as well as nocturia. He is not interested in surgery except as a last resort.

What is the role of cinacalcet in normalizing PTH and serum calcium and preventing the skeletal complications of PHPT?

A. Cinacalcet, the first approved calcimimetic agent, works on the calcium-sensing receptor (CaSR) in the parathyroid cell by increasing the sensitivity of the receptor to extracellular calcium and therefore inhibiting PTH secretion and gene transcription and parathyroid cell proliferation. In an early trial, cinacalcet was tested in a placebo-controlled trial in escalating doses as a bid dose for 2 weeks in patients with mild PHPT. Over all, the combined doses resulted in a 16% decline in serum calcium and a 35–50% decline in PTH 4 hours after administration, but the levels both returned to baseline by the next dose. A larger 52-week study in 78 patients with PHPT was done to determine the effects of cinacalcet on biochemical parameters as well as markers of bone turnover and bone density. Twice daily cinacalcet either lowered or normalized serum calcium in 73 % of patients treated during the study. This was accompanied by a fall in PTH of 13% and a slight but significant increase in serum phosphorus. There were no changes in 1,25-hydroxy-vitamin D levels, urinary calcium excretion, markers of bone turnover, or bone density. This study was followed by a 4.5-year open-label extension. During this extension phase, the serum calcium was maintained in the normal range in all of the patients, with a 1–21% decrease in PTH, but there was no effect on bone density. Cinacalcet was recently approved for the treatment of PHPT in the United States in patients with

severe hypercalcemia who are unable to undergo parathyroidectomy. Consultation with an endocrinologist would be appropriate for help with management of severe hypercalcemia.

CONCLUSIONS

The surgical criteria and monitoring recommendations have been updated for patients with asymptomatic PHPT. For those who do not meet surgical criteria or for those who cannot or will not undergo surgery, medical options for treating the skeletal complications and hypercalcemia of PHPT should be considered. The bisphosphonates and HRT can effectively decrease bone turnover and increase BMD in patients with PHPT as much as is seen with parathyroidectomy. Neither the bisphosphonates nor HRT significantly lowers serum calcium or PTH levels during long-term therapy, so these agents should be reserved for patients who are unable to undergo parathyroidectomy and who are at high risk for skeletal complications due to PHPT. The effects of the antiresorptive agent raloxifene, a SERM, on BMD have not been studied in PHPT, and there are no fracture studies any of the antiresorptive agents in cohorts of patients with PHPT. In patients in whom hypercalcemia is a primary concern, the calcimimetic cinacalcet can be considered for long-term lowering of serum calcium and PTH. This agent, however, does not appear to have beneficial effects on bone density. In all patients with PHPT, it is important to replace vitamin D before making a decision about medical or surgical therapy. It is critical to avoid significant volume depletion, immobilization, and thiazide diuretics, as they may significantly worsen hypercalcemia.

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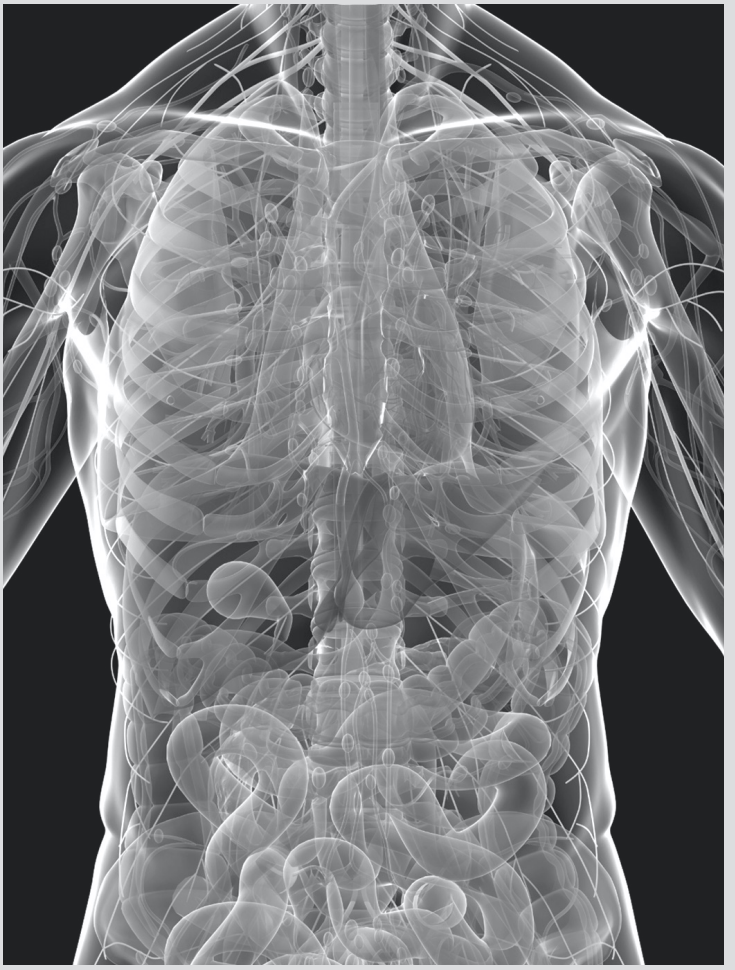
DIABETES MELLITUS



9 Monogenic Diabetes:

Who Needs MODY Screening?

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SIGNIFICANCE OF THE CLINICAL PROBLEM

MODY stands for maturity-onset diabetes of the young, now better thought of as a subset of the monogenic diabetes syndromes. It is defined as non-obese diabetes with onset before the age of 25, with demonstration of dominant familial inheritance. However, the terminology is undergoing revision.

Recent cases and extensions of the phenotypes resulting from mutations in MODY genes show this definition is too restrictive both in terms of age of onset and familial expression.

Best estimates, although limited in scope, suggest that MODY forms account for 2–3% of all diabetes. There are few data on the prevalence of monogenic forms of diabetes in most regions. At the lower end, it has been suggested that collectively they may account for up to 1–2% of all cases [5]. In the United States, where the total number of cases of diabetes in 2010 was estimated to be 25.8 million people [10], there could be 240,000–600,000 individuals with a monogenic form of diabetes [5].

BARRIERS TO OPTIMAL PRACTICE

- Diagnosis depends on recognition of the syndrome. Lack of family history does not rule out a de novo mutation.
- Tests for antibodies indicative of autoimmune type 1diabetes are best done at diagnosis (anti-GAD, anti-IA2, anti-ICA, anti-ZnT8, and anti-insulin antibodies, as available, should be considered).
- Barriers to genetic testing:
  A. Lack of insurance coverage, a very high co-pay, or large out-of-pocket expense may limit availability of genetic studies
  B. Uncertainty about which genes to have sequenced
     ◊ Uncertainty about how to interpret results
     ◊ Uncertainty about how to follow up negative or ambiguous sequence results
     ◊ Limited access to genetic counselor
  C. Limited access to expertise and longitudinal follow-up of families

with monogenic diabetes

◊ Optimal diagnosis and management of monogenic diabetes require ready access to experts in monogenic diabetes and programs for long-term follow-up of these patients. We have partially addressed the need for long-term follow-up through the use of registries. Two notable registries are maintained at the University of Chicago: www.kovlerdiabetescenter.org, www.monogenicdiabetes.org and at Exeter/Peninsula Medical Center: www.diabetesgenes.org

A list of laboratories that carry out clinical genetic testing for monogenic forms of diabetes, such as Athena Diagnostics, can be found at www.genetests.org.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Identify likely candidates for testing for monogenic diabetes
- Know the most common forms of monogenic diabetes in adults and children
- Understand key aspects of treatment for glucokinase diabetes/MODY2
- Appreciate the use of sulfonylureas in MODY3 and 1
- Appreciate the need for renal and uterine evaluation in HNF1B/MODY5 diabetes

OVERVIEW OF MODY AND MONOGENIC/ATYPICAL DIABETES MELLITUS

MODY is often misdiagnosed as type 1 or type 2 diabetes. However, a correct genetic diagnosis impacts treatment and identifies at-risk family members. An analysis from a health economic view point (see References) recently demonstrated the importance of making a diagnosis of neonatal diabetes, and a similar improvement in overall health and lower cost with fewer complications are likely to arise from making a MODY diagnosis as well. Thus, it is important to consider a diagnosis of MODY in appropriate individuals and to pursue genetic testing to establish a molecular diagnosis.

Maturity-onset diabetes of the young (MODY) is a clinically heterogeneous group of monogenic disorders characterized by autosomal dominant inheritance of young-onset, non-insulin dependent diabetes. Together, monogenic forms are estimated to cause about 2% of all diabetes cases. The genes involved are important in beta cell development, function, and regulation and lead to disorders in glucose sensing and insulin secretion. Most of the genes involved are transcription factors that have effects in beta cell development but can also have various effects in other tissues in which they are expressed. They may also have effects on function of the cells. The term MODY itself, while popular, obscures the genetic heterogeneity of these types of diabetes, and a change to terminology to the specific gene name has been advocated (e.g., HNF1A diabetes replaces MODY3). New gene mutations, deletions, duplications, and methylation defects can also cause MODY-like diabetes, so that a revised terminology should be more informative than MODY-X.

The term MODY (maturity-onset diabetes of the young) has been used to describe a monogenic form of non-insulin dependent diabetes presenting usually before age 25 years [7-9]. Since MODY now includes at least seven separate subtypes [5] that differ as to presentation, treatment, and associated conditions, we will follow the suggestions of Fajans et al.[1] and Murphy et al.[5] and describe them based on their gene names.

An important special case is that of GCK mutations. Heterozygous GCK (glucokinase) mutations cause impaired glucokinase activity or function (MODY2). These mutations result in stable, mild hyperglycemia due to the roles GCK plays in both insulin secretion and hepatic glucose regulation. GCK diabetes is usually non-progressive and rarely requires treatment. In children and younger adults, GCK mutations are the most likely to be diagnosed, since they cause fasting hyperglycemia from a very early age. GCK mutations can also cause hypoglycemia, so it is important to request the appropriate genetic interpretation.

HNF1A mutations (MODY3) are the most common cause in young adults, leading to a progressive insulin secretory defect that is sensitive to oral sulfonylureas. Such treatment most often results in improved glycemic control compared to other diabetes, but hypoglycemia may occur even at very low doses. Still, sulfonylureas at very low doses when effective are the preferred treatment.

MODY due to mutations in the HNF4A gene results in a similar phenotype, including sensitivity to sulfonylurea treatment, even though the transfer factor activity of HNF4A is important at an earlier stage of development than HNF1A. HNF1B mutations (especially deletions) most frequently cause developmental renal disease (particularly renal cysts) but may also cause MODY in isolation. HNF1B defects underlie the “renal cysts and diabetes syndrome” (RCAD syndrome) and may also cause uterine abnormalities.

Mutations in the genes NEUROD1, PDX1 (IPF1), INS and CEL are other rare causes of MODY. While the first two are transcription factors, INS is the insulin gene itself. While INS mutations usually cause neonatal diabetes, later onset diabetes has occurred. CEL is primarily an acinar pancreas disease with pancreatic atrophy caused by mutations in carboxyl-ester lipase and is very rare.

Several recent reviews have discussed the genetics of neonatal diabetes and other forms of monogenic diabetes. They can be consulted for more detailed information [1–6, 15–18]. In addition, several excellent websites are continually updated and will provide new information about the diagnosis and management of monogenic forms of diabetes :www.diabetesgenes.org , www.monogenicdiabetes.org , and www.diabetes.niddk.nih.gov/dm/pubs/mody/.

The challenge is to identify those individuals whose diabetes is monogenic in origin. In some cases it may be familial, whereas in others it may be sporadic; i.e. a result of a de novo mutation. However, individuals whose diabetes is due to a de novo mutation are also carriers, and diabetes will be familial in subsequent generations.

Mutations in genes thought to be exclusively related to permanent and transient neonatal diabetes are also important to consider in some patients with MODY-like presentations [17–18]. Neonatal diabetes mellitus is a rare form of

diabetes diagnosed in infancy. Nearly half of patients with permanent neonatal diabetes have mutations in the genes for the ATP-sensitive potassium channel (KCNJ11 and ABCC8) that allow switching from insulin to sulfonylurea therapy. Although treatment conversion from insulin therapy to oral agents has dramatic benefits, the cost-effectiveness of routine genetic testing is unknown. We recently showed that making a diagnosis of neonatal diabetes improves quality of life and lowers costs. A case study [21] highlights the potential economic impact of applying the concepts of personalized genetic medicine to other disorders in the future.

STRATEGIES FOR DIAGNOSIS AND THERAPY

Suspicion is absolutely central to making the correct diagnosis. Genetic testing involves sequencing the gene of interest in the proband, including the promoter, protein coding regions, splice acceptor and donor sites, and sites of RNA processing (e.g., polyadenylation). In addition to sequencing, analyses to detect deletions of the gene or parts of the gene may be necessary [11,12]. Since genetic testing can be expensive, >$1000 per gene, knowledge of the relative incidence and key features of the various gene mutations can greatly reduce the expense of testing. Careful and complete family histories will often uncover multiple additional cases. These additional cases can be confirmed with limited single amplicon testing at reduced cost. Referral to centers with expertise in diagnosis and testing can be extremely helpful for interpretation and follow-up of highly suggestive cases with persistently normal testing.

Patients with monogenic diabetes due to mutations in the transcription factor genes HNF1A and HNF4A may be best treated, at least initially, with low doses of oral sulfonylureas, as the beta cells in these patients are particularly sensitive to these agents. Individuals with glucokinase (GCK)mutations have a stable form of impaired fasting glucose with few, if any diabetic complications and they do not usually require any glucose-lowering treatment. Pregnancy is a special, important case and the reader is referred to one of the more comprehensive reviews for an in-depth discussion of the concerns for both mother and child.

A correct diagnosis of monogenic diabetes means that the patient may be spared treatment either with multiple oral agents or intensive insulin regimens, as is often the case when the patients are incorrectly classified. For most patients with a GCK mutation, no specific treatment is usually necessary to achieve HbA1c levels within an acceptable range below 6.5% [13].

For research purposes, our group as well as several others are investigating the use of whole exome sequencing (WES) and whole genome sequencing (WGS) in monogenic diabetes. The cost of these techniques has dropped dramatically in the last 2 years, although the problems in information technology are still formidable. These next generation of sequencing techniques is being studied both as an approach to discover new causes of monogenic diabetes and as a possible standard clinical technique of the future, since it will be more cost effective and possibly faster to sequence the entire exome or even the genome rather than individual genes [19].

CLINICAL PEARLS: WHEN TO SUSPECT A DIAGNOSIS OF TYPE 1 OR TYPE 2 DIABETES MAY NOT BE CORRECT *(Figure 9-1)*

Type 1 Diabetes: Is this the correct diagnosis or not?
The following points raise the possibility that the diagnosis should be reconsidered.

- Diagnosis before 6 months of age is usually not autoimmune diabetes and can be either permanent or transient neonatal diabetes. Rare mutations in the FOXP3 gene cause neonatal polyautoimmune endocrinopathy, which is X-linked (IPEX syndrome).
- In type 1 diabetes, fewer than 1/10,000 cases occur before 6 months of age.
- Family history of a parent with type 1 diabetes suggests the possibility of monogenic diabetes; in type 1 diabetes, fewer than 10% of patients have parents with type 1 diabetes.
- Family history with mixed type 1 and type 2 diabetes. Type 2 diabetes is much more common than monogenic diabetes, when the pedigree suggests many relatives with type 1 and type 2 diabetes or an autosomal dominant pattern of inheritance, monogenic diabetes should be considered.
- Evidence of endogenous insulin/C-peptide production outside the honeymoon period (after 3 years of diabetes). This is still an evolving area, with estimates ranging from fewer than 10% to 30% of true autoimmune diabetes patients having continued detectable C-peptide.
- Pancreatic islet autoantibodies are absent; the majority (70–97%) of patients with type 1 diabetes have islet cell autoantibodies.
- Presentation with diabetic ketoacidosis does not exclude MODY forms; some families with HNF1A or 4A mutations typically present with ketones but are antibody negative and C-peptide positive. Rare cases are recently being reported with both antibody positivity and monogenic diabetes, but these are extremely rare.

Type 2 Diabetes: Is the diagnosis correct or not?
The following points raise the possibility that the diagnosis should be reconsidered.

- If the patient has a normal BMI or is not markedly obese and/or other diabetic family members are of normal weight, a diagnosis of atypical diabetes should be considered.
- Evidence of dominant inheritance or more than two generations of diabetes.
- Family history of gestational diabetes.
- Ethnic background with a low BMI and low prevalence of T2DM.
- No evidence of insulin resistance, with low C-peptide or within normal range.
- History of renal cysts or uterine structural abnormalities.

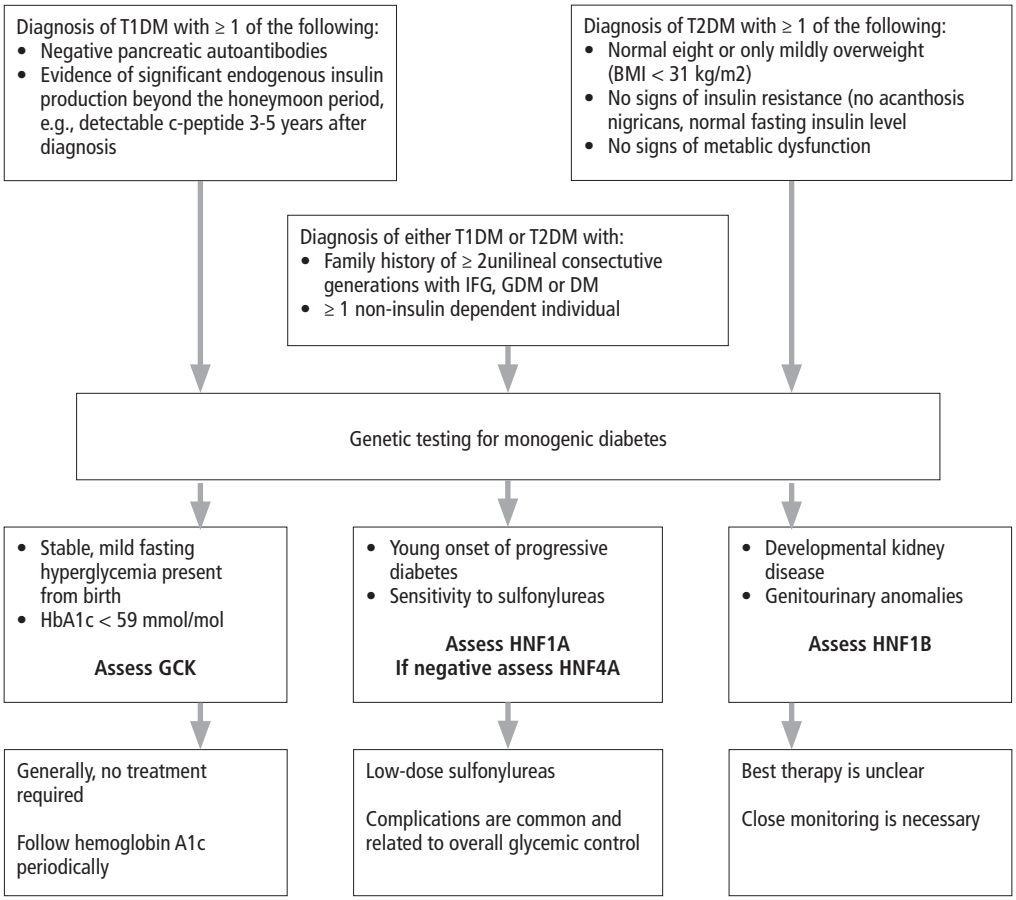

Figure 9-1. Approach to genetic testing for suspected monogenic diabetes. From: Naylor, R., and Philipson, L.H., Who should have genetic testing for MODY? Clin Endo, 2011 in press

CASE 1

The arrow in pedigree 1 *(Figure 9-2)* indicates the propositus, who was 45 years old at the time of presentation. Onset of his diabetes was at age 18, with ketoacidosis. His BMI at age 18 was 18. At various times he had been treated with insulin, metformin, and thiazoladinediones. Autoantibodies against islet antigens were negative, and fasting C-peptide with a blood sugar of 120 mg/dl was at the low end of detectability. He was initially treated with 2.5 mg of glipizide per day for 15 years but more recently has been maintained on a basal/bolus regimen of four insulin injections per day. All of the family members with diabetes were similarly thin, with onset in the late teen years, and DKA was frequent at onset. Nephropathy was present in the index case and several other family members. Most of them were being treated with insulin.

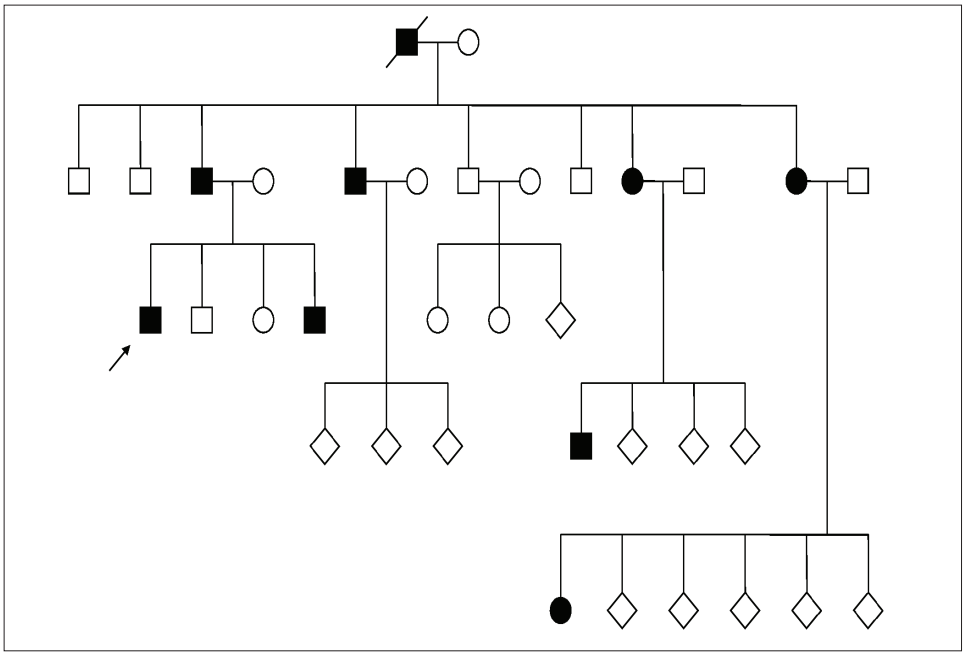

Figure 9-2

DISCUSSION

This case illustrates many key aspects of transcription factor diabetes, including early onset in thin individuals, across several generations, with absent autoantibodies and detectable C-peptide. A sequence evaluation of HNF4A and HNF1A revealed a normal HNF4A but HNF1A carried the S121P mutation, previously published as a cause of HNF1A diabetes (MODY3). A transition to sulfonylurea was attempted but the blood glucose control was suboptimal. The patient eventually stabilized on a basal dose of long-acting insulin in the evening and a sulfonylurea during the day, and this has been stable for several years, with HgbA1c of 6–6.5%. In subsequent years, one of his children, also thin, was diagnosed with diabetes at age 16 and has responded well to low-dose sulfonylurea.

CASE 2

The propositus in this family was 26 years at the time of presentation, *(Figure 9-3)* with a 14-year history of intensive insulin treatment for presumed type 1 diabetes. He was initially diagnosed after a discovery of glycosuria in a sports physical at age 12 and was immediately started on intensive basal/bolus insulin. In the intervening years, he maintained HgbA1c levels of 6–6.5% regardless

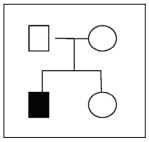

Figure 9-3

of occasional missed doses of insulin. Three different endocrinologists noted absent islet cell autoantibodies and positive C-peptide. His BMI was 20. There was no family history of diabetes.

DISCUSSION

After evaluation, genetic testing was performed and a mutation in HNF1A previously reported to cause MODY3 was revealed. The patient was transitioned to low-dose glyburide treatment. Over the next 3 years, his A1c was maintained between 5.8 and 6.3% without hypoglycemia.

CASES 3 AND 4

In these families, both mother and son were diagnosed with diabetes. In pedigree 3, *(Figure 9-4)* the mother was diagnosed with gestational diabetes with a BMI of 18. The family was of Southern India origin. The son tested a fasting blood sugar at age 18 and was found to be 140 mg/dl without ketones or antibodies, consistent with type 1 diabetes. A pediatric endocrinologist referred him to our group. In pedigree 4, the mother was also diagnosed with gestational diabetes. At the time of referral she was on a program of basal insulin and three classes of oral agents. When her son was 8, he was found to be hyperglycemic and was started on four injections per day. They came to our group for a second opinion before starting the son on an insulin pump.

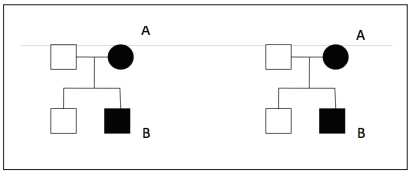

Figure 9-4

DISCUSSION

In both families, genetic testing revealed known mutations in GCK, consistent with MODY2. In family 3, all diabetes medications were stopped and the HgbA1c levels were maintained just above 6%. In family 4, the transition was very difficult, as a large part of their identity was related to having type 1 diabetes. Oral agents and insulin were gradually withdrawn over many months but eventually both mother and son were free of all anti-diabetic therapy and maintained A1c levels of 6.2–6.5%.

Acknowledgments

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10 Difficult Diabetes Cases

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Though diabetes management for the majority of patients is appropriately focused on cardiovascular disease reduction, primary care clinicians and endocrinologists are charged with developing effective approaches to managing glucose levels in a wide variety of complex scenarios. Clinicians need to be thoughtful about the underlying pathophysiology and its effects on insulin resistance and clearance and consider behavioral and therapeutic strategies that help patients achieve whatever glycemic goal is most appropriate for them.

BARRIERS TO OPTIMAL PRACTICE

Diabetes can be a challenging disorder to treat, since the disease has a variety of social and personal impacts that may make it difficult for patients to engage constructively with treatment. As insulin deficiency emerges, erratic glucose levels and difficulty of getting to target A1c can be sources of great frustration for patients. The polypharmacy that is often needed to effectively manage the cardiovascular risk for patients with diabetes can result in problems with adherence and in drug-drug interactions.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Understand reasons why patients hesitate to start insulin, and opportunities to overcome this reluctance
- List common causes of severe insulin resistance, and be able to choose appropriate therapies to attain glucose control
- Interpret HbA1c, anticipate the effect of dialysis on glucose values, and choose appropriate glucose-lowering agents for patients with end-stage renal disease
- Identify some causes of erratic glucose levels, and begin to choose strategies that can lower variability and restore sensitivity to hypoglycemia

CASE 1. INSULIN REFUSAL

A 64-year-old woman with a history of type 2 diabetes for 12 years is referred for diabetes management. She has a BMI of 44, hypertension, hyperlipidemia, osteoarthritis, sleep apnea, and depression. Her A1c is 8.8% despite treatment

with metformin, sitagliptin, and glipizide at maximal doses; she did not tolerate exenatide. Her primary care physician has encouraged her to start insulin, but she has consistently refused, citing a fear of needles. She comes to see you seeking advice on non-insulin diabetes treatments to try.

1. ***Why is the initiation of insulin so challenging for some patients?***
   A. The initiation of insulin therapy is often one of the most difficult obstacles for patients with diabetes to overcome. As many as 75% of type 2 patients beginning a diabetes education program where insulin was to be started were reluctant to do so at first. This psychological resistance involves negative perceptions about insulin that are influenced by past experiences, their understanding of the disease process, the attitudes of others, negative self-perceptions, fear of adverse effects, lifestyle adaptations, and social stigma *(Table 10-1)*. Consequently, both the decision and the therapy may present an emotional and logistical hurdle.

Table 10-1. Causes of psychological insulin resistance

Beliefs about diabetes and insulin
• Belief that insulin causes chronic complications • Insulin is for severe disease • Insulin means that their illness has progressed or is becoming terminal • Consequences of not starting insulin may seem remote • Once on insulin it can never be discontinued
Negative self-perceptions
• Insulin requirement means they have 'failed' to control their disease • Insulin is a punishment for poor self-care • Procrastination and wishful thinking that insulin is not necessary • Belief that they are ill-equipped to handle the daily demands of insulin treatment
Fear of Injections
• Technical concerns that they will hurt themselves • Injections will be painful • Anxiety about the proper technique • Needle phobia
Lifestyle adaptations
• Insulin adds to the burden and stress of a chronic disease • Insulin will result in loss of personal freedom • Insulin will impose new daily restrictions that limit choice
Fear of adverse effects
• Hypoglycemia • Weight gain • Cardiovascular risk
Social Stigma
• Needles and syringes associated with drug addiction and severe illness • Social embarrassment and rejection • Need to hide diagnosis and treatment

A particularly common belief is that insulin, not diabetes, causes serious health problems and severe or chronic complications, because many patients may have witnessed friends' or relatives' health deteriorate at the time of insulin initiation. Patients may also perceive that insulin indicates more severe disease and/or that insulin initiation means that they are becoming sicker and that their disease has dramatically progressed. Clinicians might contribute to these beliefs by creating a perception that the need for insulin reflects the patient's failure to control the disease. This may leave the patient with feelings of failure and guilt and a belief that they will be unable to control the disease in the future, regardless of treatment, and that insulin will not be effective and will not make a positive difference to their overall health.1 Insulin may also be perceived as a threat or punishment, resulting in anger or betrayal, because patients may feel unfairly punished for poor self-care.

2. ***What steps can be taken to overcome psychological insulin resistance?***
   A. Physicians transfer their own beliefs to their patients, so reflection on one's own attitudes to insulin can be a first step in gaining patients' confidence and trust. It is critical to try to understand why a patient is refusing insulin. The issue is often more complex than a patient's first justification, and probing about their views on insulin, their personal observations of others' experiences with insulin, and their thoughts about what it means can be particularly important *(Table 10-2)*.

Table 10-2. Strategies to facilitate initiation of insulin therapy

• Reflect on your own attitudes about insulin
• Understand the barriers your patients perceive. Ask why, probe.
• Acknowledge their fear, communicate your understanding of their dilemma
• Demonstrate an insulin injection in the office
• Suggest a non-committal trial
• Review the short-term symptomatic benefits that accompany improved glycemic control.
• Use the simplest device (e.g., pen with 31G needle)
• Choose an initial regimen with a low risk of hypoglycemia
• Acknowledge and revisit fears and barriers at future visits

A demonstration of an injection in the office using the simplest and smallest device can overcome many of the initial fears. When a patient engages with insulin treatment, other fears or reactions may develop and the patient should be encouraged to share their initial reaction to the treatment in the subsequent months. Even if a patient remains firm in the decision to refuse, continued follow-up, support, and willingness to revisit the decision may provide the psychological space to overcome their fears and engage in what can be a lifesaving treatment.

CASE 2. SEVERE INSULIN RESISTANCE

A 44-year-old man is newly diagnosed with diabetes type 2, hypertriglyceridemia, and a low HDL. He is treated with rosuvastatin 20 mg daily, lisinopril 40 mg daily, and metformin 1g twice daily. Treatment with insulin is initiated with insulin detemir, and the dosage is titrated first to 100 U daily, then to 100 U bid. During this time, the patient engages in a weight management program and his BMI drops from 32 to 31 kg/m2 (217 lbs to 210 lbs) and his A1c drops from 8.6% to 8.3%. LDL is 66 mg/dl and triglycerides are 257 mg/dl. What are your management options?

The prevalence of obesity and diabetes is epidemic. Severe insulin resistance (defined as the need for ≥ 200 units of insulin per day to achieve glycemic control) is commonly seen with obesity and can complicate diabetes management. The management of patients with diabetes who have severe insulin resistance is difficult, and at times frustrating, and requires a multifaceted approach.

For obese patients, weight loss is the best treatment option, but weight loss can be a challenging task for patients to achieve and maintain. Medications that decrease insulin needs like metformin, thiazolidinediones (TZDs), and GLP agonists might help, but many patients still need high doses of insulin. In addition, treatment with TZDs is generally associated with weight gain, particularly when combined with insulin.[1] Bariatric surgery is highly effective for obese patients with severe insulin resistance.

Delivering an appropriate insulin volume to these patients can be difficult and inconvenient and may be best accomplished with U-500 regular insulin by multiple daily injections or with continuous subcutaneous insulin infusion, rather than with standard U-100 insulin.[2] Improved control may occur because of better compliance with dosing (fewer total daily injections) or better insulin action and absorption. U-500 kinetics are similar to pre-mixed or NPH insulin. Many require large doses of insulin, culminating in a transition to U-500 bid in addition to prandial insulin (as this patient eventually did).

CASE 3. MANAGING DIABETES WITH END-STAGE RENAL DISEASE

A 76-year-old woman with type 2 diabetes mellitus was initiated on hemodialysis 4 months ago after presenting with uremic symptoms. Her renal failure was attributed to both diabetes and hypertension. Her oral medications (glyburide and pioglitazone) were discontinued, and she was started on NPH insulin twice daily and erythropoietin. Her A1c has fallen to 6.7% but her glucose levels have been high, typically 200–300 mg/dl, and she has had erratic glucoses ever since. What are your management options?

Patients with chronic kidney disease undergoing maintenance dialysis treatment have a high mortality, currently over 20% per year in the U.S., largely due to cardiovascular events. [3] Though poor glycemic control is associated with a poor outcome in patients with end-stage renal disease (ESRD), the various and opposing effects of ESRD and dialysis can make blood glucose levels fluctuate widely and make control very difficult.

In ESRD, both uremia and dialysis can complicate glycemic control. Uremic

toxins may increase insulin resistance in ESRD, leading to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose utilization. Insulin secretion is blunted in ESRD because of concomitant metabolic acidosis. Renal gluconeogenesis capacity is lost, and insulin clearance is reduced. Hemodialysis further alters insulin secretion, clearance, and resistance as the result of periodic improvement in uremia, acidosis, and phosphate handling.[4, 5]

1. ***How can A1c be interpreted among patients with ESRD?***
   A. According to continuous glucometry data, A1c levels are inappropriately low for the equivalent mean glucose levels in dialysis patients compared to those with normal renal function.6 This is due to the shorter life span of red blood cells, iron deficiency, recent transfusion, and use of erythropoietin-stimulating agents, which cause a falsely low reflection of the patient's glycemic control. In contrast, in a minority of available assays, the A1c can be falsely elevated by ESRD since the formation of carbamylated hemoglobin is enhanced in ESRD and is measured in the assay. Consequently, self-monitored glucose levels remain a primary method of evaluating control in many ESRD patients.

2. ***What are the goals of care for patients with ESRD and diabetes?***
   A. Though higher A1c is associated with increased mortality, the relative contribution of dysglycemia to this risk is modest (HR <1.5 for A1c >10 vs. A1c <6). 3 Consequently, the goals of diabetes care in patients with ESRD are to avoid hypoglycemia and to aim for an equivalent A1c of <7.5% (attainable if fasting glucose is <140 mg/dl and peak post-prandial glucose is <200 mg/dl) *(Table 10-3)*.

Table 10-3. Tips for management of diabetes mellitus in patients with renal disease

ESRD Stage	GFR	Tips for Management
1	>90	Add ACEI/ARB if malb/cre ratio >30 mg/g
2	>60	ACEI/ARB for all
3	>30	Discontinue orals except glipizide, nateglinide, acarbose, GLP1 Reduce dose of DPP4i Refer to nephrology Monitor for anemia (epo if Hgb <9) and hyperpara (start calcitriol if 1,25 vitamin D is low or PTH >2x upper limit of normal)
4	>15	Insulin therapy; continue ACEI/ARB but watch K+
5	<15	Dialysis. Insulin/DPP4i

ACEI: angiotensin converting enzyme inhibitor
ARB: Angiotensin receptor blocker
DPP4i: dipeptidyl dipeptidase 4 inhibitor
Hgb: hemoglobin
K+: potassium
PTH: parathormone
malb/cre: microalbumin to creatinine ratio
GLP1: glucagon-like peptide-1

3. ***How can hyperglycemia be managed among ESRD patients?***
   A. Insulin is the preferred drug, since most oral hypoglycemic drugs and GLP-1 analogs are generally unsuitable for use in patients with ESRD. However, DPP4 inhibitors are increasingly being successfully utilized in these patients: sitagliptin and saxagliptin can be used with dialysis. Glipizide can be used in carefully selected patients with ESRD. On the basis of available evidence, the most effective approach for most patients with ESRD and diabetes whose glycemic control is inadequate on a DPP4 inhibitor appears to be a basal-bolus insulin strategy. The basal insulins that can be used for this purpose include insulin glargine or NPH. Any of the short-acting analogs (lispro, aspart or glulisine) can be used.

In general, dialysates with lower dextrose concentrations are used in patients with diabetes, but these may lead to hypoglycemia. Conversely, dialysates with higher dextrose concentrations are occasionally used in peritoneal dialysis to increase ultrafiltration, but this can lead to hyperglycemia.[7] Because glucose generally drops during dialysis, patients may need a different algorithm for dialysis- and non-dialysis days.[4, 5]

This patient responded well to treatment with sitagliptin and was able to maintain good glycemic control without needing insulin.

CASE 4.

A 31-year-old woman presents for management of type 1 diabetes. She was diagnosed with type 1 diabetes at the age of 12. She has been on a basal-bolus regime and her A1c has been consistently <7%. She checks her glucose level about 4 times a day but does not keep a diary. She takes glargine insulin 30 units at 10 pm daily, and the following are her recollections of glucoses during the day and associated lispro doses: Before breakfast 50–230 mg/dl, 5 U; before lunch, 75–180, 12 U; before dinner, 100–220 mg/dl, 15 U; at bedtime, 100–320, 5 U.

She reports headaches and weakness with low blood glucose readings almost daily that can occur at any time of day depending on her food intake and insulin use. However, she denies sweating, tremulousness, palpitations, or syncope. She snacks frequently. Her hemoglobin A1c (HbA1c) was 5.8% 6 weeks ago and 5.9% 3 months ago. She weighs 130 lbs pounds with a body mass index of 20.4 kg/m2.

Patients with highly erratic glucoses are sometimes inappropriately referred to as 'brittle' and can include patients with type 1 and type 2 diabetes. These patients can generally benefit from referral to an endocrinologist. Determining the cause of erratic glucoses necessitates inquiry into the patient's personal life and medical history. Clinicians should also be aware of the possible presence of other co-morbidities that can affect glycemia.

1. ***How should erratic glucoses be evaluated?***
   A. Key components of the initial history in these patients includes questions about patterns of highs and lows, treatment of these lows and highs, frequency of snacking and missed doses, injection site rotation, and storage of insulin *(Table 10-4)*. The patient should be examined for signs

Table 10-4. Etiologic Factors in Erratic Glucoses

• Erratic insulin administration
• Erratic or under-reported eating
• Incorrectly stored or expired insulin
• Overcompensating from hypoglycemic events
• Incorrect carb counting or corrections
• Lipoatrophy
• Gastroparesis
• Mental illness, including eating disorders
• Occult infection (abscess, osteomyelitis)
• Endocrinopathy (Addison's, hypothyroidism)
• Malabsorptive disorders

of lipoatrophy and hypertrophy at sites of injection and generalized or partial lipodystrophy, as well as acanthosis nigricans and signs of other medical conditions that could be causing insulin resistance or poor insulin absorption. Specific elements that should be considered are listed below:

◊ Education, insight into their disease, or reaction to their disease are the most common reasons why patients have erratic glucoses. Cost, particularly of the analogs, may play a role in underdosing for patients with higher co-payments. These barriers lead to reduced compliance and inappropriate reactions to highs and lows, and a sequence of actions that can result in wide swings in glucose concentrations.

◊ For patients on complex regimens, such as basal/bolus insulin dosing, appropriate glucose monitoring should be performed to determine the appropriateness of the basal dose as well as carb and correction factors. Inadvertent interchange of insulins should be considered when patients are taking more than one type, particularly if the patient is elderly or cognitively impaired.

◊ Since insulin is a growth factor for adipose tissue, lipohypertrophy and lipoatrophy can develop when a patient reuses the same depot for insulin injections without site rotation. Even newer analog insulins and human insulin can cause lipoatrophy.8 Absorption of the insulin from an abnormal depot will become erratic. This can be an especially common issue for pump patients. If this problem is found, patients should be directed to alternative injection sites.

◊ Mental health issues are among the most common causes of erratic glucoses and can substantially interfere with compliance with a complex treatment regime that necessitates patient self-activation and cognitive insight. Patients may be reluctant to share their mental health issues, so careful inquiry and clinical instinct are essential. Engagement of mental health professionals can be instrumental in resolving the complex problems that arise when insulin use and

psychiatric problems intersect. Binge eating with or without purging can be a cause of erratic control and is difficult to diagnose without sympathetic questioning

◊ Gastroparesis is a known cause of erratic glycemic control but is relatively uncommon until late in the diabetes disease course, and then it usually occurs with other findings of autonomic impairment. Insulin given at mealtime may result in immediate postabsorptive hypoglycemia and delayed hyperglycemia as the insulin and carbohydrate dynamics become mismatched. Marijuana exacerbates the gastroparesis. These patients may benefit from use of regular insulin rather than the short-acting insulin analogs, or a pump.

◊ Malabsorption, particularly celiac disease, can cause erratic carbohydrate absorption and erratic glucose levels. When celiac disease is diagnosed, glycemic excursions can be expected to improve within two weeks of initiating a gluten-free diet.

◊ If insulin antibodies are suspected as the cause of severe insulin resistance, plasma anti-insulin antibodies can be measured.

2. ***How should a patient with erratic glucoses be managed?***

A. The initial management approach is to thoroughly review self-care techniques, including insulin preparation and injection and glucose testing. Increased frequency of self-testing may reveal previously unrecognized patterns and provides the patient with helpful feedback. A thorough dietary history, including timing of meals and snacks, should be taken to identify potential contributions to poor control. Educating patients about carb counting, dosing, and treatment of high and low episodes is generally necessary.

Hypoglycemia is common and some is to be expected at low levels of HbA1c. Overtreatment of hypoglycemia is a common cause of hyperglycemia in insulin-treated patients. Approximately 4 oz of juice and some patience is adequate for most circumstances.

For some patients, there is no immediately obvious cause for the erratic glucoses. In these patients, a continuous glucose monitor (CGM) can be both part of the investigation and part of the treatment. These devices measure glucose on a near-continuous basis and provide insight into glycemic profiles, allowing patients to understand their glucose trajectory and to make therapeutic adjustments to improve metabolic control. Motivated and technologically adept patients with erratic glucoses derive particular benefit. Most trials that investigated the use of real-time CGMs showed a decrease in HbA1c, reduced glycemic variability, and a diminished number and length of hypo- and hyperglycemic events.[9] In addition, real-time CGM devices can improve quality of life by reducing the fear of unexpected hypoglycemic events.

3. ***Can hypoglycemic unawareness be reversed?***
   A. Hypoglycemic unawareness is a reversible phenomenon that can resolve as patients allow their glucoses to drift higher. Avoiding glucoses below 40 mg/dl for about 6 weeks usually re-establishes a higher and safer threshold for hypoglycemic symptoms.10 Until hypoglycemia is appropriately addressed, patients need to be informed about the risks of driving or operating machinery; at a minimum, patients should check their glucose levels before operating such machinery and keep carbohydrates to hand.

      This patient needed to keep a written or digital diary and to count carbs and she needed a reduction in the doses of glargine and lispro (to 20 U and 10–12 U ac, respectively). Glucagon was prescribed, snacking needed to be restricted, and hypoglycemia needed to be managed more appropriately. As HbA1c rose (to 7.3%), hypoglycemia awareness was restored.

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11 Management of CVD Risk in Diabetes

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes. Among patients with type 2 diabetes mellitus (T2DM), the incidence of a first myocardial infarction is similar to that of recurrent MI in nondiabetic persons who have had a previous MI. Cardiometabolic risk factors, including insulin resistance and associated manifestations, predispose to the increased CVD in type 2 diabetes (T2DM). Glycemic control with hemoglobin A1c (HbA1c) targets of ~7% resulted in ~50% relative reduction in the incidence of CVD in patients with type 1 diabetes enrolled in the DCCT/EDI C study. In contrast, several recent studies have failed to demonstrate CVD risk reduction through more intensive glycemic control (HbA1c targets <6.0–6.5%) in patients with type 2 diabetes (T2DM). Therefore, a comprehensive approach targeted at the multiple CVD risk factors is the most effective management strategy in patients with type 2 diabetesT2DM.

BARRIERS TO OPTIMAL PRACTICE

Clinicians often encounter multiple obstacles and challenges in their effort to improve the lives of patients with diabetes and to prevent or to decrease the risk of CVD. Some of these barriers and challenges include:

- Overcoming patients' misperception regarding the benign nature of diabetes and their failure to associate their diabetes with increased CVD risk.
- Staying current with many guidelines from numerous professional organizations regarding treatment goals for diabetes, hypertension, dyslipidemia, etc.
- Staying current with emerging data from randomized controlled trials in the ever-changing landscape of evidence-based practice.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Utilize CVD risk assessment in routine clinical decision making
- Become familiar with current treatment goals for hypertension, dyslipidemia, and diabetes
- Recognize appropriate uses of cardiac screening tests in patients with diabetes

- Understand updated recommendations regarding aspirin use
- Adopt a comprehensive approach to CVD risk reduction in diabetes

Identifying Risk Factors and Diagnosing CVD

The traditional risk factors for CVD *(Table 11-1)* are similar in people with or without diabetes. However, diabetes accelerates and amplifies the atherosclerotic process, leading to 2–4-fold increased risk for CVD and stroke compared to the non-diabetic population. In the United Kingdom Prospective Diabetes Study (UKPDS), the five most significant predictors of first MI (in descending order) were the following: 1) LDL cholesterol, 2) HDL cholesterol, 3) HbA1c, 4) systolic blood pressure, and 5) smoking. In the INTERHEALTH Study, psychosocial stress was identified as a predictor of first MI, with a population attributable-risk equivalent to the risk of hypertension and hyperglycemia combined. The presence of autonomic neuropathy constitutes a risk factor for sudden death in diabetes patients.

Table 11-1. Risk Factors for CVD

Demography: Age, Gender, Other
Family history of premature coronary artery disease
Dyslipidemia
Hypertension
Hyperglycemia
Smoking
Obesity
Psychosocial stress

The clinical presentation of coronary artery disease (CAD) in diabetes patients may be atypical or painless. This knowledge had led to widespread cardiac stress testing to detect "silent" disease in the past. However, a recent randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes (T2DM) and normal ECGs. Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, the overall effectiveness, especially the cost-effectiveness, of such an indiscriminate screening strategy is in question.

The current 2011 American Diabetes Association recommendations identify patients with an abnormal resting ECG for further cardiac screening.

APPROACH TO MANAGEMENT

In all patients with diabetes, cardiovascular risk factors *(Table 11-1)* should be assessed at least annually. Documented modifiable risk factors should be treated to recommended targets *(Table 11-2)*. Lifestyle modification should be promoted in all patients. Medical nutrition therapy, increased physical activity, and weight loss (in the overweight) all improve glycemic control, blood pressure, lipids, and associated cardiometabolic risk factors. Dietary practices that restrict saturated

fat intake, with augmentation of dietary fiber, fruits, and vegetables, offer distinct metabolic and cardiovascular benefits. Fat intake should be limited to ~30% of total calories (saturated fat should be <7 %). The intake of trans fatty acids should be reduced drastically to < 1% of energy consumption.

Table 11-2. Approach to Management of CVD in Diabetes

Lifestyle modification
Smoking cessation
Control dyslipidemia
Control hypertension
Aspirin/antiplatelet prophylaxis
Decrease micro- or macroalbuminuria
Optimize glycemic control
Nontraditional targets

The Mediterranean-type diet, based on generous servings of fruits, vegetables, and nuts, has been shown to reduce CVD risk factors, reverse components of the metabolic syndrome, and improve morbidity and mortality. Physical fitness also is a potent predictor of good CV outcome and survival. Smoking cessation should be promoted using at least two strategies: behavioral intervention, nicotine substitution (gum, patch), and medications (bupropion, varenecline) that decrease craving.

Pharmacological Intervention and Treatment Targets

Hyperglycemia

The 2011 American Diabetes Association Clinical Practice Guidelines recommend a glycemic goal of HbA1c < 7% for most people with diabetes. More stringent control has not been demonstrated to decrease CVD outcomes but could increase the risk of hypoglycemia. None of the ~30 different medications approved by the FDA for treatment of diabetes has been proven to significantly decrease CVD events in randomized controlled trials. The thiazolidinedione (TZD) drugs are contraindicated in patients with congestive heart failure. Metformin may be used in patients with stable CHF if renal function is normal. It should be avoided in unstable or hospitalized patients with CHF.

A post-hoc analysis of a subgroup of patients treated with metformin in the United Kingdom Prospective Diabetes Study (UKPDS) shows CVD risk reduction compared to patients in the other treatment arms of the study. A 10-year follow-up report further showed that UKPDS subjects in the intensive treatment arm (median HbA1c of 7.0% during the study) had decreased risk of CVD events compared to subjects randomized to the conventional arm (median HbA1c level of 7.9%). [The intensive treatment arm of the UKPDS utilized sulfonylureas, metformin, and insulin for glycemic control.] Beginning in December 2009, the FDA requested the manufacturers of newly approved glucose-lowering medications to conduct randomized controlled trials with CVD events as the primary outcome measure. Many such studies are in progress.

Dyslipidemia
Recent recommendations by a joint ADA and American College of Cardiology (ACC) consensus panel emphasize focusing on non-HDL cholesterol and/or apolipoprotein B (apo B) levels in conditions, such as diabetes, that are associated with formation of small, dense LDL particles. For very-high-risk patients treated with statins whose LDL cholesterol target is <70 mg/dl (non-HDL cholesterol <100 mg/dl), apo B levels should be measured and treated to a target of <80 mg/dl. For other statin-treated patients with an LDL cholesterol target of <100 mg/dl (non-HDL cholesterol <130 mg/dl), apo B should also be measured and treated to a target of <90 mg/dl. In the lipid arm of the ACCORD trial, the addition of fenofibrate to raise HDL and decrease triglycerides in patients taking simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and statin in diabetes patients whose LDL cholesterol has been well controlled on a statin drug. Of course, treatment needs to be individualized, as patients may present with features that are quite different from the population that was studied in ACCORD.

Hypertension
Control of blood pressure is another area of emerging clarification. The BP arm of ACCORD randomly assigned 4733 participants with T2DM to intensive therapy (SBP target <120 mmHg) or standard therapy (SBP target <140 mmHg) and followed them up for a mean of 4.7 years. The primary composite outcomes were nonfatal MI, nonfatal stroke, or CVD death. After 1 year, mean SBP was 119.3 mmHg in the intensive group vs. 133.5 mmHg in the standard group. The annual rate of primary outcome was 1.87% in the intensive group vs. 2.09% in standard group (HR 0.88; 95% CI 0.73–1.06; P=0.20). The all-cause mortality was 1.28% vs. 1.19% (HR 1.07; 95% CI 0.85–1.35; P=0.55). Thus, intensive BP control did not decrease overall CVD outcomes or mortality. However, there was a 40% reduction in strokes among the group with intensive BP control.

Antiplatelet Therapy
Recent randomized controlled trials have failed to show CVD benefit from the routine use of aspirin for primary prevention in patients with diabetes. The current recommendations by an Expert Committee of the ADA, American Heart Association, and ACC are as follows: 1) Aspirin is recommended for secondary prevention in diabetes patients with documented CVD events; 2) Aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events >10%) and who have no known risk for bleeding. Examples: most men >50 years old and women >60 years old, with major risk factors (smoking, hypertension, dyslipidemia, FH of premature CVD, albuminuria). In younger persons and those with 10-yr risk of CVD <5%, the benefit from aspirin is offset by bleeding risk. Physicians should use clinical judgment regarding aspirin prophylaxis in persons with intermediate risk (10-year CVD risk is 5–10%).

Clopidogrel (75 mg/day) is an alternative for persons with aspirin allergy. Combination therapy with aspirin (75–162 mg/day) and clopidogrel (75 mg/day) for up to a year is appropriate following an acute coronary syndrome.

Patients with pre-existing CVD or Prior MI
ACE inhibitor, aspirin, and statin therapy (if appropriate) should be used to reduce the risk of cardiovascular events. Beta-blockers should be continued for at least 2 years after an MI. Longer-term use of beta-blockers in the absence of hypertension is reasonable if well tolerated, but data are lacking.

CONCLUSIONS

A comprehensive approach to the prevention and management of heart disease in diabetes patients is advocated. This is best accomplished through a combination of lifestyle modification and targeting of the multiple cardiometabolic risk factors and comorbidities. Patients at increased CVD risk should receive aspirin, a statin (for dyslipidemia), and ACE inhibitor or angiotensin receptor blocker (ARB) therapy (for hypertension or albuminuria), in the absence of contraindications. Evidence from the DCCT/EDIC in type 1 diabetes (and negative data in type 2 diabetes) support an HbA1c target of ~7% rather than more aggressive goals. The optimal blood pressures is <130/80 mmHg and LDL-cholesterol levels of much lower than100 mg/dl may be indicated in high-risk patients. Concurrent targeting of multiple risk factors is of proven efficacy and has been demonstrated to reduce CVD risk by ~50% in type 2 diabetes patients (Steno-2 Study).

Patients with stable CAD derive equivalent benefits from intensified medical management compared to early revascularization. When a revascularization procedure becomes necessary, coronary artery bypass surgery has been reported to be superior to angioplasty in 5-year survival and recurrent MI rates in patients receiving pharmacologic treatment of type 2 diabetes mellitus.

CASE 1

History: A 61-year-old man presents for a routine diabetes visit. He has had T2DM for 11 years.
Past medical history: Hypertension x 2 years, “Slightly” high cholesterol—recognized about 1 year ago
Family medical history: Father-T2DM, fatal MI, age 51; Mother has T2DM
Medication: Metformin 1000 mg BID, Lisinopril 40 mg QD, Herbals and vitamin supplements
Social history: Banker, Smokes 2–3 cigars/day, Alcohol: 2–3 beers/weekend, No regular exercise
Physical Exam: BP 166/93; HR 82/min; BMI 29 kg/m2; Waist 44 in; Neck-No bruits or goiter
Heart, Lungs, Abdomen: Normal; Extremeties: Decreased sensation
Labs: Fasting glucose 145 mg/dl, LDL-cholesterol 137 mg/dl, HDL 35 mg/dl, total cholesterol 210 mg/dl, triglycerides 195 mg/dl, serum creatinine 1.2 mg/dl, urine microalbumin/creatinine 33 mg/g, ECG normal

List all cardiometabolic risk factors in this man.
Answer: Family history of MI, diabetes, hypertension, dyslipidemia, tobacco use, sedentary, microalbuminuria, overweight, ? job stress

1. ***What is this patient's 10-year risk of having a CVD event?***
   A. Patient's Framingham Risk Score *(see Table)*:
      ◊ Male age 61 = 10 points
      ◊ Cholesterol 210 mg/dl = 1 point
      ◊ HDL 35 mg/dl = 2 points
      ◊ SBP: 166 mm Hg = 3 points
      ◊ Smoker = 1 point
      ◊ Total 17 points: Patient's estimated 10-year risk of MI/CHD death >30%

Framingham Risk Tables for Men

Point Score										
Age	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Age points	-9	-4	0	3	6	8	10	11	12	13
TC										
<160	0	0	0	0	0	0	0	0	0	0
160-199	4	4	3	3	2	2	1	1	0	0
200-239	7	7	5	5	3	3	1	1	0	0
240-279	9	9	6	6	4	4	2	2	1	1
>280	11	11	8	8	5	5	3	3	1	1
Smoking status										
Non-smoker	0	0	0	0	0	0	0	0	0	0
Smoker	8	8	5	5	3	3	1	1	1	1
HDL										
60 -1										
50-59 0										
40-49 1										
<40 2										
Systolic BP										
<120 Untreated 0; treated 0										
120-129 Untreated 0; treated 1										
130-139 Untreated 1; treated 2										
140-159 Untreated 1; treated 2										
>160 Untreated 2; treated 3										

POINTS for 10-yr risk of MI or CAD death (%)

< 0 points = <1%	0-4 points = 1%	5-6 points = 2%	7 points = 3%	8 points = 4%
9 points = 5%	10 points = 6%	11 points = 8%	12 points = 10%	13 points = 12%
14 points = 16%	15 points = 20%	16 points = 25%	>17 points = 30%	

CAD = coronary artery diseases; HDL = High-density liopoprotein; TC = total cholesterol.
Data from the Third Report of the Expert Panel on Detection, Education, and Treatment of High Blood Cholesterol in Adults. National Institutes of Health, National Heart, Lung and Blood Institute, 2001.

2. ***Would you order cardiac stress test? If yes, why? If not, why not?***
   A. No. According to the 2011 American Diabetes Association recommendations, only patients with an abnormal resting ECG need to be referred for further cardiac screening. Recent research has shown no benefit of routine cardiac screening of asymptomatic patients with normal ECGs.

3. ***What additional treatments are needed now?***
   A. Lifestyle intervention, smoking cessation, add statin, aspirin, optimize BP control. The persistently elevated urinary microalbumin/creatinine ratio is of concern, a trial of ACE inhibitor plus ARB combination would be reasonable.

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12 Prevention of Diabetic Nephropathy

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Diabetic nephropathy (DN) is characterized by progressive proteinuria and glomerular filtration rate (GFR) decline in patients with diabetes. In the USA, nearly half of patients entering end-stage renal disease (ESRD) programs have diabetes. DN develops in 15–35% of type 1 diabetic (T1DM) patients, with a peak in the incidence around 15–20 years of diabetes. DN rates in type 2 diabetes (T2DM) are similar to or higher than those of T1DM. The much higher prevalence of T2DM accounts, at least in part, for the greater contribution of these patients to the ESRD incidence. Although there are data suggesting that the incidence of DN may be declining, the incidence of ESRD due to DN is 35% higher in the United States (after adjustment for population growth) than a decade ago. The reasons for this increase are unclear.

Once overt DN, manifested as proteinuria and decreased GFR, is present, ESRD can be postponed, but in most instances not truly prevented, by effective antihypertensive treatment or glycemic control. The mortality rate of patients with DN is high. A marked increase in cardiovascular (CV) risk accounts for more than half of the increased mortality in DN patients and for much of the >80% 5-year mortality rate among diabetic patients on chronic dialysis. One possible explanation for this unfavorable outcome is that the natural history of DN is one of clinical silence for years to decades, during which time serious underlying renal lesions may be developing.

While many patients with T1DM are cared for by endocrinologists, the majority of T2DM patients are followed by primary care providers. The misconception that T2DM is a "less severe" form of diabetes, along with the alarming growth in the incidence and prevalence of T2DM, now no longer restricted to adult populations, adds to this problem.

BARRIERS FOR OPTIMAL PRACTICE

- Lack of detailed knowledge on how to use clinically available data to predict DN risk
- Patients' inaccurate perception of DN risk
- Conflicting data on strategies aimed at prevention of DN
- Lack of a single marker that precisely identifies the risk of DN in individual patients

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Identify patients at increased risk of DN
- Appropriately use treatments that prevent the development or progression of DN
- Apply the most current biomedical and clinical scientific knowledge of DN to patient care

STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

DN is classically defined by the presence of increased amounts of albumin in the urine. Urinary albumin excretion rate (AER) is ideally measured in timed urine collections (overnight or 24 hrs). Patients are classified as normoalbuminuric if AER levels are <20 μg/min (or <30 mg/g Cr in spot urine), as microalbuminuric if AER is between 20 and 200 μg/min (or 30–300 mg/g Cr), and as macroalbuminuric (or proteinuric) if AER is >200 μg/min (or >300 mg/g Cr). These values should be confirmed in a subsequent urine sample, collected within 6 months.

Although longstanding normoalbuminuric patients were considered not at risk for DN, newer evidence reveals that this is not the case. Some normoalbuminuric patients not only have advanced structural glomerular lesions, overlapping in severity with those seen in microalbuminuric and proteinuric patients, but may also have reduced GFR. Thus, current guidelines from the American Diabetes Association (ADA) and the National Kidney Foundation (NKF) recommend assessment of both AER and GFR annually when screening for DN. In addition, information on glycemic control, presence of other chronic complications of diabetes, evaluation of blood pressure (BP) and lipid levels, smoking history and family history of hypertension, CV disease and ESRD in diabetic and non-diabetic first-degree relatives should be considered.

The major therapeutic interventions for prevention and treatment of DN include near normal blood glucose control, BP control, lipid lowering, and restriction of dietary proteins. The impact of these strategies on primary (progression from normoalbuminuria to microalbuminuria), secondary (microalbuminuria to proteinuria), and tertiary (proteinuria to ESRD) prevention is detailed below.

Primary Prevention

Glycemic Control

The beneficial effect of intensive glycemic control in T1DM, initially demonstrated in small studies, was corroborated and extended by the Diabetes Control and Complications Trial (DCCT), where intensive therapy reduced the development of microalbuminuria by 39% and of macroalbuminuria by 54%. After the DCCT study was completed, many of the patients were followed long term in the Epidemiology of Diabetes and Complications (EDIC) study. Within 4 years of discontinuation of the DCCT, the glycated hemoglobin (A1c) levels were similar in the subjects randomized to the intensive vs. conventional glycemic control arms of the DCCT. However, the benefits of intensive glycemic control

persisted way beyond the end of the DCCT trial.

The Kumamoto study demonstrated the beneficial impact of strict glycemic control on progression from normoalbuminuria to microalbuminuria or macroalbuminuria in Japanese T2DM subjects. These findings were also confirmed and extended by the United Kingdom Prospective Diabetes Study (UKPDS), documenting a progressive beneficial effect of intensive glycemic control on the development of microalbuminuria and overt proteinuria, and, more recently, by the Action in Diabetes and Vascular Disease (ADVANCE) study.

Blood Pressure Control

Elevated arterial BP is a risk factor for microalbuminuria in most observational studies. ACEi and ARB have not been demonstrated to decrease progression to DN in normotensive normoalbuminuric patients with DM. Thus, in general, use of antihypertensive agents (angiotensin converting enzyme inhibitors [ACEi] or other agents) for primary prevention of microalbuminuria in normotensive (BP <130/80 mm Hg) normoalbuminuric subjects with diabetes is not recommended by current guidelines. However, results of a 5-year randomized multicenter trial in normoalbuminuric normotensive T1DM patients showed that ACEi or angiotensin receptor blocker (ARB) slows the rate of progression of retinopathy. This benefit was limited to patients with A1c >7.5%. No group differences in the rate of progression of DN lesions were detected, but higher rates of microalbuminuria were seen in subjects randomized to ARB compared to ACEi. Beneficial effects of aggressive BP control on albuminuria, retinopathy, and incidence of stroke were demonstrated in "normotensive" (BP <160/90 mmHg) T2DM patients enrolled in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, and this was independent of the initial BP-lowering agent used.

In hypertensive normoalbuminuric T2DM patients, ACEi, dihydropyridine calcium antagonists, and ß-blockers have similar renoprotective effects. The UKPDS study reported a 29% reduction in the risk of microalbuminuria, with a non-significant 39% reduction in the risk of proteinuria (P = 0.061) after 6 years in patients randomized to tight BP control. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) demonstrated that ACEi reduced BP and development of microalbuminuria in normoalbuminuric hypertensive T2DM patients, while the effect of verapamil alone was similar to that of placebo. In the ADVANCE study, a combination of ACEi and diuretic reduced by 21% the rate of new-onset microalbuminuria in normotensive and hypertensive T2DM patients.

Secondary Prevention (Prevention of progression from microalbuminuria to macroalbuminuria)

Glycemic Control

Poor glycemic control is a risk factor for progression from microalbuminuria to macroalbuminuria. Although studies in T1DM patients have shown conflicting results, perhaps related to short follow-up, the UKPDS documented a progressive beneficial effect of improved glycemic control on the development of proteinuria and doubling of serum creatinine in T2DM during a 15-year follow-up period. Moreover, maintenance of euglycemia by pancreas transplantation in T1DM

patients did not improve glomerular lesions after 5 years, but led to reversal of glomerulopathy after 10 years.

Blood Pressure Control
Compared to placebo, ACEi reduce the risk of macroalbuminuria by 62% in microalbuminuric T1DM patients.

Normotensive microalbuminuric T2DM patients treated with ACEi also showed reduced rates of progression to proteinuria (12% versus 42%) when compared to placebo. Renal function was stable in the ACEi treated group, while it declined by 13% in the placebo group. Studies in microalbuminuric T1DM and T2DM patients with early diabetic glomerulopathy also showed that agents blocking the renin-angiotensin system (RAS) have a beneficial impact on glomerular structural changes.

In hypertensive microalbuminuric T2DM patients, antihypertensive treatment has a beneficial effect on progression of nephropathy. It has been suggested that agents that block the RAS have a beneficial effect on kidney function beyond their effect on systemic BP. However, limited power and short duration may explain the different results obtained by different trials.

In addition to the microvascular complications, CV morbidity and mortality are a major burden in patients with T2DM, and the risk increases with increasing AER. In the STENO-2 study, a multifactorial intervention strategy, including lifestyle modification (exercise, diet, smoking cessation) and polypharmacologic intervention targeting several risk factors [hyperglycemia, hypertension, microalbuminuria (with RAS blocking agents) and aspirin] was compared to conventional treatment in microalbuminuric patients with T2DM. After 8 years, patients receiving intensive therapy had a lower risk of CV disease, nephropathy, retinopathy and autonomic neuropathy. These effects where sustained or magnified 5 years after the study closed, and development of ESRD was significantly reduced by the multifactorial intervention. More important, mortality was reduced in the intensively treated group (hazard ratio 0.54), corresponding to an absolute risk reduction of 20%. Thus, a long-term intensified intervention aimed at multiple risk factors in patients with T2DM and microalbuminuria reduces mortality and the risk of CV and microvascular events by approximately 50%.

Tertiary Prevention (Prevention of progression of DN to ESRD)
Glucose Control
Intervention studies failed to demonstrate a beneficial effect of improved glycemic control on the progression of DN in T1DM patients. The rate of GFR decline and the increase in proteinuria and arterial BP were not affected by improved glycemic control. None of these studies were randomized, and the number of patients investigated was small.

Blood Pressure Control
It is well established that long-term antihypertensive treatment reduces the rate of GFR decline in proteinuric hypertensive T1DM patients. Prior to use

of antihypertensive therapy, the median survival after the onset of persistent proteinuria was about 5–7 years, and ESRD was the primary cause of death in 66% of the patients. Use of antihypertensive therapy has significantly improved survival to 14–21 years after DN onset, while reducing the death rates due to ESRD to about 35%. Also, remission of nephrotic range albuminuria in T1DM and T2DM patients, induced by aggressive antihypertensive treatment with or without ACEi, is associated with a slower progression towards ESRD and a substantial improvement in the survival rates.

Studies in T1DM patients with DN showed a significant 48% risk reduction for doubling of serum creatinine in patients receiving an ACEi in comparison to those receiving conventional antihypertensive treatment, suggesting that an ACEi confers renoprotection in DN, e.g., a beneficial effect on renal function beyond that expected from the BP-lowering effect alone.

Similarly, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (INDT) in hypertensive T2DM patients with proteinuria and elevated serum creatinine showed a significant 16–20% reduction in the relative risk for doubling of serum creatinine, ESRD, or death in patients randomized to ARB. This was, at least in part, independent of BP reduction. Of clinical relevance, the initial reduction in proteinuria predicted a beneficial long-term treatment effect on the rate of GFR decline.

Head-to-head comparisons of ACEi versus ARB suggest similar ability to reduce albuminuria and BP in diabetic patients with elevated AER. High dosages of ACEi and ARB are required for full renoprotection. The optimal renoprotective dose of losartan is 100 mg daily, candesartan 16 mg daily, irbesartan 900 mg daily, and valsartan 640 mg daily. There is less information regarding optimal ACEi dosage, but for lisinopril the optimal antiproteinuric effect was obtained at 40 mg per day.

As ACEi and ARBs act on different sites of the RAS, combination of the two agents (dual blockade) has been tested. The Candesartan and Lisinopril Microalbuminuria (CALM) study evaluated almost 200 hypertensive microalbuminuric T2DM patients and found that the ACEi/ARB combination was more effective in reducing BP and microalbuminuria than either agent alone, but there are no long-term data on the potential renoprotective effects. On the other hand, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which followed over 25,000 subjects (some of whom had diabetes and proteinuria), found no beneficial effect of dual blockade on the primary CV outcome after 5 years' follow-up. This study was not designed to evaluate the renoprotective effect in DN.

Lipid Lowering As already discussed, patients with diabetes and elevated albuminuria have an increased risk for CV disease. To reduce this risk, these patients should be treated according to current guidelines for high-risk patients.

In observational studies of T1DM patients with DN, elevated cholesterol levels are associated with accelerated renal function decline. The renoprotective effects of HMG-CoA reductase inhibitors ("statins") in microalbuminuric or

macroalbuminuric T1DM or T2DM patients is variable. However, all studies were of short duration, had small numbers of patients, and evaluated only a surrogate end-point, AER. A meta-analysis suggested a small positive effect of statins on AER and renal function, mainly in patients with known CV disease, but not in patients with established DN.

Dietary Protein Restriction

Short-term studies in normoalbuminuric, microalbuminuric, and macroalbuminuric T1DM patients have shown that a low-protein diet (0.6–0.8 g/kg/day) reduces AER and hyperfiltration independently of changes in glucose and BP control. Long-term trials in T1DM patients with DN suggest that protein restriction reduces GFR loss. Now, a dietary protein intake of 0.8 g/kg body weight per day is recommended by the KDOQI guidelines for patients with diabetes and chronic kidney disease stages 1-4.

CONCLUSIONS

Aggressive blood glucose control reduces the incidence of microalbuminuria and proteinuria in normoalbuminuric and microalbuminuric T1DM and T2DM patients. The benefits of intensive glycemic control in patients with proteinuria are unclear.

Hypertension should be aggressively treated in patients with diabetes, independent of AER levels. The current ADA guidelines state: "In patients with T1DM, hypertension, and any degree of albuminuria, ACEi have been shown to delay the progression of nephropathy. In patients with T2DM, hypertension, and microalbuminuria, both ACEi and ARBs have been shown to delay the progression to macroalbuminuria. In patients with T2DM, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy."

RAS blocking agents do not offer renal protection benefit in normoalbuminuric, normotensive T1DM or T2DM patients, but these agents reduce progression of diabetic retinopathy in normoalbuminuric, normotensive T1DM patients. This benefit might be limited to patients with suboptimal glycemic control.

CASE 1

A 26-year-old male with T1DM for 18 years presents for follow-up. The patient is currently on glargine twice a day and aspart with meals, the dose of which he tries to estimate without doing carbohydrate counting. He is also on an aspart correction scale of 1 unit for every 50 mg/dl over 150 mg/dl, and he reports frequent hypoglycemic episodes in the afternoon. Hypertension was diagnosed a few years ago and managed with lisinopril, which was discontinued about 1 year ago due to cough. The patient is not on antihypertensive medications. Last eye exam 6 months ago revealed no diabetic retinopathy. The patient denies numbness or tingling in his hands or feet. No chest pain or dyspnea on exertion. No other medications. Allergy to penicillin. No tobacco use. Mother with T2DM and hypothyroidism.

Physical Exam: BP 121/75 mmHg, HR 93 bpm, weight 230 lb, BMI 35. Normal funduscopic exam; thyroid normal size and texture; distal pulses are ample and symmetrical; normal light touch and vibratory sensation in the lower extremities, normal biceps and patellar reflexes. Remaining exam is normal.
Laboratory Results: (Non-fasting) cholesterol 161 mg/dl; triglyceride 214 mg/dl; HDL-cholesterol 50 mg/dl; LDL-cholesterol 69 mg/dl. Thyroid function tests are normal. Microalbuminuria undetectable. A1c is 7.6% (down from 8% 6 months ago; reference range 4.3–6.0%).

1. ***Is this patient at increased risk of DN?***
   A. He is at the peak of incidence of DN. The fact that he has no evidence of chronic diabetic complications, including DN, is reassuring. AER levels are normal; GFR is unknown. There are accumulating data in both T1DM and T2DM showing that some patients with normal AER already have decreased GFR. In one study in T1DM, decreased GFR in normoalbuminuric subjects was associated with the presence of more serious glomerular lesions.

2. ***Would this patient benefit from intensified glycemic control?***
   A. Diabetes control is suboptimal (A1c 7.6%) and the patient has frequent hypoglycemic episodes. His insulin therapy needs to be modified. In multiple studies, intensified glycemic control (aiming for an A1c 7.0%) has been shown to delay the development of microalbuminuria and proteinuria in both T1DM and T2DM.

3. ***Are antihypertensive agents recommended for primary prevention of DN?***
   A. The patient has an unconfirmed history of hypertension that was previously managed with an ACEi. When present, hypertension is an independent risk factor for DN and needs to be treated. BP goals for patients with diabetes are 130/80 mmHg. There are strong data supporting the concept that aggressive BP control may prevent/delay the development of DN in hypertensive T1DM and T2DM patients. Patient's BP levels are at target. However, RAS-blocking agents may have an additional beneficial effect beyond that of blood pressure lowering. Although BP medications are not recommended for primary prevention of DN, we should discuss with the patient the potential benefit of RAS-blocking drugs to delay progression of diabetic retinopathy.

4. ***Should dyslipidemia be treated with pharmacological agents?***
   A. Hypertriglyceridemia needs to be confirmed in a fasting sample. Target triglyceride levels are 150 mg/dl. Patient should follow a low-fat diet, lose weight, and exercise regularly. Hypertriglyceridemia is associated with increased risk of progression from normoalbuminuria to microalbuminuria, but there are no data to indicate that lipid-lowering agents are effective for primary prevention of DN in normoalbuminuric T1DM patients with a normal lipid profile.

5. ***Should this patient be referred to an endocrinologist?***
   A. The patient will benefit from reviewing carbohydrate counting and proper use of insulin as well as discussing the use of an insulin pump and glucose sensor. These can be done by a diabetes educator in association with a primary care provider or an endocrinologist.

CASE 2

A 69-year-old Mexican woman with a 12-year history of T2DM, statin-induced myopathy, hypertension, dyslipidemia, and osteoporosis is seen for follow-up. Patient takes glimepiride 4 mg daily, insulin detemir twice daily and lispro with meals. She also uses a sliding scale of 2 units for every 50 mg/dl above 150 mg/dl. Blood glucose values are never above 100 mg/dl. Weight is stable. She does physical therapy at home but is not otherwise exercising. Recent eye exam showed non-proliferative diabetic retinopathy. Hypertension is managed with lisinopril 40 mg daily; losartan 25 mg daily; metoprolol 50 mg twice daily; prazosin 6 mg twice daily, and furosemide 20 mg twice daily. Dyslipidemia has been managed with fish oil 2000 mg twice daily. She is also on cyanocobalamin 1000 mcg daily; omeprazole 20 mg daily; vitamin D 1,000 IU daily; gabapentin 600 mg 3 times daily; docusate sodium 120 mg twice daily; levothyroxine 75 mcg daily; aspirin 325 mg daily; alendronate sodium 70 mg once a week; potassium chloride 20 mEq daily. Allergies to fenofibrate, ketoconazole, and simvastatin. The patient has no complaints. No tobacco or illicit drug use.

Family History: Father deceased at age 62 of heart attack; had T2DM; Mother is 85 years old, T2DM for the past 40 years, no known chronic complications, legally blind (cataracts?); 6 siblings: 2 brothers with T2DM (both deceased), one had bilateral amputation of lower extremities; 4 healthy sisters.

Physical Exam: BP 133/62 mmHg, HR 61 bpm, weight 181.8 lb, BMI 32.5. Physical exam is otherwise normal.

Laboratory Results: (Non-fasting) cholesterol 186 mg/dl; triglyceride 124 mg/dl; HDL-cholesterol 23 mg/dl; LDL-cholesterol 138 mg/dl; serum creatinine 0.68 mg/dl (0.52–1.04); eGFR 86 ml/min/1.73m2, A1c 7.1% (4.3–6.0%); ALT 25 u/l (0–50 u/l); AST 63 u/l (0–45 u/l); TSH 6.10 mU/L (0.4–5.0 mU/L); Free thyroxine 1.21 ng/dl (0.7–1.85 ng/dl); microalbuminuria 270 mg/L. A1c is 7.1%, improved from 8.3%.

1. ***Is this patient at increased risk of progressing to ESRD?***
   A. Yes, she has multiple risk factors. She is Hispanic, and epidemiological data suggest an increased risk of DN in this population. She also has a strong family history of diabetes and CV disease. In addition, she has microalbuminuria and a slightly reduced GFR.

2. ***What strategies could delay DN progression in this patient?***
   A. Data from STENO 2 suggest that a multifactorial approach is warranted. Intensified glycemic and BP control have been proven to delay progression of DN in this scenario. Her glycemic control is already reasonable. (Her A1c is 7.1%.) There are strong data supporting

aggressive BP control in hypertensive T2DM patients, and a target blood pressure of <130/80 would be optimal. Although her hypertension has been managed with multiple agents (including 2 RAS blocking agents) it would be important to confirm adherence to the regimen and add another drug if necessary. Her LDL-cholesterol is elevated and HDL-cholesterol is low, but her hypothyroidism is undertreated. Her lipid levels need to be re-assessed in a fasting blood sample after her TSH has been normalized. Although it is not clear whether or not antilipemic agents may prevent DN, use of these agents has been show to reduce CV risk in patients with diabetes. We should also encourage weight loss and regular exercise, which will likely have a positive impact in glycemic, BP, and lipid control.

3. ***Should this patient be evaluated and/or followed by an endocrinologist?***
   A. This patient is at increased risk of ESRD and death. The prevalence of CV disease is increased in microalbuminuric and proteinuric patients, and this is directly related to the excess mortality in T2DM. Thus, evaluation and management of additional risk factors (dyslipidemia, obesity, smoking) are essential. This patient is being appropriately managed, but an endocrinologist might help setting therapeutic goals and selecting appropriate therapeutic agents.

4. ***Should this patient be referred to a nephrologist to rule out other causes of renal dysfunction?***
   A. No, this patient has multiple risk factors for renal dysfunction (diabetes, hypertension, obesity), but her case is typical for DN. It is unlikely she would have another condition that is causing her renal dysfunction. T1DM patients with proteinuria and less than 10 years duration of diabetes, and T2DM patients with proteinuria and no retinopathy should be referred to a nephrologist and be fully evaluated for other renal diseases. In these cases, renal biopsy should be strongly considered both for diagnostic and prognostic purposes.

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13 Insulin Management of Diabetes

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Insulin replacement therapy is essential for anyone with type 1 diabetes, many women with gestational diabetes when blood glucose (BG) cannot be controlled with diet and exercise alone, and a large percentage of individuals with type 2 diabetes when acceptable levels of glucose control cannot be achieved with oral agents or non-insulin injectable therapy [1].

The majority of patients with diabetes are cared for by primary care physicians, who often have the responsibility for advancing diabetes therapy to achieve desired levels of glycemic control, defined as an A1c of less than or approximately 7%, provided there are no contraindications to intensification of therapy [2]. While many physicians feel comfortable prescribing basal insulin to patients with type 2 diabetes, there is less comfort in titration of doses to levels that achieve glycemic targets. In addition, many physicians know less about when to initiate or modify prandial (bolus) insulin with rapid-acting insulin (RAI) analogs or regular insulin. What is often observed in clinical practice is an increase in doses of NPH or long-acting insulin (LAI) analogs, such as glargine or detemir, to doses beyond their physiologic ability to reduce A1c appropriately. This results in prolonged periods of suboptimal glycemic control, with the associated increase in risk for diabetes-related complications [3, 4].

BARRIERS TO OPTIMAL PRACTICE

Several barriers to the initiation and intensification of insulin therapy have been identified [5]. Physician factors include the time requirement for teaching and adjusting insulin therapy, concerns about weight gain and severe hypoglycemia, a sense that patients will not accept insulin therapy, and lack of comfort with the proper timing, dosing, or adjustment of different insulin preparations [6].

Patients can present barriers to initiation of insulin therapy. Some patients view the need to start insulin as evidence of personal failure. Others erroneously associate insulin with the onset or progression of complications or even death. Some patients express concern that insulin injections will be painful, increase the chance of hypoglycemia, or result in a loss of independence [6].

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Define the following components of insulin therapy: basal, bolus

and correction insulin
- Prescribe basal-bolus insulin therapy to a newly diagnosed patient with type 1 diabetes
- Identify patients with type 2 diabetes who are candidates for insulin therapy
- Initiate and adjust each of the components of an insulin regimen necessary to achieve desired levels of glycemic control in patients with type 1 and type 2 diabetes
- Define methods for minimizing risk for hypoglycemia in insulin-treated patients

Types of Insulin Preparations

There are now at least eleven different insulin preparations available for prescribing. They can be divided into groups according to their pharmacokinetic profiles *(Table 13-1)* and can be prescribed in a manner that meets each of the three major components of exogenous insulin therapy listed below [1]:

- Basal insulin (glargine, detemir, NPH) contributes to overall glycemic control by regulating metabolic processes (gluconeogenesis, lipolysis, and ketogenesis) between and during meals. These insulin preparations almost always need to be continued even when a patient is not eating.
- Prandial (bolus or nutritional (meal-related) regulates glycemic excursions following a meal or other nutritional supplements. This is usually given as a short-acting (regular) or RAI (lispro, aspart, glulisine) before each meal. Prandial insulin can be held when a person does not eat.
- Supplemental (correction) insulin refers to additional units of short or RAI that are usually given in combination with prandial insulin to correct elevations in BG above goal range. Correction insulin is often required to maintain glucose concentrations in the desired range even when patients are not eating, such as during an illness, as it is usually calculated to bring the glucose into the desired range.

Table 13-1 Pharmacokinetic Properties of Available Insulin Preparations

Type	Component	Names	Onset	Peak	Duration
Short-acting	Bolus	Regular	30–60 min	2–3 hrs	6–8 hrs
Rapid-acting	Bolus	Glulisine, lispro, aspart	5–15 min	1–2 hrs	4–5 hrs
Intermediate-acting	Basal	NPH	2–4 hrs	4–10 hrs	12–18 hrs
Long-acting Long-acting	Basal Basal	Glargine Detemir	2–4 hrs 2 hrs	Flat Broad	20–24 hrs 12–22 hrs
Premix	Basal	NPH + R 70/30 NPH + R 50/50	Onset, peak and duration of action vary by component		
Biphasic	Basal+ Bolus	Protaminated Lispro + Lispro 75/25 Protaminated Aspart + Aspart 70/30			

Type 1 Diabetes

Patients with type 1 diabetes require all three components of insulin therapy. A typical regimen for a person with type 1 diabetes consists of basal insulin administered once or twice a day in combination with RAI administered prior to each meal. The starting doses of insulin can be calculated at 0.2–0.3 units per kg/day as the total daily dose (TDD). Approximately 50% of the TDD can be administered as basal insulin in a single injection and 50% as RAI in three divided doses.

Example: Patient Case

A 24-year-old otherwise healthy woman presents with a 1-week history of mild weight loss with polyuria and polydipsia. Her confirmed laboratory glucose is 264 mg/dl. Serum electrolytes are normal and her urine is negative for ketones. Her A1c is 9%. Her body weight is 60 kg and her BMI is 22 kg/m2.

A diagnosis of new-onset type 1 diabetes is made and she is started on basal-bolus insulin therapy. Based on her lean body habitus, her TDD is calculated at 0.3 units per kg (60 kg x 0.2 units per kg = 18 units per day) that is given as glargine 9 units at bedtime and 3 units of lispro insulin prior to each meal.

Based on her young age of onset, the absence of any comorbidities, and the absence of any diabetes-related complications, her fasting and pre-prandial glycemic goal range is established at 70 to 120 mg/dl.

Correction Insulin

A correction insulin scale is based on a patient's sensitivity to insulin and reflects the expected decline in BG for each one unit of administered RAI. One suggested method for estimating correction insulin doses is to divide 1500 (for regular insulin) or 1800 (for RAI) by the TDD of scheduled insulin. In the example above, this calculation results in a recommendation to add 1 additional unit of RAI for each100 mg/dl increment in BG above the upper end of target fasting glucose range (120 in the above case). Many providers will bypass this calculation and instead prescribe one additional unit of short or RAI for every 40 to 100 mg/dl increment in BG above the goal range.

Measured BG – 120/100 = number of additional units of insulin to administer.

For BG below 70 mg/dl, she should reduce her premeal insulin dose by 1 unit.

Patients who have a persistent requirement for correction insulin before one or all meals will usually require an adjustment in their dose of basal or bolus insulin doses (see discussion below regarding dose titrations).

Carbohydrate counting

An alternative method for calculating premeal and pre-snack insulin doses is based on the planned carbohydrate content of a meal [7]. The advantage of carbohydrate counting is based on the associated flexibility with food intake. The amount of insulin required for a meal consisting primarily of pasta will be greater than what is required for a meal consisting of meat and vegetables or a salad. Patients can be taught to calculate one unit of regular or RAI for every 15 (10–20 based on insulin sensitivity) grams of planned carbohydrate intake.

The correction insulin scale is used for adjusting doses according to BG outside goal range

Type 2 Diabetes

Indications for insulin therapy in people with type 2 diabetes are [1]:

- Persistent hyperglycemia with use of oral agents or non-insulin injectable therapies
- Patients intolerant to oral agents or non-insulin injectable therapies
- Latent autoimmune diabetes in adults (LADA)
- Gestational diabetes
- Pancreatic disease
- Glycemic management during periods of acute or critical illness

Patients with type 2 diabetes have more options for initiation of insulin therapy, including initiation of basal insulin or prandial insulin, or a premix insulin usually administered in combination with oral agents. In a recent 3-year open-label multicenter trial, 708 patients with type 2 diabetes with suboptimal glycemic control on combination therapy with metformin and a sulfonylurea were randomly assigned to one of three different insulin regimens [8]:

- Basal detemir insulin given once or twice a day
- Premeal aspart insulin administered three times a day before each meal
- A premix preparation containing biphasic Protaminated Aspart + Aspart 70/30 before the morning and evening meal

Similar improvements in glycemic control were observed in all groups. However, there was less weight gain and less hypoglycemia in those randomized to an initial strategy of basal insulin [8]. While the majority of patients in each group required the addition of a second insulin to achieve the desired level of glycemic control for this study (A1c < 6.5%), these results support the recommendations for stepwise progression of insulin therapy in patients with type 2 diabetes, as recommended by the American Diabetes Association (ADA) *(Figure 13-1)* [9].

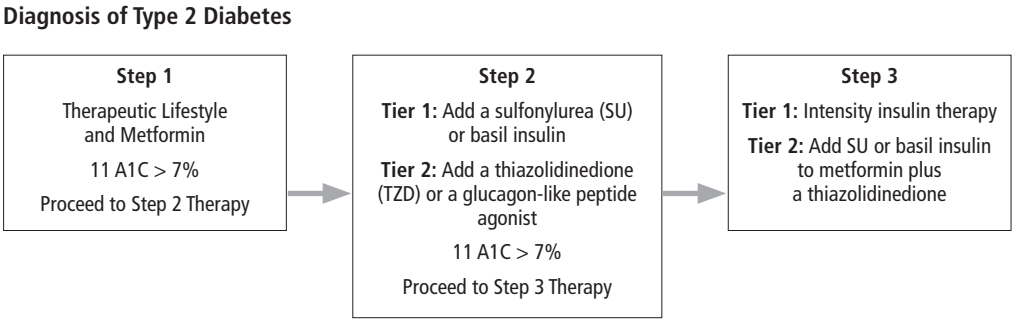

Figure 13-1. ADA Consensus Algorithm for Initiation and Adjustment of Therapy in Type 2 Diabetes

The decision about which basal insulin to choose can be based on results of home glucose measures. In patients with isolated morning hyperglycemia and daytime near normoglycemia, addition of a bedtime dose of NPH is effective at lowering fasting glucose levels. In patients with elevated fasting and daytime BG levels, addition of long-acting insulin (detemir or glargine) administered once daily can be effective.

Initiating Basal Insulin in Patients with Type 2 Diabetes

The starting dose of basal insulin can be determined in one of two ways. One method calculates the initial dose based on body weight at 0.2 units/kg/day.

Example: Patient Case

A 52-year-old man with a 10-year history of type 2 DM complicated by mild peripheral neuropathy and microalbuminuria has an A1c that ranges between 7.6 and 8.4% for the past 6 months. Therapy with pioglitazone resulted in a weight gain of 4 kg, prompting him to discontinue this on his own. He was unable to tolerate exenatide due to nausea. His current diabetes medications are metformin XR 2000 mg a day and glipizide XL 20 mg a day. He also takes lisinopril 20 mg a day for hypertension and atorvastatin 20 mg a day for dyslipidemia. His BP is well controlled at 128/76. He weighs 90 kg and his BMI is 33.5 kg/m2. His physical examination is otherwise normal with the exception of a 50% decrease in vibratory sensation at his MTP joint. His A1c at his current visit is 7.8%. A review of his home glucose readings performed before meals and bedtime demonstrates a range of 148–202 mg/dl. You feel he is a candidate for insulin therapy, but you are not sure what type of insulin to start.

While there are several options available for treating this patient, it is reasonable to start him on basal insulin in combination with his current medications. Based on his body weight of 90 kg and a starting dose of 0.2 units per kg, he would start 18 units of a LAI as his BG is elevated throughout the day. Alternatively, a starting dose of 10 units or even lower could be prescribed. Starting with a low dose allows patients to become accustomed to insulin injections at dosages with a low risk for hypoglycemia. It is important to note that this initial dose may not be sufficient to achieve the desired level of glycemic control. Several studies have demonstrated that the majority of patients with type 2 diabetes will require doses of at least 0.4 to 0.5 units per kg/day to achieve desired glycemic targets [10].

Titrating the Dose of Basal Insulin in Patients with Type 2 Diabetes

Patients can be safely instructed to adjust the dose of basal insulin gradually over a period of several days to weeks until glucose levels are in the desired range. A commonly used strategy is to advise patients to increase the dose by one or two units every four days until they achieve a fasting glucose of 100–140 mg/dl [10, 11]. Many patients will require support during this titration phase of insulin. It is useful to inform patients of the expected dose they will achieve as a way of improving comfort and compliance with the titration schedule.

When a patient does not achieve the desired level of glycemic control with

basal insulin at a dose of 0.5 to 0.6 units per kg/day, this is usually an indication to initiate prandial insulin therapy with a rapid-acting insulin analog, as basal insulin is not sufficient for overcoming the glycemic excursions that occur following meals. In the case of the patient above, if he fails to achieve the desired level of glycemic control with basal insulin 45 to 54 units once a day, it is reasonable to add premeal insulin to his regimen.

Initiating Prandial (Bolus) Insulin in Patients with Type 2 Diabetes

Bolus insulin can be started at the meal identified as being associated with hyperglycemia, or by converting the patient to basal-bolus insulin therapy. The decision for starting premeal short- or rapid-acting insulin can be based on results of home glucose monitoring:

- If pre-lunch BG is out of range, add regular or RAI before breakfast
- If pre-dinner BG is out of range, add regular or RAI before lunch
- If bedtime BG is out of range, add regular or RAI before dinner
- If all BG are out of range, change to basal-bolus insulin therapy

The starting dose of bolus insulin can again be based on body weight, with an initial dose of 0.1 units/kg or at a starting dose of 4 units before the meal associated with hyperglycemia. In either case, the dose requires titration to achieve the desired level of glycemic control by looking at the BG level 4–5 hours after the insulin injection. Using the 90 kg individual above, the starting dose for bolus insulin would be 9 units of RAI or regular insulin.

Patients with type 2 diabetes can also use carbohydrate counting to calculate their premeal insulin doses. Referral to a dietitian who can guide the patient in learning how to calculate the carbohydrate content of different foods is recommended. There are several commercially available resources that patients can use as a guide.

Combination Basal-Bolus Insulin Therapy

The progression from addition of basal insulin alone to gradual requirement for premeal insulin is described above. Many patients with type 2 diabetes may require initiation of basal-bolus insulin therapy as the first step in insulin therapy. This includes patients who experience more marked and rapid deteriorations in glycemic control, who are treated with high doses of glucocorticoids for an unrelated condition, or who require hospitalization for an acute illness.

When initiating basal-bolus insulin in type 2 diabetes, the starting dose can be calculated as 0.3 to 0.5 units per kg/day. For example, a patient weighing 90 kg with an A1c > 9% on maximal doses of oral agents will require a transition to basal-bolus insulin therapy:

- 90 kg x 0.4 units per kg = 36 units per day as total daily dose (TDD)
- 50% of the TDD dose can be given as glargine insulin 18 units at bedtime
- 50% of the TDD can be divided into 3 premeal insulin doses of 6 units of lispro insulin

It is again important to establish the desired BG range. In the 52-year-old patient with type 2 diabetes, this may range from 90 to 140 mg/dl but can be individualized based on the patient's comfort level and the presence of other comorbidities. In the hospital setting, a glycemic goal of 100–180 mg/dl is considered to be both safe and achievable [12].

Correction insulin is again calculated as 1800/TDD or 1 additional unit of RAI for each 50 mg/dl increment in BG above the goal range. Instructions to reduce the dose of premeal insulin by 1–2 units for a BG below the goal range can help minimize the risk of a hypoglycemic event.

Insulin Pump Therapy or Continuous Subcutaneous Insulin Infusion (CSII)

While insulin pump therapy is used more frequently in patients with type 1 diabetes, those with type 2 diabetes who are using basal-bolus insulin therapy can also be considered as candidates. Insulin pump therapy usually requires that the patient be motivated to check their BG at least four times a day, that they have the ability to calculate premeal doses based on carbohydrate counting and correction scales, and that they are willing to change the site of the subcutaneous insulin infusion every 2–3 days.

An insulin pump delivers a rapid-acting insulin preparation at a continuous rate that is programmed into the pump. Ideally, this basal rate maintains the desired level of glycemic control without need to ingest meals at specific times. The patient can program the pump to deliver a premeal insulin bolus based on carbohydrate content of the planned meal or snack and the current BG level. The advantages of insulin pump therapy are a reduction in the frequency of low blood sugars and the ability to have more flexibility with timing of meals. The reader is referred to several reviews of insulin pump therapy for more in-depth information [13, 14].

Minimizing Risk for Hypoglycemia

Hypoglycemia is the critical limiting factor in glycemic management. It is broadly defined as any BG <70 mg/dl; however, some patients with diabetes can experience symptoms at a level higher than this [15]. Common causes of hypoglycemia include inadvertent administration of an inappropriate or incorrect insulin dose, administering the dose of basal insulin as RAI, an increase in physical activity, or alcohol consumption without adequate food intake. Frequently, the cause of a single hypoglycemic event may not be readily identified. It is important to review a patient's glucose logs to determine if they are trending toward lower levels of BG at a certain time of the day. This can allow for adjustments of the insulin regimen.

Some patients may eventually fail to experience the early adrenergic warning symptoms of hypoglycemia, such as palpitations or tremor, putting them at high risk for a severe hypoglycemic event, which is defined as a BG <50 mg/dl in which the patient requires the assistance of another person [16]. Risk factors for severe hypoglycemia include a prior history of an event, recurrent prior hypoglycemia, hypoglycemia unawareness, tight glycemic control, defective glucose counterregulation, and autonomic neuropathy [16].

To minimize risk of any hypoglycemic event, patients require education regarding symptoms and treatment, peak times for insulin action, and adjustments of the insulin dose for planned exercise or food intake. Insulin-treated patients can be taught to decrease their prandial insulin by 1–2 units for the meals preceding and following exercise as a way of reducing risk for a hypoglycemic event. Patients who use an insulin pump can be advised to program a temporary 25–50% reduction in basal rate during exercise. It is important that all insulin-treated patients be given a prescription for a glucagon emergency kit and that a family member or companion be instructed in how to use this in the event that hypoglycemia is associated with loss of consciousness.

CONCLUSIONS

- Insulin regimens for type 1 diabetes consist of basal insulin, premeal insulin, and instructions for how to modify doses of premeal insulin for BG above or below the goal range. The initial dose of basal-bolus insulin can be calculated as 0.2–0.3 units per kg per day, with 50% of the calculated dose given as basal insulin and 50% as regular or RAI in divided doses before meals.
- Carbohydrate counting is an alternative method for calculating premeal insulin doses.
- Patients with type 2 diabetes who fail to achieve glycemic control with oral agents alone can have basal insulin added to their regimen at a starting dose based on body weight. A usual starting dose for basal insulin is 0.2 units per kg/day.
- Patients can be taught to gradually increase the dose of basal insulin until the desired level of glycemic control is achieved or a dose of 0.5 units per kg per day is reached.
- If glycemic control is not achieved with basal insulin alone, intensification of insulin therapy with the addition of regular or RAI prior to meals is indicated.
- The risk for hypoglycemia in insulin-treated patients can be minimized by educating patients about warning symptoms, peak times of insulin action, and modification of insulin doses when trends toward lower BG readings are observed.
- Providing a prescription for a glucagon emergency kit with instructions for use allows for rapid intervention by a family member or companion in the event of a severe hypoglycemic reaction.

CASE 1

A 55-year-old woman with type 2 diabetes has an A1c of 7.6% despite therapy with metformin 1.0 gram twice a day, glipizide 10 mg twice a day, and glargine insulin 48 units at bedtime. Her weight is 72 kg. Her home glucose readings reveal the following:

Fasting	Lunch	Dinner	Bedtime
146	136		210
156		130	198
138	122	126	256

What do you recommend?

a. Add lispro 7 units before evening meal
b. Increase glargine insulin by 4 units
c. Increase metformin to 850 mg three times per day
d. Increase glipizide to 20 mg twice a day
e. Add pioglitazone 30 mg a day

CASE 2

A 45-year-old man with type 2 diabetes has an A1c of 9.4% despite therapy with metformin 1.0 gram twice a day and glipizide 10 mg twice a day. His weight is 82 kg. His home glucose readings reveal the following:

Fasting	Lunch	Dinner	Bedtime
176		190	210
184	220	241	198
193	267		256

What do you recommend?

a. Start a GLP-1 analog
b. Add glargine insulin 16 units once a day and titrate dose upwards by 2 units every 3 days until a fasting glucose of <140 mg/dl is achieved
c. Start basal bolus insulin with glargine once a day and a RAI prior to meals
d. Add pioglitazone 30 mg a day
e. Add acarbose 25 mg before each meal

CASE ANSWERS AND DISCUSSION

Case 1. Correct answer: a

This patient's BG readings are in a reasonable range most of the day, with the exception of bedtime. She states that her heaviest meal of the day is in the evening. Adding a RAI prior to the evening meal will help to lower her bedtime readings and may even help to lower her fasting glucose levels as well. Increasing the dose of glargine would lower all BG to a similar extent, which would still leave her with significant evening hyperglycemia. In addition, she is already

on more than 0.5 units per kg of basal insulin without achieving an A1c of <7%. Increasing the metformin or glipizide would have minimal effect on lowering either her bedtime BG or her A1c. Adding pioglitazone has the potential to cause edema and weight gain, since she is already on insulin.

Case 2. Correct answer: c

This patient's BG readings are above goal throughout the day. The expected decline in A1c with a GLP-1 analog or pioglitazone is approximately 0.8–1.0%, and with acarbose approximately 0.5% if he is able to take it as directed. The degree of elevation in his A1c and his home glucose measures suggests that he will need short or RAI to control his postprandial glucose excursions in addition to a basal insulin. One question that arises in situations like this case is whether or not to continue the insulin secretagogue with glipizide. There is no absolute correct answer here. While it would not be incorrect to discontinue it after initiation of basal bolus insulin, some physicians would decrease the dose to 5 mg twice a day with initiation of insulin therapy as a potential way of achieving glycemic control [17].

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14 Insulin Pumps

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Although it is common knowledge that type 2 diabetes is increasing in prevalence, it is less commonly recognized that type 1 diabetes is also increasing in prevalence and that it affects more than a million people in the USA. As insulin deficiency becomes more marked during the course of type 1 (or type 2) diabetes, a more physiological delivery of insulin becomes mandatory for both efficacy and safety. Insulin pumps have increasingly become a preferred therapy to achieve mimicry of physiological insulin delivery.

Insulin pumps continue to evolve in their sophistication and many types are available. The new types and new features often have a bewildering set of menus to negotiate. New insulin pumps are also used with ancillary tools for monitoring, such as continuous glucose monitoring systems (CGMS), either as a part of the same system or in tandem as separate units. It has become hard for most clinicians to keep up with these practice tools and their appropriate usage.

BARRIERS TO OPTIMAL PRACTICE

Clinicians often do not have formal instruction or training regarding insulin pumps and new tools, such as CGMS and online data analysis of monitoring. Practice patterns and pump use are changing rapidly and it is difficult to have the time to learn the new methods and tools. It is not easy to learn the practical aspects of insulin pump use, online patient data recording and analysis, and CGMS by simply reviewing the current medical literature.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Select appropriate candidates and understand preparation needed for use of insulin pumps
- Identify basic elements of pump management and assessment of basal rates, meal bolus, and correction dosing of insulin
- Appreciate advanced features, including use of temporary basal rates and alternatives to usual meal boluses, and to show their application to situations like exercise and high-fat meals
- Understand the methods for troubleshooting, pattern therapy, CGMS and use of online patient monitoring data analysis

WHY CHOOSE AN INSULIN PUMP FOR A PATIENT?

Pros

Flexible and adjustable basal rates

Basal insulin needs may vary significantly throughout the day, and the insulin pump allows one to program basal rates that can be adapted to changing life circumstances, which gives the patient considerable flexibility. Weekend and weekday basal rates can be programmed with modern pumps. Seasonal changes in length of day and outdoor activity may dictate the need to test and to validate the basal rates over time.

More reliable absorption

When insulin pumps are inserted properly and changed with the needed frequency (every 2–3 days for most), they deliver insulin more consistently than injection therapy to meet basal needs and to match boluses with meals or snacks.

Less variability

Glycemic variability is one of the most important and frustrating features of type 1 diabetes. One often hears that "I do things the same, eat the same and time my activity similarly but I still find my blood sugars go up or down at times without obvious explanation." Although pumps do not eliminate variability of blood sugar levels, proper use of insulin pumps markedly reduces this variability. Reduction in variability of blood sugar levels makes it more likely that patients will safely achieve glycemic targets. Nonetheless, it should be understood that misuse of pumps can lead to extreme variability, as with inappropriate proportions of basal and bolus insulin within regimens.

Temporary basal rates

Increased temporary basal rates are particularly useful with acute illness and stressful situations and allow for more effective and consistent control than multiple extra boluses of insulin used alone in catch-up (correction) dosing. Temporary basal rates are also very useful for reducing insulin to compensate for exercise, with its immediate and delayed risks of hypoglycemia.

Precision in dosing

Patients who are quite insulin sensitive and who therefore use very low doses of insulin can give more precise delivery of the intended dose, with an accuracy of 1/10th to 1/20th of a unit.

Variable bolus formats & bolus calculators

Being able to deliver insulin boluses of both different duration and distribution (early vs. late) allows for more physiological mimicry of the way the body would deliver insulin when eating rich meals. Bolus calculators help with accuracy in remembering and compensating for the insulin on board from prior boluses.

Cons

Body Image issues

Many people are concerned about an external device attached to the body and find that it makes them uncomfortable even to contemplate.

It is just a machine and machines do fail

Although initially it is not uncommon to feel that a pump has "deus ex machina" properties, patients (and clinicians) need to understand that it is just a tool that must be used properly and will require considerable attention and learning.

Not for everyone

It is unwise to "sell" a patient on an insulin pump if they are uncomfortable with the idea or don't themselves see an advantage. Useful things to consider are to let them review pumps and their management with a diabetes educator and perhaps get to know others with insulin pumps who have had considerable success after learning how to use them.

Requires knowledge and skills

Most patients will need to attend classes and individual instruction on how to use insulin pumps. For safe, effective use, one must learn the "rules of the road" to successfully acquire the skills that make a pump a good tool for controlling blood sugars.

Involves dexterity, technical skills, good hearing

People with physical, intellectual, or other limitations may not be good pump candidates. Nonetheless, even young children can learn pumps quite quickly.

It is more, not less, work for patients

Many patients want to use an insulin pump because the patients have the false impression that pumps will automate glycemic control. Far from that, insulin pumps require extra work. Will the extra work lead to better, safer glycemic control? If properly used, the answer is yes.

WHO IS A PUMP CANDIDATE?

A pump candidate is first of all someone who is motivated. They must be committed and capable of learning carbohydrate counting and demonstrate that mastery prior to embarking on pump therapy. They must be willing to keep good records and to do frequent monitoring. It is not appropriate to "coast" or to go on "autopilot" (i.e., insufficient monitoring and dose adjustment) with a pump because it can be dangerous. Patients need good dexterity and visual acuity to use a pump. Their hearing should be acute enough to hear the alarms for the pump. There is a significant financial commitment for pump use and there is also a need to be comfortable with the technology of such machines. Finally, and in some ways most importantly, the patient must commit to communicate information about blood sugar levels and the factors that influence them in an honest and open fashion to the diabetes educators and doctors they work with.

PREPARATION FOR INSULIN PUMP THERAPY

- Start on basal-bolus therapy
- Assessment of patient's understanding of advanced carbohydrate counting
- Establish the patient's carbohydrate ratio, insulin sensitivity, and glucose targets (You may teach the 450 rule, 1800/1700 rule and use overall lability estimation to judge safe targets.)
- Have patient demonstrate knowledge of carbohydrate counting skills
- Have patient send in blood glucose records with adequate information to assess their knowledge base and skill acquisition

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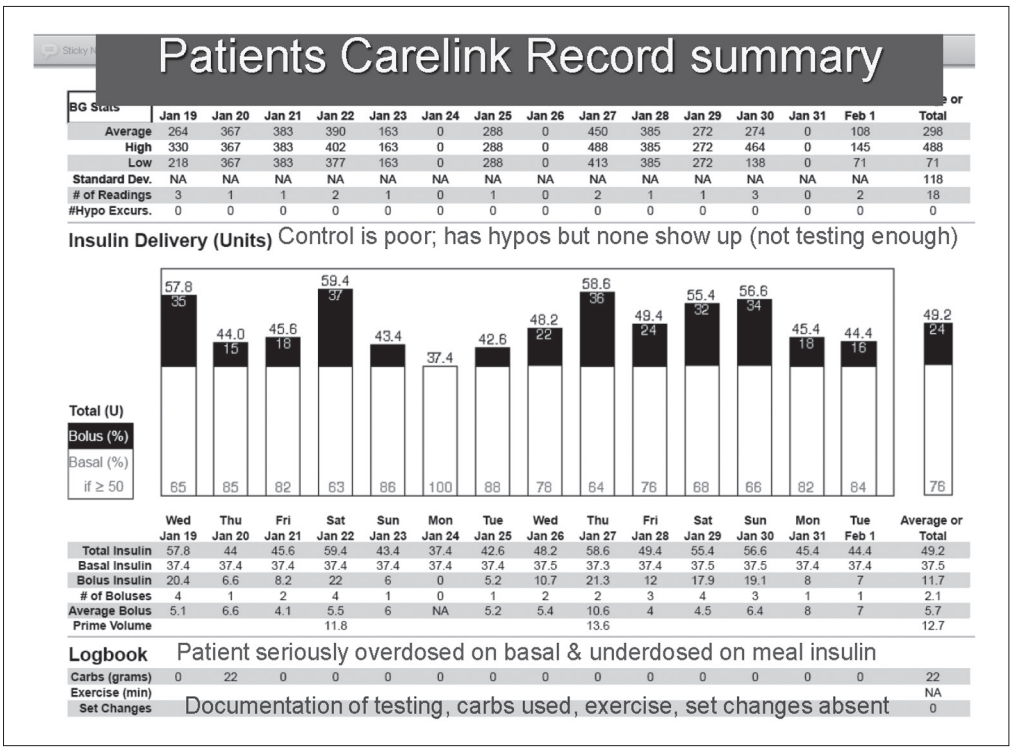
CASE 1

A Patient with Poor Control and Multiple ComplicationsA 55-year-old man with type 1 DM has a long history of poor glycemic control, known retinopathy, neuropathy, and gastroparesis. Patient is fearful of hypoglycemia with bolus insulin and he constantly snacks ("grazes")or drinks sodas during the day if he is working and he eats a large fatty meal and grazes in the evening. He has daytime hypoglycemia if he is working or has increased physical activity.

A1c = 10.5%–11%. He has been on insulin pump therapy for 3 years, with a total daily dosage of insulin of 37–60 units. He is working with DM educator to achieve better control (just started).

After two weeks he returns to see you to review his data *(See Figure 14-1)*.



BG Stats	Jan 19	Jan 20	Jan 21	Jan 22	Jan 23	Jan 24	Jan 25	Jan 26	Jan 27	Jan 28	Jan 29	Jan 30	Jan 31	Feb 1	Total
Average	264	367	383	390	163	0	288	0	450	385	272	274	0	108	298
High	330	367	383	402	163	0	288	0	488	385	272	464	0	145	488
Low	218	367	383	377	163	0	288	0	413	385	272	138	0	71	71
Standard Dev.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	118
# of Readings	3	1	1	2	1	0	1	0	2	1	1	3	0	2	18
#Hypo Excurs.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

	Wed Jan 19	Thu Jan 20	Fri Jan 21	Sat Jan 22	Sun Jan 23	Mon Jan 24	Tue Jan 25	Wed Jan 26	Thu Jan 27	Fri Jan 28	Sat Jan 29	Sun Jan 30	Mon Jan 31	Tue Feb 1	Average or Total
Total Insulin	57.8	44	45.6	59.4	43.4	37.4	42.6	48.2	58.6	49.4	55.4	56.6	45.4	44.4	49.2
Basal Insulin	37.4	37.4	37.4	37.4	37.4	37.4	37.4	37.5	37.3	37.4	37.5	37.5	37.4	37.4	37.5
Bolus Insulin	20.4	6.6	8.2	22	6	0	5.2	10.7	21.3	12	17.9	19.1	8	7	11.7
# of Boluses	4	1	2	4	1	0	1	2	2	3	4	3	1	1	2.1
Average Bolus	5.1	6.6	4.1	5.5	6	NA	5.2	5.4	10.6	4	4.5	6.4	8	7	5.7
Prime Volume				11.8					13.6						12.7

Logbook															
Carbs (grams)	0	22	0	0	0	0	0	0	0	0	0	0	0	0	22
Exercise (min)															NA
Set Changes															0

Figure 14-1

POSSIBLE STRATEGIES AND ISSUES FOR PATIENT IN CASE 1

He needs to validate basal rates if he is to safely give boluses. He would benefit from dietary counseling. Changing from a high-fat diet might help his gastroparesis.

Patient returns with following blood glucose (BG) results from finger sticks:

- ◊ 7 am BG 365 bolus 6 units (ISF was presumed to be 50), BG 320 9 am, 245 11 am, 167 1 pm

How do you interpret this?
What type of bolus would be useful in patients with gastroparesis?

A. This patient wanted to increase his basal rate, but he more likely needs is to increase his bolus dosing. His ISF (insulin sensitivity factor) has been set too high. The ISF is an estimation of the drop in insulin per unit of insulin administered; an ISF of 50 indicates that his blood sugar level should decline by 300 with 6 units of insulin near the peak of bolus effect, which is usually 90–120 minutes. He should increase his bolus insulin gradually and decrease his daytime basal insulin rate (to reduce the risk of hypoglycemic episodes. Gastroparesis usually needs a square wave (a bolus of insulin administered continuously over a set amount of time) or alternatively a dual wave bolus (an initial bolus with the meal that is extended for a short duration to start with, perhaps 30–120 minutes beyond the usual, and looks a bit like a camel with two humps). It would often be given with a reduction in first component (e.g., 30% in the first wave of the dual wave bolus and 70% in the second) wave to avoid early post-meal hypoglycemia; the ratio of early to late delivery depends on what you eat. This patient is thought to have gastroparesis and thus should avoid high-fat, high-fiber foods that will further delay gastric emptying. Liquids with carbohydrate are much less affected by gastroparesis.

As with injections, the lag time, which is the time between bolus initiation and food consumption, can be varied with pumps as well to enhance safety. For example, a patient with a low blood sugar just prior to eating may choose to have the bolus start after the meal.

CASE 2

HPI: Ms. P is 43-year-old woman with 20 years of T1DM. She has coronary artery disease, hypertension, retinopathy, neuropathy, congestive heart failure, mixed hyperlipidemia, tobacco abuse (half a pack to a pack a day), and cerebrovascular disease, and is overweight. She had an amputation of right foot third toe. She has few complaints, butshe recently had one severe hypoglycemic reaction, about 7 o'clock at work that occurred 5 hours after lunch with a meal-time bolus of 4 units. She has few if any premonitory symptoms prior to severe hypoglycemic episodes.

MEDS: Insulin pump: Basal rates: 0.25 units at midnight with 3 a.m. starting at 0.7 units, 5 a.m. 0.9 units, 7 a.m. 1.2 units, and noon to midnight 1.4 units. Her

ISF has been estimated at 50 and her insulin to carbohydrate ratio 1:15. (The insulin to carbohydrate (I:C) ratio is an estimate of the number of units of insulin to take per 15 grams of carbohydrate.) She is supposed to administer insulin boluses of 3–5 units of NovoLog with meals, but sometimes "she is too busy to administer the bolus." Her other medications include atorvastatin 20 mg daily; ezetimibe 10 mg daily; aspirin 325 mg twice daily; clopidigrel 75 mg daily; carvedilol 6.25 mg twice daily; furosemide 60 mg daily; alprazolam 0.25 mg prn;and a multivitamin.

Lab: Last A1c was 9.1%. Microalbumin was negative, TSH was 0.98. Lipid panel: total cholesterol 93, triglycerides 57, HDL 30, and LDL 54.

Exam: Pleasant white female, alert, oriented, and appropriate. BP 124/76, weight 142 pounds, heart rate is 78. BMI is 29. Cheiropathy of her hands and feet. PERRL; retinal scarring, proliferative diabetic retinopathy. Thyroid normal size. Clinically she is euthyroid. Carotids no bruits. JVP not increased. Lungs are clear. Heart regular rate and rhythm. Normal S1 and S2—no murmurs or gallop. Abdomen is soft. There are no problems with the pump site. No liver or spleen enlargement. Ext: She has fragile skin, dry skin.

Feet: amputation of 3rd toe.

1. ***What other information do you need to seek?***
   A. You need to know how much of her insulin is basal vs. bolus. (The answer when her pump was interrogated was 21.5 of 22.5 units on the day she came to clinic was basal insulin—way out of usual 50/50 proportion!)

2. ***What should be done with her pump?***
   A. Reinforce that meal-time insulin boluses must be given and reduced basal is usually going to be needed if you are to raise the meal insulin dose to an appropriate level and avoid hypoglycemia.

3. ***What caused her hypoglycemia?***
   A. She was primarily managing her glucose with basal insulin. She missed her dinner, and she has a high basal rate. It is the same reason she has to graze to avoid hypoglycemia and why it has been hard for her to take bolus insulin without hypoglycemia.

4. ***Her blood glucose is usually very high (often >250 mg/dl) in the evening and always comes down by morning to 130–140. What does this mean?***
   A. Overdose of basal insulin and underdose of meal insulin typically manifest as progressive daytime hyperglycemia followed by precipitous drops in blood glucose overnight. Because she is using basal insulin as the primary mechanism for managing her blood sugar levels, she has programmed her pump to administer higher basal rates in a progressive, step-wise increase from 7 AM until 3 AM. Her blood sugar levels follow a staircase pattern *(see Figure 14-2)*, where the blood sugar levels drop dramatically at night due to no intake of food and a high basal rate.

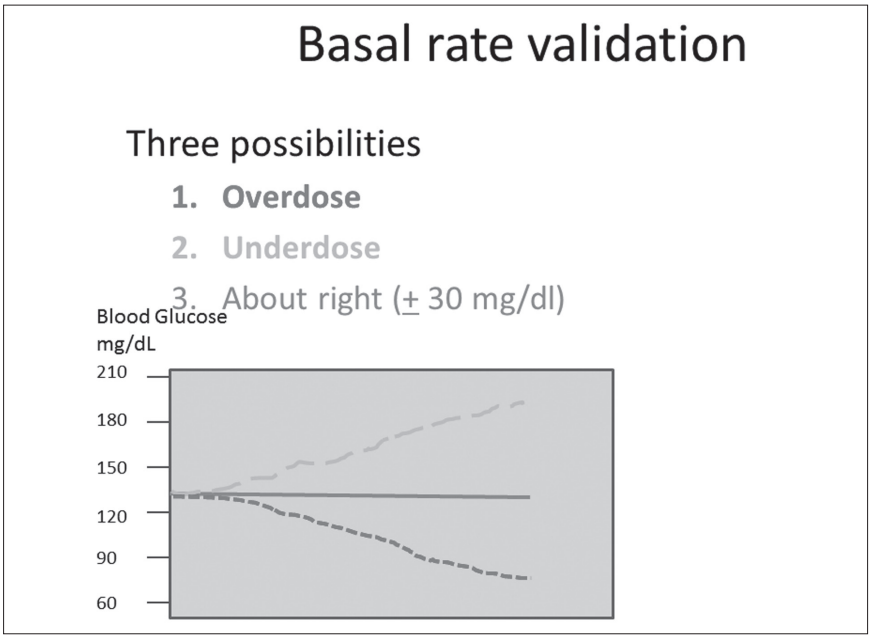


Figure 14-2

5. ***What do you advise for her, given that she has little warning about her hypoglycemia?***
   A. She needs to test her blood sugar levels frequently and scrupulously follow an appropriate basal-bolus ratio (close to 50-50). Continuous glucose monitoring might be useful for her, too. If she can avoid frequent hypoglycemic episodes, then she will likely recover some of her hypoglycemic awareness.

CASE 3

Mr. E is a 36-year-old man with 12 years of type 1 DM. He also has HTN, hyperlipidemia, and mild background diabetic retinopathy, but no other complications. He is frustrated by his generally poor glycemic control based on his A1c levels (8.5–9%) and stubbornly resistant fasting hyperglycemia. He usually eats three meals daily and his evening meal generally has generous portions of meat. He eats out frequently after long working hours and has no regular exercise program. Eats 6–7 pm—notes BG is pretty good for a few hours but then CGM show that BG rises until 4–5 am. He has a CGM system to help him and comes to you for advice on how to determine ways to improve his glycemia. He has a family history of both type 1 and type 2 DM *(Figure 14-3)*.

Meds: ramipril 10 mg, HCTZ 25 mg daily, pravastatin 20 mg daily, alpha-lipoic acid
Basal insulin rates: MN-1.55, 5a-2.0, 7a-1.4, 3p-1.1, 6p-1.55, ISF 24 MN to noon, 35 noon to MN, I:C 1:10
Exam: Weight 89 kg, BMI 28.5, no obvious complications, some central adiposity
A1c 8.5%, lipids ok

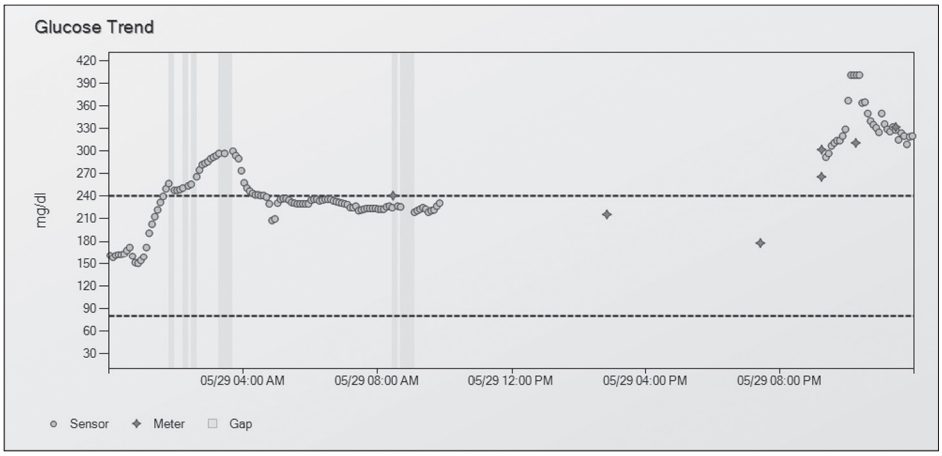


Figure 14-3

1. ***What are causes of fasting (AM) hyperglycemia?***
   A. Common causes of fasting hyperglycemia and appropriate investigation
      ◊ Somogyi phenomenon (night-time hypoglycemia followed by rebound hyperglycemia in morning due to response to glucagon and other counterregulatory hormones that raise blood glucose) Check middle of the night for lows. Note that this is actually not very common.
      ◊ Extended post-dinner or snack hyperglycemia Check middle of the night for highs
      ◊ Too little basal insulin Check middle of the night for highs
      ◊ Dawn phenomenon(rise in blood glucose levels in early morning due to normal circadian rhythm of some counterregulatory hormones, such as cortisol). Check middle of the night for good sugars.

The common diagnostic denominator for all of these causes of fasting (AM) hyperglycemia is to check night-time blood glucose levels. The results of his blood glucose monitoring are shown *below*.

2. ***How do you interpret these results?***
   A. This patient had large high-fat evening meals, resulting in extended postmeal hyperglycemia well into the night and into the next day. Possible solutions include the following: Eat lighter dinners and evening snacks, dual wave bolus with several hour extension, increase activity late in the day, or add pramlintide (least desirable option), a drug that increases glucose absorption and reduces insulin requirements by delaying gastric emptying, promoting satiety, and decreasing glucagon secretion. Although it may reduce post-meal hyperglycemia, it does so early and not late after the meal and thus would not fit the situation here.

CASE 4

Mr. P is a 35-year-old man with many years of type 1 diabetes who uses an insulin pump. His basal rates are: MN -1.4, 4 AM -1.7, 10 AM -1.4, 8 PM -1.5.

His ISF is 30, his I:C is 6 but he admits he is largely guessing. He eats a diet rich in protein. He is using correction boluses of insulin with a target blood glucose range of 70–120 mg/dl, but his glucose control is poor, with an A1c of 9.0–9.5%. Such an aggressive target range is inappropriate when the glycemic control is erratic or poor.

History: Non-proliferative diabetic retinopathy, mild neuropathy, microalbuminuria

Exam: Muscular overweight young man. BMI 32.7. BP 118/70, P 72. The rest is consistent with history—decreased vibration sense, some retinopathy.

His blood glucose levels are high late in the day and sometimes high in the morning. He has had some hypoglycemia when he tries to increase exercise in the late afternoon or watch his diet more closely. He eats small meals or none during the day and comes home late and eats a large dinner. You recommend a basal test. A basal test is used to determine if the basal rate is correct. It is done in 4–8 hour segments in the morning, afternoon, evening, and night. The patient fasts and avoids strenuous activity during these segments and checks blood sugar levels frequently (except the night-time segment, when the blood glucose is checked before falling asleep and 4 hours later when awakened). The patient does NOT provide correction bolus of insulin during basal testing *(see Figure 14-4)*.

Basal test: Morning basal tests: 08:29, 360; 09:29, 324; 10:29, 308; 11:44, 346; 12:34, 315; 13:39, 355; 14:30, 333 (stable poor control—basal rate is okay).

Afternoon: 12:56, 123; 14:10, 105; 15:01, 99; 15:58, 114; 16:47, 131 (stable control—basal rate okay).

Evening basal rate testing: 15:55, 147; 17:30, 103; 18:30, 87; 19:28, 72 began feeling hypoglycemic; 20:00, 72; 20:30, 74 (basal rate overdose and dose to be reduced by 0.1 units per hour and retest).

Labs: A1c 9.3%

Based on the above, what is the cause of night-time hyperglycemia?

A. He is over-treating with his evening basal rate to help control his blood glucose levels because he under-boluses at meals. Note how his blood sugar levels decline significantly in the evening during the basal testing! He needs to reduce his evening basal rate and increase his meal boluses of insulin. He will be able to get a better sense of the need for meal insulin when his basal dose is correct. His I:C ratio is likely to be much lower than 1:15. One simple way to estimate the insulin to carbohydrate ratio is the "450 rule." To apply this rule, total daily insulin dosage (TDD; basal plus bolus) by 450. For example, a patient using a TDD of 30 units would have an I:C ratio of 1:15. Based on the 450 rule, Mr. P has a I:C ratio of close to 1:4. The estimated I:C ratio should be confirmed by 2-hour postprandial glucose values. Note that this rule depends upon the patient's understanding how to accurately count carbohydrate (grams) calories and that the patient does so with each meal.

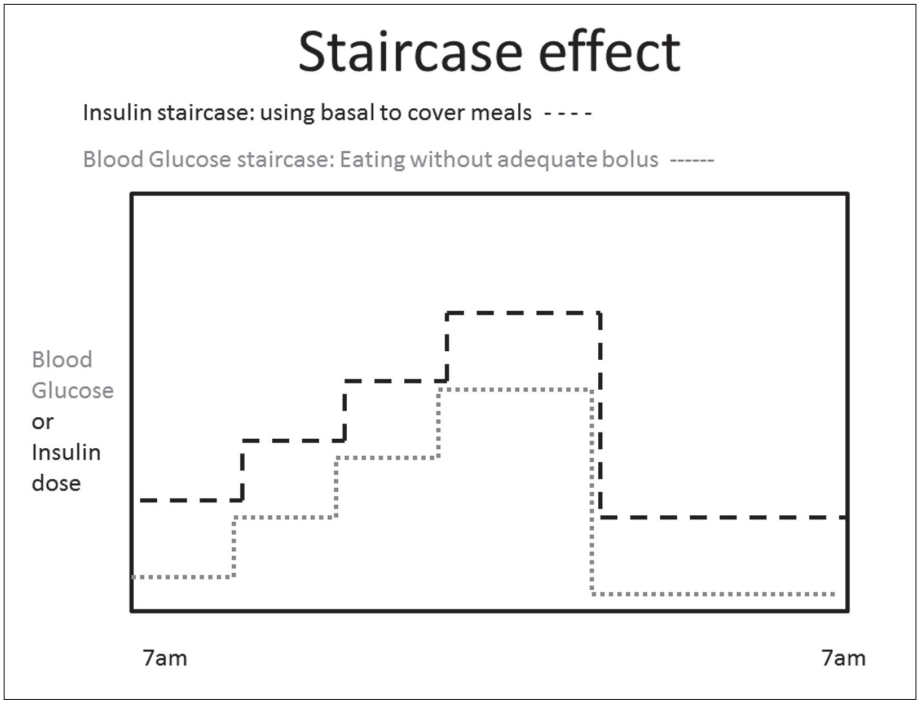


Figure 14-4

To verify overnight basal rates

- Eat dinner at 5 PM—preferably not a very high-fat meal
- Test blood sugar at 9 PM (food should now have been absorbed)
- Skip the bedtime snack/test blood sugar
- Test blood sugar at 3 AM
- Test blood sugar at 7 AM

We are looking to see if blood sugar stays within about 30 mg/dl of the starting point. Relay these results to your diabetes educator or clinician to discuss necessary changes.

Basal rate testing morning

When you obtain the correct overnight basal rates and awaken with blood sugars consistently within your target range, you can test to verify morning basal rates as follows:

- Check your blood sugar at 7 AM
- Skip breakfast
- Test blood sugar at 10 AM
- Test blood sugar at noon

Afternoon basal rate testing

When both overnight and morning rates are correct, you may proceed to checking the afternoon rates by:

- Test your blood sugar at noon
- Skip lunch

- Test blood sugar at 2 PM
- Test blood sugar at 5 PM

Evening basal rate testing

Finally, the evening basal rates are determined:

- Eat lunch at noon
- Test blood sugar at 5 PM
- Skip dinner
- Test blood sugar at 7 PM
- Test blood sugar at 10 PM

When to refer to an endocrinologist

All patients on insulin pumps may benefit from co-management with an endocrinologist or at least episodic review by an endocrinologist.

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15 CGM and Its Role in Diabetes Management

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SIGNIFICANCE OF CLINICAL PROBLEM

The introduction of home blood glucose monitoring over 3 decades ago, especially for type 1 diabetes, was seen as a "revolutionary" advance. Still, it wasn't until the publication of the DCCT in 1993 that this technology was embraced by the medical establishment.

We have now had real-time continuous glucose monitoring (CGM) available for about 6 years and, like home blood glucose testing, initial uptake has been relatively slow. There have been several reasons for this. (This current discussion focuses on only "real-time," or "personal CGM" and not masked, or "professional CGM," which is blinded to the patient, who wears it for 3 days before it is downloaded in the physician's office.) First, the technology is not yet perfected in terms of sensor accuracy, although it is significantly better now than it was several years ago. Secondly, we are now in an era of "evidence-based medicine" where often both we and the payers are expecting randomized controlled trials to show benefit before the therapy is adopted. Third, despite the publication of the JDRF Sensor Study in October of 2008 and the STAR-3 study in June of 2010 many (and in some regions, most) insurance companies will not reimburse for the materials (both hardware and software). (Although the initial report of the JDRF study had mixed results, further publications of this study and other studies have demonstrated that for patients with baseline A1c levels >7% and who wear the sensor frequently, A1c outcomes are improved.) Finally, and perhaps most importantly, many diabetes clinics/offices in both private and academic settings do not have an appropriate infrastructure to efficiently administer CGM. Due to all of these issues, the uptake of CGM in the endocrinologist's clinics/offices has not been as widespread as some predicted and use in primary care has been negligible. Nevertheless, there has been a slow but steady increase in the use of CGM by interested patients and, despite the challenges, more physicians are prescribing CGM for appropriate individuals.

What the primary care phyisician needs to know about

CGM is performed by inserting a SC catheter with a pinpoint sensor that is in contact with interstitial fluid (ISF). In the setting of glucose oxidase (that is placed at the end of the sensor), ISF glucose can generate hydrogen peroxide. The current generated from the hydrogen peroxide is in proportion to the glucose level in the interstitial fluid (which is in proportion to the blood glucose). Thus, there is a lag time between the ISF glucose and the blood glucose. This lag may be

anywhere from 5 to 15 min and needs to be appreciated by the patient. What this means is that "real-time" is not exactly so with this technology.

While the accuracy of CGM devices has improved, they are far from perfect. Perhaps the greatest barrier is the blood glucose calibrations themselves, since our current glucose monitors can have an inaccuracy of 20% when the blood glucose is above 75 mg/dl and 15 mg/dl when the blood glucose is below this level. Between the potential for glucose monitoring inaccuracies and drift of the CGM device itself, current labeling for CGM is that home glucose monitoring is still required for insulin dosing decisions. Furthermore, it is the trend of glucose, as opposed to the glucose level itself, that makes CGM so powerful. Patients who don't appreciate this will not have a good experience. Knowing that the glucose is 110 mg/dl on a sensor and going down is much more important than seeing a glucose of 110 mg/dl on a home glucose meter and assuming it is stable or even going up (for example, after a meal). The trend of glucose is a dimension not addressed in past generations of "glucometrics."

Perhaps the most important, if not critical, advantage of CGM is the ability to intercept hyper- or hypoglycemia before it occurs. Patients can both watch the glucose levels in (almost) real-time or be alerted by an alarm when the glucose level is above or below a pre-arranged setting. The newer sensors can also provide a "predictive alarm" that alerts the patient prior to the critical glucose level. Over time, many patients develop "alarm fatigue." In our clinic, we have become more selective with the alarm settings as we try to have them activate only when there is the risk of severe hyperglycemia or hypoglycemia. For example, for most patients, we set the high glucose alert at 220 mg/dl and the low glucose alert at 70 mg/dl. For certain patients, however, different setings would be more appropriate. For example, for a pregnant woman, the high alert might be set at 140 mg/dl. For a patient with hypoglycemic unawareness, the low alert might be appropriately set at 90 mg/dl. Assuming the patient reacts to the alarms, potential problems might be averted with CGM.

Clinical trials have shown a reduction of both hyper- and hypoglycemia exposure. Patient selection is important. Patients must be willing to make changes in the timing of their insulin in relation to food, confirm and calibrate glucose readings with their monitor, and regularly wear the device in order to benefit from CMG. As of 2011, third-party payers are most likely to pay for CGM for patients with type 1 diabetes and hypoglycemia unawareness or patients with type 1 diabetes who are considering pregnancy.

It should be noted that as our experience continues to grow for this therapy in type 1 diabetes, there is emerging evidence that CGM might be helpful for those with type 2 diabetes, even for those not requiring insulin therapy. Any patient with diabetes using CGM should be willing to change their lifestyle and medication adherence when using this new technology.

BARRIERS FOR OPTIMAL PRACTICE

Several barriers ideally should be addressed up front.

- *Appropriate patient population* There is no consensus on this point, but all of the major sensor trials seem to have a common theme. In general, to

successfully use CGM, patients with type 1 diabetes should be performing most or all of the basic elements of continuous subcutaneous insulin infusion (CSII) or multiple injection therapy (MDI). There is not enough experience yet with type 2 diabetes to make firm recommendations.

- *Appropriateness of clinician population* There are few data to guide us, but the clinician needs to have a good understanding of the principles of insulin therapy and be willing and able to spend extra time with these patients. Time has been one of the largest barriers for the endocrine community because there have been no codes for billing the additional time until very recently.
- *Downloading* There isn't much known about how often clinicians review the downloaded data from their patients' meters and pumps, but it appears that clinician review of CGM downloading is infrequent. The only way to adequately review patients' progress at an office/clinic visit is by reviewing a download of glucose results, and clinicians need to be able to download the CGM devices at their offices (or the patients can download at home). Several programs, including smart phone applications, are in development that should make this part of the experience easier and faster.
- *Administrative hassles* This is particularly problematic in areas where reimbursement for the devices is poor. Clinicians often must intercede with third- party payers to obtain access to CGM for those who could have the greatest benefit (patients with hypoglycemia unawareness and pregnant women).

LEARNING OBJECTIVES

As a result of reading this chapter, participants should be able to:

- Understand the basic mechanics of current-day CGM devices
- Understand the most appropriate patients who can benefit from this technology
- Understand the potential benefits of CGM
- Understand the barriers to effective CGM use
- Understand when the appropriate patient should be referred and who is the best referral candidate for CGM
- Review how CGM has affected the risk of severe hypoglycemia in T1DM

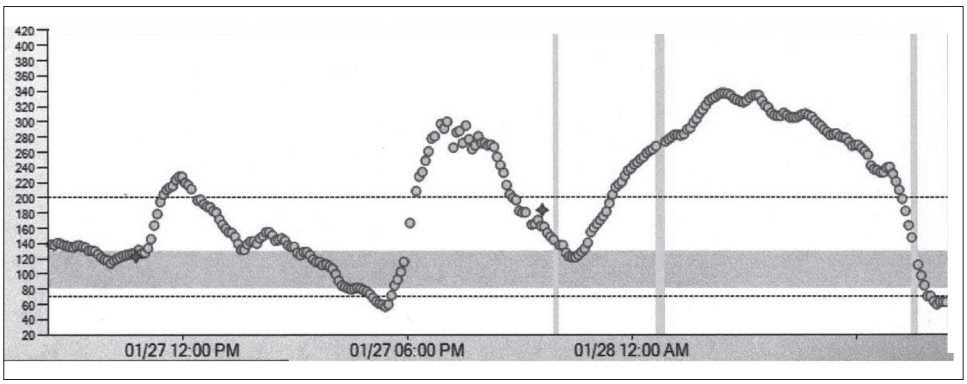

Figure 15-1

CASE 1

This patient is home at with her infant. She returns to her endocrinologist 5 months postpartum. She takes bedtime insulin glargine and premeal insulin lispro. The patient was delighted that her A1c was 6.4%, but the CGM download *(see Figure 15-1)* shows dangerous hypoglycemia with little attention to when she gave her insulin. It is clear her current diabetes therapy is unsafe, as she is paying little attention to her diabetes. The detail of this type of information would not be available with routine home blood glucose monitoring.

CASE 2

(Figure 15-2) illustrates the CGM download of a patient on an insulin pump wearing CGM. Note that around 11 am she gave a bolus of 9.3 units of insulin based on her glucose level and the 75 grams of carbohydrate she was planning to eat. However, she became hypoglycemic 2 hours later and she ate a carbohydrate-rich snack. Unfortunately, she over-treated her hypoglycemia. When she checked her glucose at about 1 pm, her pump's calculator indicated to take additional insulin. The pump's calculator could not know that she had over-treated her hypoglycemia. With her glucose level rising so rapidly by 1 pm, she needed additional insulin. When her glucose level rose above 300 mg/dl, she finally infused additional insulin, but she was quite frustrated by the rapid changes in glucose levels. This patient's experience with CGM can allow her to learn how to avoid these vicissitudes. First, when the glucose level drops rapidly, she needs to eat prior to hypoglycemia. Second, when she treats the hypoglycemia, only 15 grams of carbohydrate is generally required. Third, when the glucose level is trending up, she will need more insulin than recommended by the pump's calculator (in this case she needed more than the recommended "0 units").

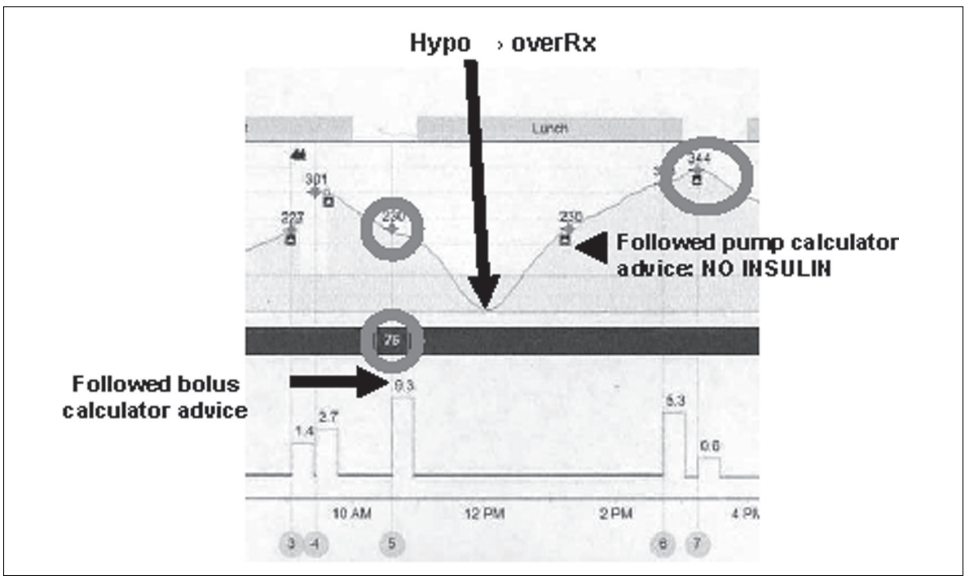

Figure 15-2

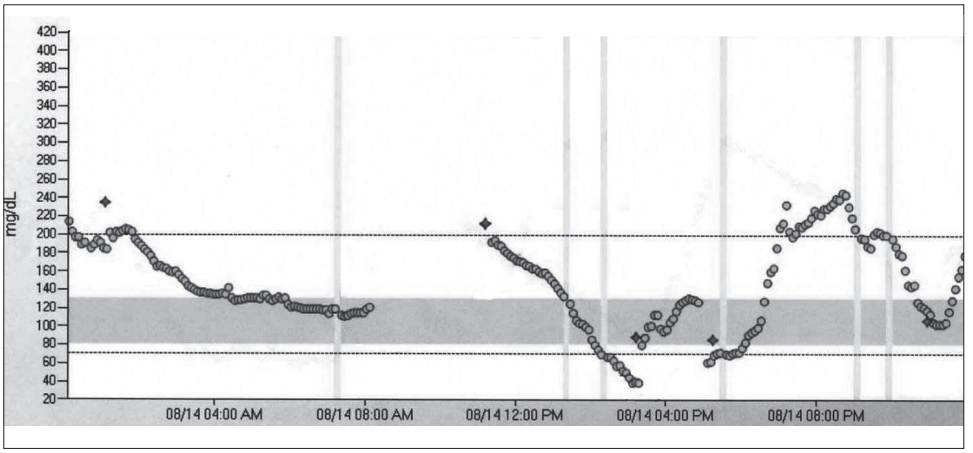

Figure 15-3

CASE 3

(Figure 15-3) illustrates the CGM download from a 55-year-old man takes basal insulin glargine and premeal aspart. He gave 4 units of aspart after he calibrated his sensor, and his glucose level at the time was just over 200 mg/dl. Unfortunately, he neither ate nor looked at his sensor; technology like the CGM only helps when it is used! After hitting golf balls, he lost consciousness and had to be treated by paramedics. The reduction of his glucose from noon to 4 pm matches exactly the expected effect of the insulin he took without eating food. This "learning experience" with CGM should convince the patient to look at his sensor and to eat a small quantity of food when the glucose level is plummeting.

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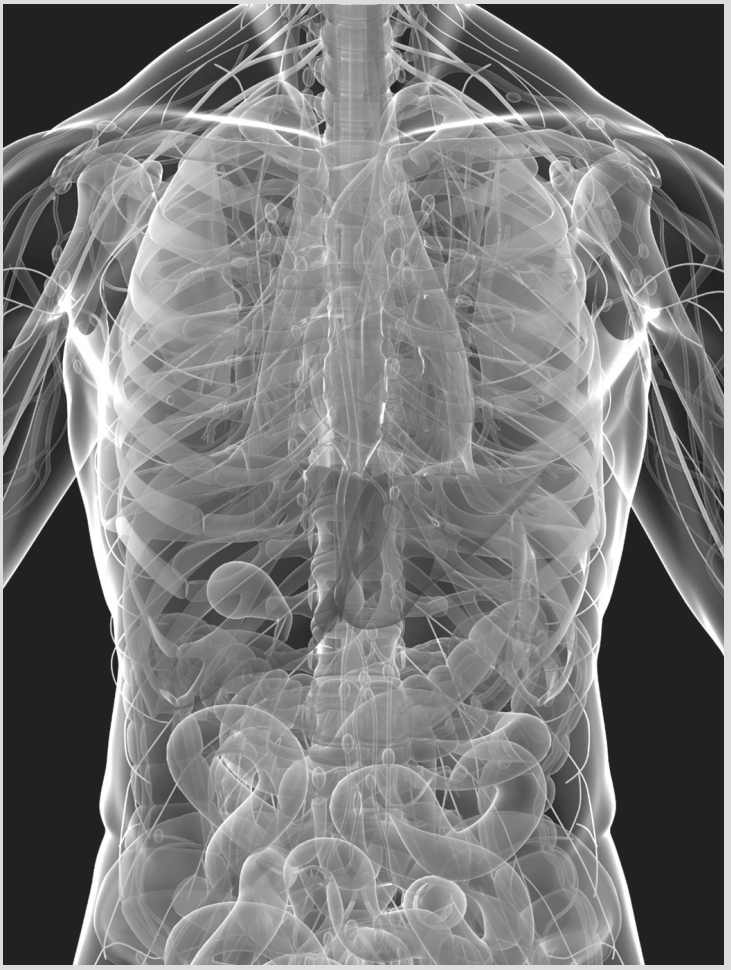
CARDIOVASCULAR ENDOCRINOLOGY



16 Dyslipidemia Beyond the Statin

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Statins are the first-line therapy for patients with risk factors for cardiovascular diseases due to robust clinical data demonstrating improvements in clinical outcomes. However, not all patients can tolerate statins; thus, providers need to understand the efficacy and safety of other lipid- lowering agents. Additionally, despite statin therapy, many patients continue to experience cardiovascular events. This is termed residual risk. Therefore, we will discuss the use of non-statin lipid-lowering agents in the treatment of dyslipidemia and review the best current evidence on combination lipid-lowering therapy for reduction of cardiovascular events.

BARRIERS TO OPTIMAL PRACTICE

There is a wealth of data demonstrating the efficacy and safety of statins,[1] but there is a relative lack of data to support the use of combination lipid-lowering therapies or to assist the provider with selecting one lipid-lowering agent compared to another for statin-intolerant patients.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Understand the efficacy and safety of non-statin lipid-lowering therapies
- Understand the efficacy and safety of combination lipid-lowering therapies
- Develop strategies to treat subjects with renal impairment

STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT.

Non-statin lipid-lowering therapies—Some patients do not reach LDL cholesterol goals even on high doses of very potent statins. In most instances, the baseline LDL levels in these patients are very high due to underlying genetic disorders, such as familial hypercholesterolemia. In patients who do not reach LDL goals, the addition of other treatment approaches is indicated, including intensive diet therapy, adding soluble fiber to the diet, plant sterols/stanols, ezetimibe, bile resin binders, niacin, and LDL apheresis. Other patients are intolerant of statins due to development of severe myalgias, myositis, or liver dysfunction. Although statins are the first choice in lipid-lowering agents, providers need to be aware of alternatives.

Myopathies are a major side effect of statin therapy and prevent some patients from using this key class of drugs.[2] The major risk factors for statin-induced myopathy are advanced age, hepatic disease, renal disease, low body mass, hypothyroidism, alcohol consumption, heavy exercise, intrinsic muscle disease, genetic polymorphisms (Cyp3A4 and OATP1B1, an organic anion-transporting polypeptide), and drugs that interfere with statin metabolism (gemfibrozil, cyclosporine, protease inhibitors, azole antifungals, macrolide antibiotics, amlodipine, verapamil, diltiazem, amiodarone). The Cyp3A4 pathway metabolizes simvastatin, lovastatin, and atorvastatin and drugs that inhibit Cyp3A4 will increase the serum levels of these statins, increasing the risk of myopathy. In contrast, pravastatin, rosuvastatin, and fluvastatin are metabolized by alternative pathways and should be used in patients taking drugs that inhibit Cyp3A4. Gemfibrozil inhibits the glucuronidation of most statins (the exception is fluvastatin), leading to increased serum levels and increasing the risk of myopathy.

The approach to patients with statin-induced myopathy includes checking for hypothyroidism and drug interactions, using statins that are metabolized by different pathways than the statin associated with the myopathy, using low-dose statin therapy, using a long-acting statin (rosuvastatin or atorvastatin) 2-3 times per week, adding coenzyme Q10, adding vitamin D in patients with low 25OHD levels, or using other treatment approaches to lower cholesterol levels. (Note, however, that there are no randomized trials showing a benefit for coenzyme Q10 or vitamin D supplements in this setting.[3,4]) Other treatment approaches that can lower LDL cholesterol levels in patients who do not tolerate statins include intensive diet therapy, adding soluble fiber to the diet, ezetimibe, bile resin binders, niacin, plant sterols/stanols, and LDL apheresis. These approaches will often result in the patient's achieving LDL goals.

Plant sterols, by competing with cholesterol in the formation of micelles in the intestinal lumen, and ezetimibe, by binding to NPC1-L1 on intestinal cells, block the intestinal absorption of cholesterol. This leads to a decrease in cholesterol delivery to the liver, a decrease in hepatic cholesterol levels, and the up-regulation of hepatic LDL receptors, resulting in a reduction in serum LDL levels. Plant sterols are available in food products, particularly margarines, and as plant stanol pills. The usual dose for stanol pills is 1-3 grams per day with meals and this can result in a 5–15% decrease in LDL cholesterol. Ezetimibe is available as a 10-mg pill and lowers LDL cholesterol between 15 and 20%. The combination of rosuvastatin 40 mg (maximum dose of the most potent statin) and ezetimibe 10 mg has been shown to result in an almost 70% decrease in LDL cholesterol levels.[5]

Bile resin binders (cholestyramine, colestipol, colesevelam) bind bile acids in the intestine and prevent the reabsorption of bile acids in the terminal ileum. A decrease in the delivery of bile acids to the liver leads to a decrease in the activation of FXR, a nuclear receptor that recognizes bile acids, and this decrease in FXR activation stimulates the synthesis of bile acids from cholesterol. This results in a decrease in hepatic cholesterol levels leading to the up-regulation of hepatic LDL receptors and a reduction in serum LDL levels. Bile resin binders decrease LDL cholesterol by 10–30%. In addition, a decrease in the activation of FXR also results in an increase in serum triglyceride levels

by several mechanisms, including an increase in hepatic triglyceride synthesis due to an increase in SREBP-1c and a decrease in the lipoprotein lipase activator apo CII, which would decrease the catabolism of triglyceride-rich lipoproteins. Bile resin binders, particularly cholestyramine and colestipol, which are taken before meals, can bind a variety of drugs, and therefore other drugs should be taken either 2 hours before or 4 hours after taking a bile resin binder. Very recent studies have shown that colesevelam improves glycemic control in patients with diabetes, resulting in approximately a 0.5% decrease in A1c levels.6 The mechanism for this beneficial effect on glucose metabolism is unknown.

The mechanism by which niacin lowers LDL levels is unclear but may be related to decreases in VLDL production. Reductions in LDL levels of 10–25% are frequently observed. In addition to lowering LDL, niacin also increases HDL and lowers triglyceride and Lp(a) levels.

LDL apheresis lowers LDL cholesterol and Lp(a) efficiently and safely when performed weekly or biweekly.[7] It is primarily used in patients with homozygous familiar hypercholesterolemia, severe heterozygous familiar hypercholesterolemia, or severe cardiovascular disease who have marked elevations in LDL or Lp(a) despite medical therapy.

Combination lipid-lowering therapies

Despite statin therapy, some patients do not reach LDL cholesterol goals or non-HDL cholesterol goals. For patients at high risk of cardiovascular disease, providers should consider combination lipid-lowering therapies, with the addition of fibrates, niacin, ezetimibe, or thiazolidinediones.

LDL not at target, patient on a statin—The addition of ezetimibe to any statin can result in a further lowering of LDL cholesterol by 20–25%. The further reduction in LDL-cholesterol attainable by this combination would be expected to reduce risk for cardiovascular events. However, studies comparing the effect of the addition of ezetimibe to a statin on cardiovascular events beyond a statin alone are not yet available. The addition of niacin to statin therapy is currently under investigation in two large cardiovascular outcomes studies, but the additional LDL lowering, as well as the potential for niacin to raise HDL and lower triglycerides, suggests that this combination will be efficacious. Studies have shown that the combination of statins + niacin reduces carotid intima-medial thickness (cIMT), a marker of atherosclerosis and increased risk of cardiovascular disease.[8]

Triglycerides and/or HDL not at target, patient on statin—Low HDL is an independent risk factor for cardiovascular disease, and, as illustrated by the Framingham data, the risk for CHD decreases by half for every 20 mg/dl increase in HDL.[9, 10] Data on the role of hypertriglyceridemia as a cardiovascular risk factor are controversial; however, when hypertriglyceridemia occurs in the setting of low HDL, there is a clear increase in risk.[11]

Adding a fibrate—ACCORD Study[12]*:* The ACCORD Lipid study compared simvastatin + placebo vs simvastatin + fenofibrate in >5000 diabetic patients on the outcome of first cardiovascular event. Although the fenofibrate group had lower triglycerides and higher HDL than the placebo group, there was no significant difference in cardiovascular outcomes between the groups. Subgroup analyses suggested that the group with the highest baseline triglyceride levels (>204 mg/dl) and lowest baseline HDL levels (<34 mg/dl) may have had cardiovascular benefit from fenofibrate, and that inclusion of subjects with less extreme dyslipidemia may have "diluted" this effect.

Adding niacin or ezetimibe—ARBITER 68: 208 subjects with LDL <100 and HDL <50 (men) or 55 (women) on long-term statin therapy were randomized to niacin (goal 2000 mg/d) or ezetimibe (10 mg/d). The primary endpoint was the change from baseline in mean cIMT at 14 months. 75 patients had diabetes. The addition of niacin to statin therapy decreased LDL and triglyceride levels and raised HDL levels; the addition of ezetimibe to statin therapy decreased HDL, LDL, and triglycerides. The statin + niacin group had a reduction in cIMT, whereas the statin + ezetimibe group had no change.

Adding pioglitazone—PROactive study[13]*:* More than 5000 diabetic patients were randomized to pioglitazone or placebo in addition to best usual care. At baseline, 43% were using statins and 10% were using fibrates. Statin use increased to 56% of patients by study end, with more of the placebo group using statins than the pioglitazone group. The effect of pioglitazone on lipids was not different between statin users and non-users, suggesting that pioglitazone and statins have additive effects (pioglitazone decreased triglycerides 13.2%, increased LDL 2.3%, and increased HDL 8.9% compared to placebo). There was a suggestion of cardiovascular benefit in the pioglitazone vs placebo group.

Two imaging studies (CHICAGO[14] and PERISCOPE[15]) comparing pioglitazone to glimepiride via cIMT or intravascular ultrasound (IVUS), respectively, found favorable effects of pioglitazone on the progression of atherosclerosis, although neither study was powered to look at clinical outcomes.

Lipid-lowering therapies in subjects with renal impairment Statins are the first line of treatment and, in the mild-moderate stage of chronic kidney disease (CKD) have been shown to be effective in prevention of cardiovascular disease. Although several studies examining the effect of statins in end-stage CKD patients have shown that, despite lowering cholesterol statins have no benefit for survival or prevention of cardiovascular events,16 the recent SHARP trial suggested that the combination of simvastatin + ezetimibe reduced the risk of cardiovascular disease in CKD patients (presented at the American Society of Nephrology, Denver, CO 11/20/2010). Note that some lipid-lowering medications require dose adjustments in CKD *(Table 16-1)*.

Summary of commonly used non-statin drugs in patients with CKD

Ezetimibe—Ezetimibe appears to have equal lipid-lowering efficacy in CKD vs non-CKD subjects, and appears to be safe; however, there are no outcome

Table 16-1. Metabolism of statins and selected non-stains in patients with CKD

Agent	Dose adjustment in CRF	Doses in CRF	Clearance	Plasma half life (hrs)
Atorvastatin	No		Mainly hepatic	14
Fluvastatin	No		Mainly hepatic	2.5
Lovastatin	Yes	20 mg/d max	Mainly hepatic	1.7
Pravastatin	Yes	CrCl < 30: 10 mg max	Renal/ hepatic	2
Rosuvastatin	Yes	CrCl < 30: 5-10 mg max	Renal/ hepatic	19
Simvastatin	Yes	CrCl < 30: Start at 5 mg	Renal/ hepatic	3
Ezetimibe	No		Intestinal/ hepatic	22
Gemfibrozil	Yes	CrCl < 50 ml/min: 300 mg bid	Mainly/ hepatic	1.5
Fenofibrate	Yes	CrCl < 50 ml/min: 40-50 mg initial dose	Renal/ hepatic	20
Niacin	Probably		Mainly hepatic	Depends on formulation
Colesevelam	No		Intestinal	n/a

studies available to support its use as either monotherapy or combination therapy at this time.[17]

Bile acid binding resins—Resins are theoretically advantageous in the setting of renal insufficiency because they are not absorbed so no dose adjustments are required. However, they are contraindicated when triglycerides >400 mg/dl due to their potential to further elevate triglycerides, and there is a potential for decreased absorption of other medications, so they must be used cautiously. There is a lack of data to support or refute their use in CKD patients.

Niacin—Niacin appears to be safe and efficacious in lipid lowering in CKD patients[18] but there is a lack of data regarding cardiovascular outcomes and high rate of side effects, which limits its use. However, ongoing studies (in non-CKD patients) suggest that, either as monotherapy or in combination with statins, nicotinic acid can reduce cardiovascular disease and events.

Fibrates—While fibrates are effective in lowering triglyceride and raising HDL in CKD patients, fenofibrate raises serum creatinine. Although there does not appear to be any adverse effect on GFR with fenofibrate,[19] any increase in creatinine may trigger further medical investigation. Thus, in the setting of significant hypertriglyceridemia, we suggest cautious use of gemfibrozil preferentially over fenofibrate.

Omega-3 Fatty Acids—There are very few studies evaluating omega-3 fatty acids in CKD. Although omega-3 fatty acids appear to be effective at lowering triglyceride levels in patients with CKD, there is no benefit on renal parameters[20] and no known effect on cardiovascular outcomes in patients with CKD.

CONCLUSIONS / POINTS OF INTEREST / CLINICAL PEARLS

Although statins are the first choice of lipid-lowering agents based on their safety profile and robust clinical trial evidence of efficacy, providers need to understand the efficacy and safety of non-statin lipid-lowering therapies for use either in individuals intolerant of statins or in combination with statins in high-risk individuals not at lipid goals. Ongoing studies evaluating combination lipid therapy will influence future combinations available and recommended, and providers are encouraged to watch for new publications. In addition, providers need to be aware of the dose adjustments necessary in patients with impaired renal function.

CASE 1

A 53-year-old Caucasian man is referred for evaluation of diabetes and dyslipidemia. He has no known cardiovascular disease. The family history is significant in that his father and a paternal uncle both had coronary bypass in their 40s, and paternal grandfather had sudden death at age 51. The patient was diagnosed with type 2 diabetes approximately 10 years ago, and has background retinopathy, symptoms of neuropathy, but no nephropathy. Medications include ASA, insulin, metformin, lisinopril, metoprolol, and simvastatin 40 mg/d. HbA1c is 7.5%. Current lipid panel: cholesterol 139 mg/dl (3.7 mmol/L), LDL 72 (1.9 mmol/L), HDL 31 (0.8 mmol/L), and triglycerides 184 (2.1 mmol/L).

What do you recommend?

CASE 2

The patient is a 49-year-old man with a history of a myocardial infarction 3 years ago. He has a family history of premature coronary artery disease. He is currently treated with rosuvastatin 40 mg qd and his current lipid panel reveals: total cholesterol 230 mg/dl, TG 100 mg/dl, HDL 50 mg/dl, and LDL 150 mg/dl (initial LDL was 320 mg/dl).

What are his target lipid goals and what therapies will you recommend?

CASE 3

A 57-year-old Caucasian woman with a recent kidney transplant is referred for recommendations for management of dyslipidemia and new onset of diabetes mellitus. She received a renal transplant 8 months ago for hypertensive nephropathy, and renal function is stable, but she has had progressive elevation in HbA1c and dyslipidemia. She has no known cardiovascular disease. Her past medical history is also significant for fibromyalgia, stably treated hypothyroidism, and hypertension now well controlled. The transplant clinic started her on metformin and simvastatin, but she developed increased muscle aches and refused to take either agent. There was no elevation in creatine phosphokinase (CPK). BMI is 27.5 kg/m2, BP is 124/71 mmHg, and HR is 78. Physical examination: numerous musculoskeletal trigger points; otherwise normal.

Medications: Gengraf 100 mg bid, Imuran 100 mg/d, diltiazem 300 mg/d,

doxazosin 4 mg/d, metoprolol 50 mg bid, lisinopril 10 mg/d, multivitamin 1/d, Novolin 70/30 12 units bid

Laboratory findings: Creatinine 1.93 mg/dl, HbA1c 8.2%, TC 209 mg/dl (5.4 mmol/L), LDL 154 mg/dl (4.0 mmol/L), HDL 34 mg/dl (0.9 mmol/L), TG 334 mg/dl (3.8 mmol/L).

What is her cardiovascular risk and what treatment options do you have?

CASE 4

A 68-year-old man had a myocardial infarction 1 month ago. He was discharged from the hospital on simvastatin 80 mg qhs. He returns for a routine follow-up visit and his chief complaint is shoulder muscle weakness and soreness bilaterally for the last 2 weeks. His serum CPK is within normal limits, and a fasting lipid panel reveals the following: LDL 65 mg/dl, HDL 44 mg/dl, and TG 97 mg/dl.

What would you recommend?
Is this patient statin intolerant, and what should you do?

DISCUSSION CASE 1

This is a case of a patient at very high risk for cardiovascular disease based on his family history and his diabetes (considered a cardiovascular event equivalent). He is near LDL goal on simvastatin, but his non-HDL cholesterol is not at goal and he has low HDL cholesterol, which is an additional risk factor for cardiovascular disease. Options include adding a fibrate, which would decrease triglycerides and may increase his HDL, but he does not fall into the subgroup that had best response to the addition of fenofibrate in the ACCORD study. Adding niacin could be expected to improve all aspects of his dyslipidemia, but there are no cardiovascular outcome studies yet available to prove a benefit to this approach, and there is the potential that the addition of niacin may worsen his insulin resistance, leading to increased insulin requirements and weight gain. The addition of pioglitazone could not only improve his HDL and triglycerides, but also improve his glycemic control, which is not at goal. Although there is no cardiovascular outcomes study directly evaluating statin + pioglitazone combination therapy, about half of the participants in the PROactive study used statins, and the addition of pioglitazone suggested a benefit in some cardiovascular outcomes. Given this patient is not at either lipid or glycemic goals, referral to an endocrinologist and certified diabetes educator and/or dietitian is appropriate.

CASE 2

This patient is a very high-risk patient who likely is heterozygous for familial hypercholesterolemia, a common genetic disorder that lead to very high LDL cholesterol levels, tendinous xanthomata and premature cardiovascular events. Treatment with the maximal dose of a very potent statin, rosuvastatin, resulted in a marked reduction in LDL cholesterol levels but this patient's LDL is still far from ideal (at a minimum, his LDL should be <100 mg/dl and ideally <70 mg/dl). The addition ofezetimibe 10 mg qd will result in synergistic lowering of LDL. It

is likely that even statin-ezetimibe combination therapy will not be sufficient to achieve the target LDL goal, and a third drug may be needed. If the LDL is not at goal with combination therapy with rosuvastatin and ezetimibe, a third lipid-lowering drug, either niacin or a bile resin binder, is indicated.

CASE 3

This is a complicated case involving a patient with recent renal transplant, apparent statin intolerance, and diabetes. Her cardiovascular risk is high due to the combination of her hypertension, diabetes, and now her renal transplant. Cardiovascular diseases are a leading cause of mortality in transplant patients, and hyperlipidemia not only increases her risk for cardiovascular disease, but also increases her risk for graft failure. There is no evidence that this patient truly has a statin intolerance (her symptoms are compatible with her previous diagnosis of fibromyalgia, and her CK was never elevated). Thus, based on the evidence showing a benefit from statins in renal transplant patients, the first priority should be attempting to re-introduce a statin, preferably one that is primarily hepatically cleared (either atorvastatin or fluvastatin). The patient should be carefully counseled re the benefits vs. risks and a low-dose statin (perhaps even using alternate-day therapy) should be attempted. If this is successful, then the statin should slowly be titrated to achieve LDL goal. Often, when patients with fibromyalgia have a flare of their symptoms, a brief statin holiday can be offered. When the myalgias have abated, the statin can be re-initiated (perhaps with repeat titration). Although this patient has a combined dyslipidemia that is unlikely to reach goal lipid levels with statin monotherapy, she is at high risk for side effects with combination lipid therapy, so that the focus should be attaining LDL as close to goal as possible using statin monotherapy. If the patient adamantly refuses statins, then consideration should be given to ezetimibe monotherapy, which is minimally absorbed, has a low risk of myalgias, and is safe in renal transplant patients. Careful attention to her other cardiovascular risk factors (hypertension and diabetes) is warranted. Due to her complicated medical history and high cardiovascular risk, this patient should be co-managed with an endocrinologist or transplant physician with multidisciplinary expertise.

CASE 4

Given the recent myocardial infarction, aggressive LDL lowering is indicated. Despite the normal CPK levels, it is important to determine if this patient's new complaints represent a statin myopathy. A trial off of simvastatin is warranted. If his symptoms resolve, a statin that is metabolized by a different pathway should be prescibed. Simvastatin, lovastatin, and atorvastatin are predominantly metabolized by the Cyp3A4 pathway. A trial of a low dose (10 mg qd) of rosuvastatin, which is metabolized predominantly by the Cyp2C9 pathway, is indicated. If he remains symptom-free, then slowly increase the dose of rosuvastatin to achieve the goal LDL level of <70mg/dl. If his symptoms did not improve with stopping simvastatin, then he would need a thorough evaluation to determine the etiology of his shoulder muscle soreness and weakness.

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17 Management of the Abnormal C's:

Coronary Calcium Scores, CIMT, CRP & Other Cryptic Markers of CAD

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Although the death rate from cardiovascular disease (CVD), especially coronary artery disease (CAD), has been falling for several decades, atherosclerotic CVD remains the number one cause of death in the US today. Since effective strategies are available for the prevention and treatment of CAD, it is critical to target therapy to those individuals with the highest risk for developing clinical events. During the past several years, effective guidelines for the management of hyperlipidemia and hypertension have been developed by several organizations, both in the US and abroad. Current strategies employed in these guidelines are based primarily on the identification of traditional risk factors for which abundant and robust evidence exists. However, many individuals are not identified by these traditional risk factors and current guidelines. This has resulted in a search for other CAD risk factors that might identify moderate- to high-risk individuals who could be missed by application of current guidelines. These include coronary calcium scores and coronary intimal medial thickness (CIMT) that might be markers of coronary artery disease before the onset of clinical events, or other risk factors, such as C-reactive protein (CRP) and other inflammatory markers.

Whether to broadly apply these newer markers or risk factors in practice remains controversial, particularly because it is unclear whether these markers add significant predictive value beyond the traditional risk factors. Moreover, there are issues regarding their accuracy, and in some cases, their expense. Nonetheless, judicious use of some of these techniques might be of value in selected cases.

BARRIERS TO OPTIMAL PRACTICE

Potential barriers include a lack of precise knowledge of when to measure these newer risk factors or markers, and whether or not they will provide cost-effective ways of improving diagnosis and outcomes in individuals at risk of CAD beyond those provided by well-established conventional risk factors.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Have a better appreciation of the pros and cons of measuring the "abnormal C's"
- Know when their measurement will not be of value
- Appreciate some of controversies surrounding their measurement

STRATEGIES FOR DIAGNOSIS AND MANAGEMENT

Traditional risk factors still account for the vast majority of coronary artery disease risk. However, newer risk factors have been suggested to help improve risk stratification. Before they are widely applied in clinical practice, they must be shown (1) to add significant predictive power to current risk models, such as the Framingham Risk Score, (2) to reliably reclassify patients into different risk groups, and (3) to be cost-effective. Availability and validity of evidence vary considerably for these newer risk factors, being more robust for some than others. These new markers will not be useful in secondary prevention, because aggressive intervention measures usually are already applied to such individuals. Their major benefit is likely to be reclassification of individuals at intermediate levels of risk.

During the past several years, the ability of the coronary artery calcification score (CACS) to predict future clinical events has become clear. In addition, the CACS adds predictive value to models such as the Framingham Risk Score, especially in patients with type 2 diabetes. A CACS of zero (determined by CT) makes the occurrence of CAD events very unlikely in the near term. However, CACS is a relatively expensive technique, involves radiation, and cost-effectiveness studies are still needed before its use should be widely adopted.

Measurement of CIMT, although in a different vascular bed than the coronary arteries, nonetheless is a predictor of CAD. Studies have varied as to whether or not it is a better predictor than the CACS.CIMT may be measured by ultrasound or MRI, and does not involve the use of radiation, but variability of measurement between operators and its expense remain issues. Insufficient data are available for recommending its routine use at this time.

Of the newer risk factors, the best studied is CRP. It is a powerful predictor of CAD risk, although its relative value as a risk predictor is lowered if other associated risk factors, such as triglycerides and HDL-C, are corrected for. It is relatively cheap to perform but does not increase predictive value to any great extent beyond that predicted by measurement of non-traditional risk factors. Moreover, evidence that lowering CRP values will lower risk is lacking. Nonetheless, CRP measurement may be of value in making therapeutic decisions in individuals who are at intermediate risk and in whom it is unclear whether or not to use drugs, such as statins.

Of the other emerging risk factors, there is reasonable support for the value of measurement of lipoprotein(a) during the evaluation for primary and secondary prevention. Most authorities believe that routine homocysteine measurements are not indicated, and insufficient evidence is currently available to support the routine measurement of lipoprotein-associated phospholipase A2 as a risk predictor. With time it is likely that measures of apoB and apoA-I will be added to or replace measurement of LDL-C and HDL-C, respectively.

MAIN CONCLUSIONS

Current evidence does not support the routine and widespread use of these newer risk factors. However, with time, some might be incorporated into specific guidelines. In the meantime, each of them might be useful in individual patients, particularly for help with decision making in intermediate-risk patients, where the presence of an increased coronary calcium score, increased CIMT, CRP, or Lp(a) might help in the decision to begin or intensify therapy.

CASE 1

A 58-year-old female lawyer with a strongly positive family history of premature CAD presents with an acute myocardial infarction. She has a personal history of treated hypertension, she smoked until about 10 years ago, and she has had difficulty with her weight since that time. Following her myocardial infarction she had a drug-eluting stent placed and was started on a high-dose potent statin, clopidogrel, a beta-blocker, and an ACE inhibitor by her cardiologist. She presents to her endocrinologist 2 months later with several questions related to some reading she has done on the web. Her BMI is 28.9, BP 132/78, LDL-C 95, HDL-C 46, triglycerides 142.

Should she have her calcium score and/or CIMT measured?
What would be the advantage of measuring her CRP level?
Should any other measurements be made to optimize her chances of preventing a recurrence?

DISCUSSION

Since she already has established documented CAD, measurement of her calcium score or CRP will not help with her diagnosis or treatment, which should be aggressive in her case.

A lipoprotein(a) level could be of use, since it might help with the selection of therapeutic options. Niacin is the most effective drug for lowering lipoprotein(a).

CASE 2

A fit, asymptomatic 45-year-old male had an intermediate calcium score during a routine measurement made at a "health fair." His fingerstick cholesterol was 192. He was told by the technician who did the scan that despite his normal cholesterol, he needs to consult his doctor because of the abnormal coronary artery calcium score.

He eats a low-fat diet, drinks two glasses of red wine per day, and runs at least 45 minutes 4–5 times per week. He has never smoked. His BMI is 25.2, BP 112/69. Physical examination revealed a fit, healthy male with no abnormal physical findings.

What other clinical and routine laboratory information would you like have?
Would you measure his CRP?
Would you obtain additional apolipoprotein measurements?
Would you measure his CIMT?

Would you request a cardiac catheterization?
How would you approach him differently if his cholesterol were 342?

DISCUSSION

Taking a complete family history is essential. A family history of early CAD would provide evidence to start a statin. A fasting lipid panel should be obtained. In this case, a CRP might provide useful adjunctive information.

Measurement of lipoprotein(a) would be useful, because he has coronary artery calcification without obvious risk factors, although details of his full lipoprotein profile are not available yet. Some experts would measure apoB and apoA-I as well.

Most people would not measure his CIMT or perform a cardiac catheterization at this time, but a functional study, such as an exercise tolerance test, might be useful.

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18 Primary Hyperaldosteronism

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Primary hyperaldosteronism (PA) is the most common secondary cause of hypertension. Although the exact prevalence is debated, the disease is unquestionably under-diagnosed by even the most conservative estimates, comprising between 1 and 10% of all patients with hypertension. The hypertension caused by PA imparts greater damage to the heart and kidneys than other forms of hypertension, but these consequences are largely reversed by surgical and targeted medical therapy.

BARRIERS TO OPTIMAL PRACTICE

Barriers include lack of experience with detailed adrenal work-ups, confusion about drug interactions, limited expertise in adrenal vein sampling, and fear of embarking on a long and inconclusive evaluation. The single largest barrier to treating PA remains low rates of screening by primary care physicians in at-risk populations, including patients with hypertension and hypokalemia, resistant hypertension, hypertension and known adrenal tumor, and suspicion for secondary hypertension.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Recognize the patient populations who benefit most from screening for PA.
- Construct a diagnostic approach to patients with PA and avoid the pitfalls of each test.
- Distinguish patients who benefit most from a complete work-up, including those who should have adrenal vein sampling (AVS), from those for whom a limited evaluation is also appropriate.
- Understand the limitations of biochemical testing in PA.
- Deduce the appropriate therapy for individual patients.

STRATEGIES FOR DIAGNOSIS AND MANAGEMENT

The most important step is to have patients screened. Patients who should be screened for PA include those with:

- Hypertension and hypokalemia
- Normal blood pressure and unexplained hypokalemia

- Resistant hypertension
- Hypertension and a known adrenal tumor
- Possible secondary causes of hypertension (PA most common cause by far)

Screening with an aldosterone-renin ratio (serum aldosterone in ng/dl/plasma renin activity (PRA) in ng/ml/hr, or ARR) is the most practical and informative initial test. The sensitivity and specificity of an ARR of 20 are both about 80%, hence the need for confirmation testing. (Note that direct measurement of renin levels is increasingly more common outside of the United States and might become commonplace in the United States, but an abnormal ARR based on a direct renin measurement should be confirmed with a renin assay that measures PRA.) The ARR must be interpreted in the context of serum potassium and concurrent medications. If the renin is low and aldosterone is high, the likelihood that the patient has PA is very high (independent of any medications that the patient is taking). If the renin is not suppressed and the patient is on anti-hypertensive medications, these drugs might need to be withdrawn before retesting. If the ARR is high with a suppressed renin and "normal" aldosterone but the serum potassium is low, then the ARR should be repeated when the patient is normokalemic. It is also useful to confirm an abnormal ARR with repeat assessment prior to embarking on a working of PA.

Confirmatory testing for PA involves saline infusion or oral salt loading for volume expansion, with serum or urine aldosterone measurement, respectively. Measuring PRA (to confirm volume expansion) and serum potassium at the end of volume expansion aids in interpretation, as hypokalemia blunts aldosterone synthesis. If the patient is only a candidate for medical management, the work-up may stop here, but if surgical cure is desirable (young patient, severe hypertension and/or hypokalemia), localization of aldosterone production must follow.

Ordinarily, CT scan is next—NOT MRI, which is practically useless for small adrenal tumors. Realize that the predictive value of a CT scan is slightly more than 50%. A patient <40 years old with a >1 cm nodule on one gland plus a clearly normal contralateral adrenal on CT might be offered surgery directly. In most cases, adrenal vein sampling (AVS) is required to localize aldosterone production, because adrenal nodules are common, and imaging studies cannot determine the steroidogenic activity of the adrenals.

MAIN CONCLUSIONS/POINTS OF INTEREST/CLINICAL PEARLS

- Screening is more about whether renin is suppressed than whether aldosterone is high.
- Confirmation testing is about whether aldosterone can be suppressed; this is the turning point of the work-up.
- It is OK to stop the work-up and treat medically at any time.
- Imaging is not about whether an adenoma is present on one adrenal gland, it is about whether the other adrenal gland is unequivocally normal.
- The most important information from AVS is whether one adrenal is not making significant amounts of aldosterone.

CASE 1

A 52-year-old white man was referred for evaluation of a left adrenal mass. He had difficult-to-control hypertension for 25 years, taking amlodipine, benazepril, carvedilol, HCTZ, and variable doses of potassium supplements. Preoperative potassium for knee surgery was 1.9 meq/L. Nephrology evaluation found high urine potassium, high aldosterone, and normal PRA. MRI showed 1 cm nodularity on the left adrenal, and renal artery Doppler sonogram was normal. Spironolactone 100 mg QD was added to his regimen, and he was referred to the endocrine surgeon, who requested endocrine consultation.

Outside lab data prior to starting spironolactone: PRA 0.6 ng/ml/hr (normal 0.3–3.6); serum aldosterone 74.5 ng/dl (normal <10 on typical high- sodium diet), potassium 4.7 meq/L; repeat PRA and aldosterone levels produce similar results.

24-hour urine: epinephrine 40 mcg, norepinephrine 286 mcg, dopamine 697 mcg, aldosterone 149 mcg, potassium 80 meq, creatinine 4.1 g

1. ***What is the likelihood that this man has PA? Would you order any tests now?***
   A. His ARR is 124, but the clinician needs to confirm whether the high aldosterone levels are due to autonomous hypersecretion from the adrenal glands (unsuppressible). A confirmatory test with measurement of serum aldosterone after saline infusion or urinary aldosterone after oral salt loading for at least 2 days is essential before making the diagnosis of PA. Options for this man would be continue medical therapy or to do confirmatory testing.

New data after starting spironolactone

PRA 1.5 ng/ml/hr (normal 0.3–3.6); serum aldosterone 55 ng/dl (normal <10 on typical high- sodium diet), potassium 4.0 meq/L

2. ***How do you interpret these results?***
   A. Evaluation for PA should not be done while a patient is on an aldosterone antagonist like spironolactone or eplerenone. These medications raise renin and aldosterone production in patients without PA and may cause markedly elevated ARR values that might be confused with PA. The other agents that may profoundly affect the ARR (and cause false positives) include renin inhibitors (aliskerin), diuretics (potassium-sparing and wasting), confectionary licorice, and chewing tobacco.
      - Spironolactone was discontinued.
      - A 24-hour urine was collected 4 weeks later with paired blood tests:
      - PRA <0.6 ng/ml/hr; serum aldosterone 29 ng/dl, potassium 3.8 meq/L
      - 24-hour urine: aldosterone 41 mcg (normal <12 on high-sodium diet) , sodium 246 meq, potassium 54 meq

3. ***How do you interpret these results?***
   A. These findings confirm the diagnosis of PA. The high ARR and markedly elevated urinary aldosterone levels while on a high-sodium diet indicate that the patient has non-suppressible primary hyperaldosteronism. (Note that >200 meq of sodium in a 24-hour urine sample confirms that the patient was consuming 5 or more grams of sodium [12 grams of table salt] daily; 40 meq of urinary sodium is ≈1 gram of dietary sodium.) Note that low potassium levels tend to depress aldosterone levels; it is best to determine ARR when a patient is normokalemic.

4. ***Should adrenal vein sampling be performed in this patient?***
   A. The differential diagnosis of primary aldosteronism is essential in order to recommend appropriate therapy. Confirming the presence of a unilateral aldosterone-secreting adenoma is important, since its surgical removal may result in significant improvement or even amelioration of the hypertension and hypokalemia. Many studies have shown that CT imaging of the adrenal glands alone may provide misleading information regarding the presence or absence of an aldosterone-secreting adenoma. Adrenal vein sampling is considered the gold standard in differentiating between unilateral and bilateral disease in patients with primary aldosteronism. Although adrenal vein sampling is a difficult procedure (at least in terms of catheterizing the right adrenal vein), there are many centers now that perform this procedure with a high degree of success and thereby provide excellent sensitivity and specificity in the differential diagnosis of primary aldosteronism. Nonetheless, some experts have suggested selective use (for example, it may not be needed in patients younger than 40 with a solitary adrenal nodule).

      AVS confirmed left-sided primary hyperaldosteronism. The patient had left adrenalectomy. Pathology showed benign cortical adenoma. Postoperative potassium and blood pressure remain normal on amlodipine monotherapy.

CASE 2

A 60-year-old African-American woman was referred by a surgeon for preoperative endocrine evaluation of an adrenal nodule and elevated aldosterone/plasma renin activity ratio. She had a 20-year history of hypertension (much worse in the past 3–4 years), includeing a hypertension emergency in July 2009 (BP: 240/160). She had normal urine catecholamines and metanephrines, but an intermittent history of hypokalemia. She was on multiple anti-hypertensive medications: amlodipine, clonidine, losartan, metoprolol, and hydrochlorothiazide.

Past Medical History: Vitamin D deficiency with secondary hyperparathyroidism (treated). GERD

Osteoporosis: Wrist fracture and low bone density: hip T score was –2.4 and Z-score was –12.8

Social History: Non-smoker; no alcohol
Family History: Both parents had hypertension
Examination: Healthy appearing woman; non-Cushingoid; BP 184/102; pulse 74; weight 186 lbs, with a BMI of 29.2; Fundi benign; Right lobe of thyroid is enlarged, but good muscle strength and no edema
Laboratory test results: Sodium, 140; potassium, 3.6; chloride, 102; bicarbonate, 25; BUN ,13; creatinine, 0.7; FBS, 102; A1c, 6.5%; calcium, 9.4; plasma renin activity, <0.3 ng/ml/hr (normal 0.3–3.6); serum aldosterone, 21 ng/dl (normal <12 on typical high-sodium diet)
CT Imaging: 3 cm right adrenal mass with attenuation value of <5 HU

1. ***Does this woman have an aldosteronoma? Is the elevated aldosterone/renin ratio high enough to diagnose primary hyperaldosteronism? What about her medication effect?***
   A. Aldosterone-secreting adrenal adenomas are the most common cause of surgically correctable hypertension, but they are rarely found as incidental adrenal nodules. This is probably related to the fact that most aldosterone-secreting adrenal adenomas are quite small and are often not easily identified on CT imaging even when the diagnosis of primary aldosteronism has been unequivocally established. This woman has an elevated aldosterone to plasma renin activity ratio (ARR). This ratio is the simplest means to screen patients with suspected primary aldosteronism and has gained widespread use. An ARR >20–40 has been generally accepted as abnormal, but most investigators suggest further confirmation of inappropriate aldosterone secretion that is non-suppressible by sodium loading. Hypokalemia should be corrected. The ARR is best secured in the morning after patients have been out of bed and upright for at least 2 hours. Since, like all ratios, the ARR depends greatly on the denominator, plasma renin must be sensitive enough to measure low levels. In the presence of a suppressed plasma renin activity, the serum aldosterone is usually >10 ng/dl (as long as the patient is normokalemic). In general, an elevated ARR should be confirmed before proceeding with an extensive evaluation for PA.

      The ARR in this woman is particularly impressive since the patient is taking an angiotensin receptor antagonist (losartan) that should raise the plasma renin activity and lower the aldosterone concentration; however, she is taking a beta-blocker (metoprolol) that will tend to decrease plasma renin activity. Most antihypertensive medications do not significantly affect the ARR, but spironolactone and eplerenone should be discontinued before assessing the ARR. These agents can be substituted with drugs that have minimal effects on the ARR, such as slow-release verapamil, hydralazine, and alpha-adrenergic antagonists, such as prazosin, doxazosin, and terazosin. In our patient, there is no need to discontinue any of her medications and this degree of ARR elevation is virtually diagnostic of primary aldosteronism.

Table 18-1

Laboratory Confirmation:			
24-hr urine	aldosterone	14 mcg	PRA: <0.1 ng/ml/hr
	sodium	211 mmol	
	creatinine	1.2 g	

Confirmation of the diagnosis was made with an elevation of urinary aldosterone secretion (12 mcg/24 hr) on a high-sodium diet. Oral sodium loading is often performed by simply having the patient increase the daily sodium intake (>5 g or >12 g of table salt) for 2–3 days prior to and during the 24-hour urine *(Table 18-1)* collection. Potassium chloride supplementation is often necessary during this period of time (because the salt load exacerbates potassium wasting seen in PA), particularly if the patient has pre-existing hypokalemia. Some investigators prefer a saline infusion test (2 liters of normal saline over 4 hours in the early morning) with an anticipated suppression of aldosterone to <5 ng/dl in normal subjects. Some clinicians offer fludrocortisone administration for aldosterone suppression; however, this increases the risk of hypokalemia and requires additional potassium supplementation and monitoring.

2. ***Should any other studies be performed?***
   A. It is not unusual for unilateral or bilateral adrenal nodular disease to be associated with autonomous co-secretion of aldosterone and cortisol. The relatively large size of this adrenal lesion and osteoporosis in a 61 year-old African American woman raises the suspicion that she may have adrenal-dependent hypercortisolism as well as primary aldosteronism. The most sensitive test to exclude autonomous cortisol secretion is the low dose (overnight 1 mg) dexamethasone suppression test (DST). A basal plasma ACTH, late-night salivary cortisol, and a 24-hour urine free cortisol should also be considered in patients with an abnormal DST or in whom there is a high level of clinical suspicion. The patient's results for the overnight 1 mg DST were: cortisol, 3 g/dl; ACTH, <1 pg/ml. 24-hour cortisol was 88 g/dl (normal <50). Basal ACTH was 6 pg/ml and DHEAS was 22 g/dl.

      These tests show that she ALSO has mild cortisol excess of adrenal origin, and she was cured of both with right adrenalectomy. The co-existence of hyperaldosteronism and hypercortisolism in some patients with nodular adrenal disease may be related to the expression of aberrant hormone receptor signaling with a remarkably diverse group of receptors (e.g., GIP, beta-adrenergic, vasopressin, angiotensin II, and gonadotropins). Physiologic changes in the ligand result in adrenal growth and increased steroidogenesis.

3. ***Finally, why did it take so many years for someone to consider a diagnosis of adrenal hypertension in this woman?***
   A. It is obvious that primary aldosteronism is a common cause of hypertension. All large-scale screening studies have found a prevalence of 5–15% in patients with hypertension. The diagnosis certainly must be considered in younger patients and those with suboptimal blood pressure control despite several agents. The diagnosis is relatively easy to establish. For many years, the dogma existed that only those hypertensive patients with hypokalemia need be screened; however, it is clear that at least one-half of subjects with primary aldosteronism do not present with hypokalemia.

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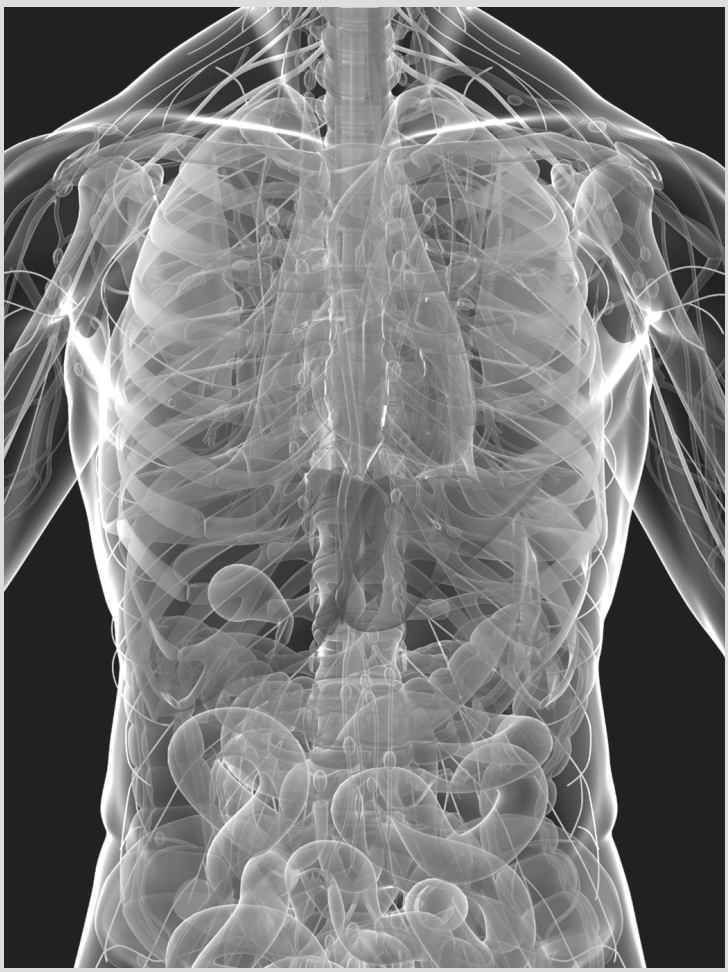
MEN'S & WOMEN'S HEALTH



19 Diagnosis & Management of Male Hypogonadism: In the Older Man

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SIGNIFICANCE OF THE CLINICAL PROBLEM

There is convincing evidence from epidemiologic studies that testosterone levels decline in men with aging. As the proportion of men over 65 years of age continues to increase, this decline has generated considerable interest and attention. However, the clinical significance of this age-related change in testosterone is unclear for a number of reasons. First, the decline in testosterone is gradual and a significant number of older men, in fact, remain eugonadal. Second, even in the cohort of older men whose testosterone level falls below the normal range for healthy young men, the threshold at which symptoms of androgen deficiency develop and adverse health outcomes ensue is uncertain.

Estimates of the prevalence of hypogonadism vary significantly depending on the definition employed. Using a purely biochemical definition without any reference to clinical symptoms, a prevalence of 20–50% has been reported, depending on the age of the cohort and the pre-defined testosterone cut-off (Harman et al., 2001; Araujo et al., 2007; Tajar et al., 2010). In contrast, the prevalence of symptomatic androgen deficiency using an arbitrary cut-off of <10.4 nmol/L (300 ng/dl) is significantly lower, at 5.6% (Araujo et al., 2007). When the diagnosis is further refined by systematically determining in a large population the testosterone threshold below which symptoms become increasingly prevalent, only 2.1% of middle-aged and elderly men meet criteria for hypogonadism, although this number increases with increasing age, obesity, and comorbid illness (Wu et al., 2010).

It is clear, therefore, that the potential exists to overdiagnose hypogonadism in older men and in some cases to institute treatment that may be neither necessary nor beneficial.

BARRIERS TO OPTIMAL PRACTICE

- Non-specific nature of the signs and symptoms associated with androgen deficiency
- Uncertainty with regard to the threshold for diagnosing hypogonadism in older men
- Variability in testosterone levels due to circadian rhythms and influences from medications and comorbid illness
- Confusion by clinicians as to when to measure total, free, and bioavailable testosterone levels

- Absence of long-term data that testosterone supplementation can safely improve clinically meaningful outcomes in older men

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Perform the appropriate evaluation for a man presenting with symptoms suggestive of androgen deficiency
- Have an informed discussion with patients about what is currently known about the risks and benefits of giving testosterone to older men

DIAGNOSIS

The Endocrine Society Clinical Practice Guidelines (Bhasin et al., 2010) recommend making a diagnosis of hypogonadism only in men with consistent signs and symptoms and unequivocally low serum testosterone levels. However, as alluded to earlier, one of the challenges in diagnosing hypogonadism in older men is that the clinical features are non-specific. In addition, data from the European Male Aging Study (EMAS) highlighted the fact that many of the symptoms characteristic of classical hypogonadism in young men are not associated with low testosterone levels in middle-aged and older men (Wu et al., 2010). The symptoms most closely associated with testosterone levels in this age group could be classified into three domains:

Sexual

- decreased frequency of morning erections
- decreased frequency of sexual thoughts
- erectile dysfunction

Physical

- inability to engage in vigorous activity
- difficulty walking >1 km
- inability to bend or stoop

Psychological

- loss of energy
- sadness
- fatigue

On the basis of this large, population-based study, the authors concluded that the presence of three sexual symptoms combined with a total testosterone level of <11 nmol/L (320 ng/dl) and a free testosterone of 220 pmol/L could be used to define late-onset hypogonadism in older men.

The Endocrine Society Clinical Practice Guidelines have proposed the following algorithm for the evaluation of a male with suspected hypogonadism; the algorithm requires the presence of both symptoms and a low testosterone level for the diagnosis.

KEY POINTS

- Hypogonadism is a clinical syndrome and the diagnosis should therefore only be made when consistent symptoms and signs are present in association with low testosterone levels.
- A morning total testosterone level is the best initial screening test for diagnosis.
- The diagnosis of hypogonadism should never be based on a single testosterone measurement, irrespective of the level, as up to 1/3 of low levels are normal when repeated.
- Clinicians should be familiar with the various assays for measuring testosterone. While an immunoassy with a well-characterized reference range will generally yield accurate and reliable information, mass spectrometry is increasingly being viewed as the gold standard for measuring testosterone.

CASE DISCUSSION

A 68-year-old retired history professor presented with a 5-year history of decreased libido, absence of night-time erections, and difficulty sustaining an erection adequate for intercourse. He had a history of type 2 diabetes (T2DM) controlled with diet alone and of benign prostatic hypertrophy for which he was receiving tamsulosin. On examination, his BMI was 35 kg/m2. His BP was 140/80 mmHg. He was well virilized and had testicular volumes of 20 ml bilaterally. Digital rectal examination (DRE) revealed mild prostate enlargement with no nodules. He had diminished pedal pulses and evidence of an asymptomatic peripheral neuropathy.

He had an initial testosterone level of 5.8 nmol/L (167 ng/dl), which was 7.3 nmol/L when repeated in a morning sample. His SHBG was 15 nmol/L with a calculated free testosterone level of 204 pmol/L. He had an LH of 4.5 U/L, FSH 8 U/L, and prolactin of 213 mIU/L (4.9 ng/ml). His PSA was 1.1 ng/ml, Hb 12.1 g/dl, total cholesterol 6.5 mmol/L (250 mg/dl), HDL 0.8 mmol/L (30 mg/dl), and HbA1c 7.1 %.

1. ***Does this patient have hypogonadism?***
   A. The patient meets the criteria for hypogonadism in that he has symptoms of androgen deficiency in association with low levels of total and free testosterone measured on more than one occasion; he can therefore be considered a potential candidate for testosterone therapy.

2. ***Is this patient's prostate disease a contraindication to testosterone therapy?***
   A. Despite this patient's history of BPH, his symptoms are well controlled on an alpha-blocker, and he has a normal PSA level and no palpable nodules on DRE. Current guidelines recommend not starting testosterone therapy in men with a palpable prostate nodule or induration, a PSA level >4 ng/ml or PSA >3 ng/ml in men at high risk of prostate cancer, such as African Americans or men with first-degree relatives with prostate cancer,

pending further urological evaluation. The prostate disease in this case is therefore not a contraindication to therapy. While long-term data are still lacking, a recent meta-analysis of the impact of testosterone therapy on prostate endpoints provided some reassurance, in that it showed no significant increase in prostate cancer risk or PSA levels or change in lower urinary tract symptom score compared to placebo (Fernandez-Balsells et al., 2010).

3. ***What potential benefits might this patient derive from testosterone replacement?***

A. This patient's major symptom is sexual dysfunction. The literature on the effects of testosterone replacement on sexual dysfunction in men with low testosterone levels suggests a beneficial effect on libido, although the data on erectile function are less consistent (Jain et al., 2000; Bolona et al., 2007). Therefore, a trial of testosterone alone or in combination with a phosphodiesterase 5 inhibitor should certainly be considered.

This patient also has a history of T2DM. A number of epidemiologic studies have reported a link between low testosterone levels and future development of T2DM. Unfortunately, data on the impact of testosterone therapy on glycemic control in men with T2DM are limited and based on small patient numbers. However, available data have reported a decrease in HbA1c levels and an improvement in insulin sensitivity with testosterone supplementation in diabetic men with low testosterone levels (Kapoor et al., 2006; Heufelder et al., 2009; Jones et al., 2011). Thus, while T2DM would certainly not be considered an indication for testosterone therapy in the absence of symptoms of hypogonadism, there is a possibility that testosterone replacement might have a beneficial effect on glycemic control. However, it is equally plausible that lifestyle modification and weight loss might have a similar effect on reducing HbA1c levels and at the same time lead to an increase in endogenous testosterone levels and thus obviate the need for exogenous replacement.

OUTCOME OF THE CASE

After a detailed discussion with the patient about what is currently known about testosterone replacement in men his age, he was concerned about the lack of long-term safety data and on that basis decided not to have a trial of testosterone therapy. Instead, he opted for a PDE5 inhibitor and lifestyle modification, from which he derived some symptomatic benefit.

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20 Erectile Dysfunction:

Who, When and What Treatment

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Erectile dysfunction (ED) is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. It is a common condition that increases in prevalence as men age. It is estimated that ED affects 20–30 million men in United States and approximately 50% of men aged 40–70 years old. The prevalence of ED increases with aging to about 70% of men in their 70's.Despite this high prevalence, only 5–10% of men with ED are diagnosed and only 60% of men diagnosed are treated.

ED is associated with the presence of co-morbid diseases that are commonly seen by primary care practitioners, such as diabetes mellitus, obesity, hyperlipidemia, metabolic syndrome, cardiovascular disease, and hypertension. ED has adverse effects on quality of life and interpersonal relationships. Endocrine diseases, including diabetes mellitus, hypogonadism, hyperprolactinemia, and thyroid disease, are common causes of ED that are managed in the primary care setting.

BARRIERS TO OPTIMAL PRACTICE

- Lack of discussion of sexual health, including the presence of ED in men who are seen in a primary care practice and are at high risk for sexual dysfunction.
- Incomplete evaluation of men with ED prior to treatment and formulation of a management plan in a primary care setting.
- Less than optimal use of therapeutic options for the treatment of ED, in particular phosphodiesterase type 5 inhibitors and testosterone treatment.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Identify the major risk factors and endocrine causes for ED in patients who come to see a primary care practitioner.
- Describe factors important in the evaluation of men with ED prior to consideration of treatment and formulating a treatment plan in a primary care setting.

- Describe the optimal use of medical treatments for ED in patients who come to see a primary care practitioner.

STRATEGIES FOR DIAGNOSIS, THERAPY, AND MANAGEMENT

Causes of Male Sexual Dysfunction

ED is a major cause of male sexual dysfunction. The major causes of male sexual dysfunction include the following separate, but often overlapping, problems:

- Reduction or loss of libido (sexual interest and desire)
- ED
- Ejaculatory dysfunction (premature or delayed ejaculation)
- Orgasmic dysfunction

ED is commonly, but not always, associated with reduced or loss of libido.

Physiology of Erection

Normal erections require a complex interaction between external sensory cues, sex hormones, and central and peripheral nervous system and cardiovascular function.

External sensory inputs to the brain may stimulate (e.g., visual erotic stimulus) or inhibit erections. Sex hormones (testosterone and estradiol) and thyroid hormone play important roles in modulating the brain regulation of erections (e.g., adequate amounts of testosterone are needed to maintain libido and spontaneous erections). Psychological stimulation or inhibition of erections is mediated by impulses from the temporal lobe and limbic system that relay signals from higher brain areas to spinal cord centers that regulate the erectile response.

Sacral spinal cord (S2-4) parasympathetic stimulation increases penile smooth muscle cGMP and cAMP, resulting in smooth muscle relaxation, arterial inflow, filling of the corpora cavernosa, and penile tumescence that impedes venous outflow as a result of compression against tunica albuginea of the penis, resulting in a penile erection. Thoracolumbar spinal cord (T11-L2) sympathetic stimulation results in penile smooth muscle contraction via 1-adrenergic receptor activation, reduced arterial inflow into the corpora cavernosa and penile detumescence that increases venous outflow, resulting in a loss of penile erection.

Phosphodiesterase 5 (PDE5) inhibitors prevent breakdown of cGMP and increase cGMP, and PGE1 (alprostadil) increases cAMP within penile smooth muscle, thereby enhancing erection. These actions provide the pharmacological basis for agents currently approved for the treatment of ED.

Risk Factors for ED

Common co-morbid conditions encountered in a primary care practice are risk factors associated with ED. These include:

- Age
- Cardiovascular disease
- Diabetes mellitus
- Hypertension

- Hyperlipidemia
- Obesity
- Physical inactivity
- Metabolic syndrome
- Depression
- Smoking and substance abuse (alcohol and drugs)
- Brain or spinal cord disease
- Endocrine disease
- Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH)
- Pelvic trauma or surgery
- Medications

Because ED may have profound effects on the quality of life and affect interpersonal relationships, discussion of sexual health and function should be initiated by primary care practitioners in men who have these risk factors. Men often do not raise issues of sexual function during the course of a routine office visit. So, it is important for the practitioner to raise the issue of sexual health. This may be done in the context of discussing other lifestyle issues, such as diet, exercise, mood, sleep, and avocation.

Classification of Causes of ED

Most causes of ED are organic in etiology, predominantly due to vascular disease, diabetes mellitus, and medications.

- Psychogenic 20%
- Organic 80%
  - ◊ Vascular 40%
  - ◊ Diabetes mellitus 35%
  - ◊ Medication 15%
  - ◊ Neurogenic 5%
  - ◊ Endocrine 4%
  - ◊ Other 1%

Main Causes of ED

It is useful to categorize the causes of ED in the context of the physiology of penile erections.

- External factors
  - ◊ Stress, strained relationship, lack of erotic stimulation, reduced sexual focus
- Central nervous system (CNS) disorders
  - ◊ Psychiatric disorders (usually associated with decreased libido)
    - ◆ Performance anxiety, depression, major psychiatric disease
  - ◊ Chronic systemic illness
    - ◆ Heart, lung, kidney, liver failure; cancer
  - ◊ Brain disease
    - ◆ Temporal lobe/limbic system disease (stroke, tumor, seizures,

neurodegenerative), multiple sclerosis, Parkinson's disease, multiple system atrophy
    - ◊ CNS-active drugs
        - ◆ Alcohol or drug abuse, antidepressants (SSRIs may also reduce libido and delay ejaculation), central antihypertensives, narcotics, sedative-hypnotics, antipsychotics
    - ◊ Endocrine disease
        - ◆ Hypogonadism, hyperprolactinemia, anti-androgens, hypothyroidism, hyperthyroidism
    - ◊ Spinal cord disorders
        - ◆ Spinal stenosis, trauma, other
- Peripheral Disorders
    - ◊ Drugs
        - ◆ Anticholinergics, antihistamines, antidepressants (tricyclic), sympathomimetic (-agonists), antihypertensives (thiazides and β-blockers)
    - ◊ Peripheral neuropathy
        - ◆ Pelvic, prostate or retroperitoneal surgery or trauma, diabetic or alcohol neuropathy, degenerative disk disease, other
    - ◊ Peripheral vascular disease or cavernosal smooth muscle dysfunction
        - ◆ Aorto-iliac atherosclerosis
        - ◆ Diabetes mellitus and aging-associated and smoking-associated vascular dysfunction
    - ◊ Penile abnormalities
        - ◆ Trauma or surgery, Peyronie's disease, micropenis, priapism, or phimosis

Diagnosis

The diagnosis of ED is made by a careful history.

ED is present if there is consistent or recurrent inability to achieve and/or maintain a penile erection sufficient for sexual performance (at least 25% of the time for at least 3 months and in the absence of an ejaculatory disorder).

It is important to distinguish ED from loss of libido, ejaculatory dysfunction, or orgasmic dysfunction, but these other causes of sexual dysfunction may occur concomitantly with ED. The International Index of Erectile Dysfunction (IIEF, 15 questions) or the Sexual Health Inventory for Men (SHIM also known as the IIEF-5, 5 questions) may be a helpful clinical tool for the diagnosis and evaluation of treatment efficacy. However, in a primary care setting, the practicality of using validated questionnaires is usually limited.

Evaluation of ED

It is important to assess both the patient's and his partner's sexual history and goals and to identify excessive anxiety, depression, or interpersonal difficulties. History should also determine whether there is loss of libido, ejaculatory dysfunction, or orgasmic dysfunction *(Figure 20-1)*.

Evaluation and Treatment of Erectile Dysfunction

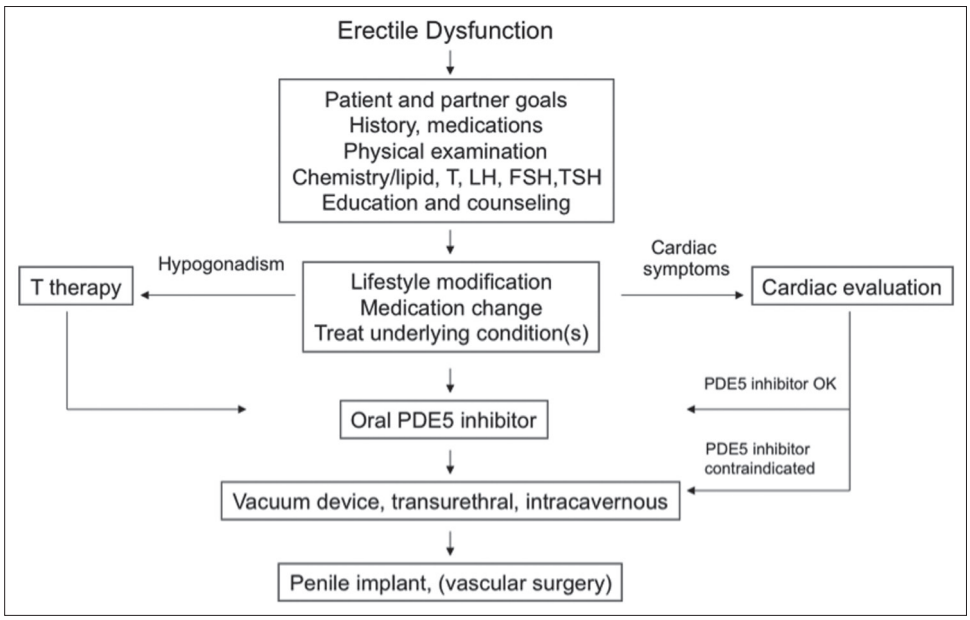

Figure 20-1. Algorithm for the evaluation and treatment of ED (see text for details)

Evaluation of the etiologies of ED (often multi-factorial) is aimed at identifying potentially reversible or treatable causes of ED and involves taking a careful history, including medication review, performing a complete physical examination, and ordering a limited number of laboratory studies.

- History
  - ◊ External factors.
  - ◊ Smoking, alcohol or drug abuse.
  - ◊ Performance anxiety, depression, major psychiatric disease
  - ◊ Sudden-onset ED, ED only in certain situations or with certain partners and persistence of nocturnal or spontaneous erections are suggestive of a psychogenic etiology.
  - ◊ End-organ failure or cancer.
  - ◊ Cortical or subcortical brain disease.
  - ◊ Use of CNS-active drugs.
  - ◊ Hypogonadism (decreased libido, gynecomastia, infertility), anti-androgen use, thyroid disease.
  - ◊ Spinal cord disease (back pain, leg weakness, urinary or fecal incontinence).
  - ◊ Use of anticholinergics, sympathomimetics, or antihypertensives (especially thiazides and β-blockers).
  - ◊ Pelvic, prostate, or retroperitoneal surgery or trauma.
  - ◊ Prolonged bicycle riding can cause excessive pudendal pressure and ED.
  - ◊ Peripheral vascular disease (buttock or hip claudication).
  - ◊ Penile abnormalities.

- Physical examination
  - ◊ Anxiety, depression, or thought disorder.
  - ◊ Abnormal heart, lung, and abdominal examination.
  - ◊ Focal neurological, Parkinson's (tremor, rigidity and bradykinesia).
  - ◊ Androgen deficiency (eunuchoidism, loss of male hair, gynecomastia, small testes).
  - ◊ Lumbar radiculopathy, cauda equina syndrome (loss of anal sphincter tone/bulbocavernosus reflex, penile/saddle sensory loss).
  - ◊ Clinical thyroid disease.
  - ◊ Peripheral neuropathy.
  - ◊ Reduced lower extremity pulses, low ankle-arm index, femoral artery bruit.
  - ◊ Penile abnormalities (penile plaques or curvature)
- Laboratory evaluation.
  - ◊ Fasting glucose and lipid panel; BUN/creatinine/EGFR.
  - ◊ Serum testosterone,TSH

Because ED commonly occurs in men with cardiovascular disease, it is important to evaluate potential cardiac risk of sexual activity in men with ED prior to therapy. Specific inquiry should be made into whether there is chest pain, shortness of breath, or lightheadedness or syncope with vigorous physical activity, or use of nitrates or β-blockers may be contraindications to the use of phosphodiesterase inhibitor therapy.

The relative risk of non-fatal MI during sexual activity is increased by 2.5 to 2.9-fold, but the absolute risk is very low (incidence = 20 cardiovascular events per million patient-hours of sexual activity). Although sexual activity is a form of physical activity, it is generally brief in duration and represents a modest overall exertion. In general, sexual activity pre orgasm is equivalent to walking on a level surface at 2–3 miles per hour (2–3 METS; METS = metabolic equivalent tasks), and sexual activity during orgasm is equivalent to walking on a level surface briskly at 3–4 miles per hour or walking upstairs slowly (3–4 METS). Men who are at low risk of cardiovascular events and who able to tolerate up to 4 METS of exercise without angina or severe dyspnea may be safely treated with ED therapy. All other men should be evaluated further prior to initiation of ED therapy *(Table 20-1)*.

Treatment

- Counseling and education.
  - ◊ This involves stress reduction, relationship counseling, and focusing on the couple's sexual relationship.
- Lifestyle modifications
  - ◊ There is established benefit on ED for cessation of smoking and substance abuse, weight loss, and improved diet and exercise.
  - ◊ There is no established benefit on ED for treatment of cardiovascular disease, diabetes mellitus, hypertension or hyperlipidemia. However, optimal treatment of these conditions has other

Table 20-1. Risk Stratification for Sexual Activity in Men with Cardiovascular Disease

Low Risk	Intermediate Risk	High Risk
Asymptomatic, <3 risk factors	3 risk factors, excluding male	
Mild stable angina	Moderate stable angina	Unstable angina
Uncomplicated MI, 6–8 weeks	Recent MI, 2–6 weeks	Recent MI, <2 weeks
CHF class I	CHF class II	CHF class III or IV
Controlled hypertension	Non-cardiac event (CVA or PVD)	Uncontrolled severe hypertension
Successful revascularization		Hypertrophic cardiomyopathy
Mild valvular heart disease		High-risk arrhythmia
		Moderate-severe valvular heart disease (especially AS)
Evaluation prior to treatment of erectile dysfunction		
Sexual activity and ED therapy OK	Cardiac evaluation prior to ED therapy	Defer sexual activity until cardiovascular risk is improved

important health benefits.

- Stop and/or switch potentially offending medications, if possible.
- Treatment of underlying medical etiologies.
- Medical treatment options for most primary care practitioners.
  - ◊ *First line:* oral phosphodiesterase type 5 (PDE5) inhibitors and/or testosterone replacement.
  - ◊ Testosterone treatment is indicated in men with established hypogonadism, i.e. clinical manifestations of androgen deficiency and consistently low serum testosterone levels, in accordance with The Endocrine Society's Clinical Practice Guideline.
  - ◊ *Second line:* vacuum erection device with or without a constriction ring.
- Medical treatment options for ED experts, including primary care practitioners and specialists, such as endocrinologists and urologists.
  - ◊ *Third line:* intraurethral or intracavernosal prostaglandin E1 (PGE1 or alprostadil). The latter is the most effective monotherapy, but also the most invasive and associated with a high dropout rate.
  - ◊ *Fourth line:* intracavernosal papaverine (non-specific PDE inhibitor) + PGE1 (bi-mix) or intracavernosal phentolamine (1-adrenergic blocker) + paperavine + PGE1 (tri-mix).
  - ◊ *Combined (salvage):* PDE5 inhibitor + vacuum erection device, or intraurethral or intracavernosal PGE1.

PDE5 inhibitors *(see Tables 20-2 and 20-3)*

- Requires sexual arousal to be effective
- Effective in 60–70% of men, but consistently effective in only 50%.
- Less effective in men with diabetes mellitus and post-radical prostatectomy or brachytherapy for prostate cancer.
- No clearly superior PDE5 inhibitor, but tadalafil is perceived by some men as more convenient and affording more spontaneity because it has a longer duration of action.

Table 20-2. Medical treatment options for ED

Treatment	Effectiveness	Advantages	Disadvantages
PDE5 inhibitors	60–70%	Oral, noninvasive Very effective	Expensive No nitrates Caution with β-blockers Side effects (HA, flushing, dyspepsia, rhinitis, visual)
Vacuum erection device with or without constrictive ring	60–70%	Noninvasive Low cost Very effective Safe No restriction on frequency of use	Cumbersome Requires dexterity/training Unnatural erection Penile trauma, pain Impeded ejaculation
PGE1 intraurethral	50–60%	Minimally invasive Effective	Lower success rate than intracavernosal PGE1 Requires dexterity/training Penile ache 15–30% Urethral irritation rare Priapism, fibrosis rare
PGE1 intracavernosal	70–80%	Highly effective	Invasive High dropout rate Requires dexterity/training Penile ache 15–30% Priapism 1–2% Fibrosis rare
Apomorphine	40–50%	Sublingual, noninvasive	Not available in US Less effective than PDE5 inhibitors Nausea, somnolence, yawning, dizziness, headache

- Usually start at middle dose and titrate up if ineffective, or down if effective but side effects.
- Lower starting dose with β-blocker, renal and liver failure.
- Dose is limited to daily for sildenafil and vardenafil, and every 2 days for tadalafil.
- Metabolism by CYP3A4
  - ◊ Increased levels and potential for side effects with medications that block CYP3A4 (e.g. INH, clarithromycin, protease inhibitors, nefazodone, or grapefruit juice)
  - ◊ Decreased levels and effectiveness with medications that induce CYP3A4 (e.g., rifampin or phenytoin)
- Main adverse effect is penile pain with erections in 25–30% of men; priapism in 1–2%
- Contraindications
  - ◊ High or intermediate cardiovascular risk *(see Table 1)*.
  - ◊ Nitrates because of potential for severe hypotension.
    - ◆ In acute coronary syndrome, no nitrates should be given for 24 hrs after sildenafil or vardenafil, and for 48 hrs after tadalafil.
  - ◊ Retinitis pigmentosa, nonarteritic anterior ischemic optic neuropathy (NAION).
- Cautions
  - ◊ Men taking β-blocker because of the potential for hypotension.
  - ◊ Use of multiple anti-hypertensive or cardiac medications.

Table 20-3. Phosphodiesterase 5 (PDE5) inhibitors

	Strength (mg)	Onset (hr)	Duration (hr)	Interactions	Side effects
Sildenafil (Viagra®)	25, 50, 100	0.5–1.0 food delays	4	Nitrates BP Caution with β-blockers CYP3A4 interaction	Headache 15% Flushing 10–15% Dyspepsia and diarrhea 5–10% Rhinitis Blue-tinged vision (PDE6 inhibition) 2–4%
Vardenafil (Levitra®)	2.5, 5, 10, 20	0.5–1.0 food delays	4	Nitrates BP Caution with β-blockers CYP3A4 interaction Slightly prolonged QT interval	Headache 15% Flushing 10–15% Dyspepsia 5–10% Rhinitis
Tadalafil (Cialis®)	5, 10, 20	0.5–1.0 no food effect	24–36	Nitrates BP Caution with β-blockers CYP3A4 interaction PDE11 inhibition; no apparent significance	Headache 15% Flushing <5% Dyspepsia 5–10% Rhinitis Myalgias/back pain 5–10%

- Reasons for failure
  - ◊ Lack of sexual arousal and stimulation
  - ◊ Not taking medication 1 hour before sexual intercourse
  - ◊ Not waiting >2 hours after a meal to take sildenafil or vardenafil
  - ◊ Inadequate number of trials (at least 6 x at maximum dose)
  - ◊ Unrecognized or untreated androgen deficiency
- If inadequate response to initial PDE5 inhibitor and no reasons for failure, trial of another PDE5 inhibitor is reasonable
- Adverse effects
  - ◊ Side effects include headache, flushing, dyspepsia, rhinitis, diarrhea, and visual disturbance (sildenafil only), back pain and myalgias (tadalafil only)
  - ◊ Discontinuation rate because of adverse effects, 2–3%
  - ◊ No increase in MI or death rates

Testosterone (T) replacement *(refer to The Endocrine Society Clinical Practice Guideline; ref 2)*

- T replacement only in men with clinical hypogonadism, confirmed by low AM serum T levels on at least two occasions and no conditions that transiently lower T levels.
- Usually, T treatment alone is inadequate therapy for ED.
- Young men with ED due to severe hypogonadism respond best to T treatment alone.
- Older men with ED who have mild hypogonadism and multiple co-morbidities that contribute to ED usually do not respond to T alone.

Vacuum erection device with or without constriction ring *(Table 20-2)*

- Vacuum device draws blood into the penis, and constriction ring applied to the base of the penis holds blood in the penis.

- Perceived as too cumbersome and mechanical by many men and their partners.
- Highly effective in 60–70% of men and least expensive ED treatment.
- Unnatural erection (joystick-like).
- Adverse effects include bruising, numbness, and impediment to ejaculation.
- Used as adjunctive therapy with other treatments, if inadequate response to monotherapy.

PGE1 *(See Tables 20-2 and 20-3)*

- Intracavernosal alprostadil
  - ◊ Requires training and dexterity to correctly inject alprostadil.
  - ◊ Most effective monotherapy for ED, 70–80% of men.
- Intraurethral alprostadil (Medicated Urethral System for Erection, MUSE)
  - ◊ Requires training and dexterity to insert small pellet of alprostadil into the urethra, followed by massaging to facilitate diffusion.
  - ◊ Less effective than intracavernosal alprostadil, 50–60% of men.
- Contraindications
  - ◊ Conditions that increase risk of priapism (e.g., sickle cell disease, leukemia, multiple myeloma).
  - ◊ Severe penile deformity (e.g., Peyronie's disease)

CONCLUSIONS

In patients who come to see a primary care practitioner, major risk factors for ED include older age, diabetes mellitus, obesity, hyperlipidemia, metabolic syndrome, cardiovascular disease, and hypertension; and common endocrine causes of ED are diabetes mellitus, hypogonadism, and thyroid disease.

In patients who come to see a primary care practitioner, medical treatment for ED should be considered after confirmation of the diagnosis and evaluation of the patient's and partner's sexual history and goals, cardiovascular risk of sexual activity, potentially treatable risk factors, and possible etiologies of ED.

In the management of patients with ED, a primary care practitioner should provide counseling and education, initiate and managelifestyle modifications, modify offending medications (if possible), treat underlying medical tiologies, and utilize effective first and second line medical treatments for ED (primarily,PDE5 inhibitor, testosterone replacement and vacuum erection device therapy).

CASE 1

An obese 68-year-old male with type 2 diabetes mellitus, dyslipidemia, hypertension, coronary artery disease with a history of non-ST segment elevation myocardial infarction and coronary artery stents, and chronic pain syndrome due to lumbar spondylosis despite multiple surgeries comes in for his routine follow-up visit. He is sedentary and smokes cigarettes but does not drink alcohol. He complains of a 2-year history of progressive difficulty achieving an erection sufficient to have sexual intercourse with his wife.

Medications include: metformin, 1000 mg twice daily; simvastatin, 20 mg nightly; atenolol, 100 mg daily; lisinopril, 40 mg daily; nitroglycerin, 0.4 mg as

needed; and acetaminophen, 650 mg four times daily.

Exam is remarkable for an obese, white male with a BMI of 34 and blood pressure of 135/89; slightly tender back to percussion; distant heart sounds with no gallops or murmurs; marked central adiposity without striae; normal-sized testes; and reduced vibration but intact 10-g monofilament sensation in both feet.

Laboratory studies are remarkable for fasting glucose of 200 mg/dl; normal creatinine and EGFR; hemoglobin A1c 8.1; fasting cholesterol 269, triglyceride 326, HDL cholesterol 30, and LDL 174.

1. ***Treatment of which of the following risk factors for erectile dysfunction may improve erections and sexual function?***
   a. Obesity
   b. Hyperlipidemia
   c. Smoking
   d. Hypertension
   e. a and c only
   f. All of the above

2. ***Serum total testosterone level was found to be 270 ng/dl (normal 280–800 ng/dl). Which of the following should be included in further evaluation of this patient's erectile dysfunction?***
   a. Inquiry regarding loss of sexual interest (libido)
   b. Serum TSH
   c. Serum calculated free testosterone
   d. Review of medications
   e. a and c only
   f. All of the above

3. ***A repeat testosterone level was found to be normal and he was started initially on sildenafil 50 mg as needed for his erectile dysfunction. The patient tells you on a follow-up visit that it did not work. So, he increased the dose to 100 mg, which resulted in a partial erection that was not adequate for sexual penetration. Which of the following may be reasons for his failure to respond to sildenafil?***
   a. An inadequate number of trials of sildenafil at the maximum dose
   b. Not treating with testosterone in addition to sildenafil
   c. Not waiting for at least two hours after a meal to take sildenafil
   d. Taking sildenafil approximately one hour prior to sexual intercourse
   e. a and c only
   f. All of the above

ANSWERS

1. *Correct answer: e. a and c only.* Weight loss (a) and cessation of smoking (c) may improve erections and sexual function. Treatment of hyperlipidemia (b) and hypertension (d) is important to reduce cardiovascular risk but won't improve erections. In fact, some antihypertensive medications may worsen ED.

2. *Correct answer: f. All of the above.* The patient has a slightly low total testosterone that could be explained by obesity-related low sex hormone-binding (SHBG). So, in this individual, it is important to obtain an accurate measure of free testosterone, either a calculated free testosterone (c, calculated from measurements of total testosterone and SHBG) or free testosterone by equilibrium dialysis performed in a commercial laboratory with established normal ranges. Free testosterone measurements performed by platform-based direct analog immunoassays are inaccurate and should not be used. Inquiry regarding loss of libido (a) should be performed to determine whether there are clinical manifestations of androgen deficiency. Serum TSH (to rule out thyroid disease) and a review the patient's prescribed and over-the-counter medications should be performed to rule out other potential causes of ED.

3. *Correct answer: e. a and c only.* Common reasons for failure of sildenafil therapy are an inadequate number of trials (at least 6) of sildenafil at the maximum dose (a) and not waiting for at least two hours after a meal to take sildenafil (c), as food, in particular fatty food, may impede absorption of sildenafil. Not treating with testosterone in addition to sildenafil (b) is incorrect because the patient had normal testosterone on repeat evaluation. Sildenafil should be taken approximately one hour prior to intercourse. So, response d is incorrect.

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21 Investigation & Management of Gynecomastia

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SIGNIFICANCE OF CLINICAL PROBLEM

Gynecomastia occurs frequently in adolescent males, tending to resolve spontaneously. It is also common in adult men. Treatable underlying pathology should be sought in men with gynecomastia of acute onset or changes in breast size. Men with asymptomatic and stable gynecomastia may still warrant evaluation to exclude sinister pathology. There are many different causes of gynecomastia, hence a systematic assessment is needed to guide diagnosis and optimize management.

BARRIERS TO OPTIMAL PRACTICE

- Gynecomastia is a common clinical finding; it is difficult to discern when there is a clinically important underlying cause
- There are many potential causes of gynecomastia
- Malignancy is rare, but it must be considered in the differential diagnosis

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- understand the pathophysiology of gynecomastia
- use a systematic approach to identify likely causes
- be familiar with uncommon causes of this condition

Introduction

Gynecomastia refers to the presence of glandular breast tissue in men. It is common, can present acutely or as an incidental finding, and requires evaluation to exclude sinister causes and to arrive at treatment tailored to the individual patient.

Adolescent gynecomastia

Pubertal breast development occurs in over half of adolescent males, with spontaneous regression usually occurring within 6 months and before the age of 18 years [1,2]. Prevalence peaks around 13 years, but overall prevalence in males age 10–19 years is low, reflecting its transient nature [3]. In cases where surgical excision has been performed, the breast tissue is almost invariably benign [4]. Nevertheless, it can be a presentation of Klinefelter syndrome or a testicular tumor even in this age group [5].

Gynecomastia in adult men

Gynecomastia, defined as palpable breast tissue, is present in about half of adult men [6,7]. At least 2 cm of breast tissue was found in 40.5% of healthy young men age18–26 years and 36% of military personnel age 17–58 years [8,9]. Gynecomastia was bilateral in 85% of cases [8]. It was present in 54% of hospitalized men age 30–49 years, 72% of those aged 50–69 years, and 47% of those aged 70–89 years[10]. Its prevalence increased with body mass index (BMI), as did the diameter of breast tissue[10].

Pathogenesis

An imbalance between the actions of androgens and those of estrogens may drive proliferation of male glandular breast tissue [6]. The majority of testosterone (T) circulates bound to sex hormone-binding globulin (SHBG) and albumin and only 1–2% circulates as unbound or free T [11]. In middle-aged and older men, total testosterone (TT) levels decline with increasing age while SHBG increases. Therefore, the age-related decline in free testosterone (FT) is steeper than that for TT [12-14]. T is converted by the intracellular enzyme 5-alpha reductase into dihydrotestosterone (DHT), a more potent ligand for the androgen receptor (AR). T is also converted to estradiol (E2) by the enzyme aromatase (CYP19A1) in fat, skeletal muscle and other tissues [11,15]. The conversion rate of T to E2 only ~ 0.2%, but up to 80% of plasma E2 originates from conversion of androgens. In the circulation, E2, like T, is bound to SHBG and albumin.

The hormonal changes of puberty are likely to underlie the development and regression of gynecomastia in adolescents [16]. In post-pubertal adult men, an excess of E2 vs. T-mediated effects on breast tissue could arise from changes in circulating hormone levels, alterations in protein binding, or changes in hormone action in tissue *(see Table 21-1)* [17]. Excessive T, by providing the substrate for aromatization, could increase E2 levels [18]. The association of gynecomastia with higher BMI may reflect adipose tissue's being a major site for aromatization of T to E2. Increased SHBG, with preferential binding of T over E2, could predispose to gynecomastia by increasing the bioavailability of E2 relative to T. Systemic illness is another cause, particularly cirrhosis and renal disease, where the predisposition to gynecomastia is multifactorial [19].

In addition to those listed in Table 1, drugs can be associated with reduced T levels (e.g., alcohol, methadone, ketoconazole, cytotoxic chemotherapy, long-acting GnRH analogs), or possess estrogenic activity (e.g., marijuana)[17,20]. Spironolactone is a weak antagonist of the AR, and it increases free E2 by displacing E2 from SHBG [6]. Of men treated with spironolactone at a dose of 25 mg for2 years, 10% developed gynecomastia [21]. Other medications associated with gynecomastia include a range of other cardiovascular medications (e.g., digitoxin, enalapril, amiodarone), several antidepressants/antipsychotics and antiretroviral therapies [7,17,22]. Of the last group, gynecomastia has been associated with the use of protease inhibitors (e.g., ritonavir), reverse transcriptase inhibitors (e.g., efavirenz), and nucleoside analogues (e.g., stavudine, didanosine) [23,24].

Table 21-1. Alternations in hormonal status predisposing to gynecomastia.

Circulating hormones	Decreased T	Hypogonadism (e.g., Klinefelter's) Drugs (e.g., Corticosteroids)
	Increased T and E_2	Exogenous testosterone or aromatisable androgens. Excess hCG (testicular or extragonadal germ cell tumor). Ectopic production of hCG (lung, kidney, liver, gastric carcinoma).
	Increased E_2	Exogenous estrogen or estrogenic compounds. Hormone production by testicular Leydig or Sertoli cell tumor, or adrenal adenoma or carcinoma. Excessive aromatisation (age, obesity, hyperthyroidism, familial).
Protein binding	Increased SHBG	Hyperthyroidism Liver disease
	Displacement of E_2	Drugs (spironolactone)
Tissue	Reduced AR activation	Prostate cancer therapy with AR antagonists (cyproterone, flutamide, bicalutamide). 5α-reductase inhibitors (finasteride). AR mutations (androgen insensitivity).

Clinical evaluation

An acute onset associated with symptoms of pain or tenderness suggests a recent and ongoing underlying pathological process. By contrast, gynecomastia may be minimally symptomatic or detected during routine clinical examination, particularly in older men. A careful history of medications (and alcohol) use is needed. Symptoms and signs of systemic illness and of testosterone deficiency should be sought. Physical examination of the breast is best performed with the patient recumbent, bringing the separated thumb and forefinger together underneath the areola to define whether a disc of glandular tissue is present [6]. This will differentiate gynecomastia from lipomastia (pseudogynecomastia), where adipose tissue is present without palpable glandular breast tissue. Testicular examination may reveal the presence of a tumor or small testes in the case of men with Klinefelter syndrome.

INVESTIGATIONS

A suitable approach would be to screen for renal, liver, and thyroid dysfunction and to assay early morning serum T, E2, SHBG, LH, and hCG [6]. *(Figure 21-1)* As testicular tumors might not always be detected by palpation, increased hCG or E2 should be followed by testicular ultrasound. Low T plus high LH levels indicate primary hypogonadism, whereas low T plus low or inappropriately normal LH levels indicate secondary hypogonadism. The man with gynecomastia due to secondary hypogonadism should be evaluated for hyperprolactinemia and Cushing's (at least with history and physical examination). Hemochromatosis should be considered in younger men with secondary hypogonadism, and sella imaging for hypothalamic or pituitary masses should be obtained in men with very low T levels (< 150 ng/dl) and secondary hypogonadism. Androgen resistance, a very rare cause of gynecomastia, might be associated with increased LH and T. Finally, increased E2 may be a sign of an adrenal neoplasm or of increased aromatase activity. If no cause of gynecomastia is found, a diagnosis of idiopathic gynecomastia can be made [6].

Another perspective would be to acknowledge that gynecomastia is common,

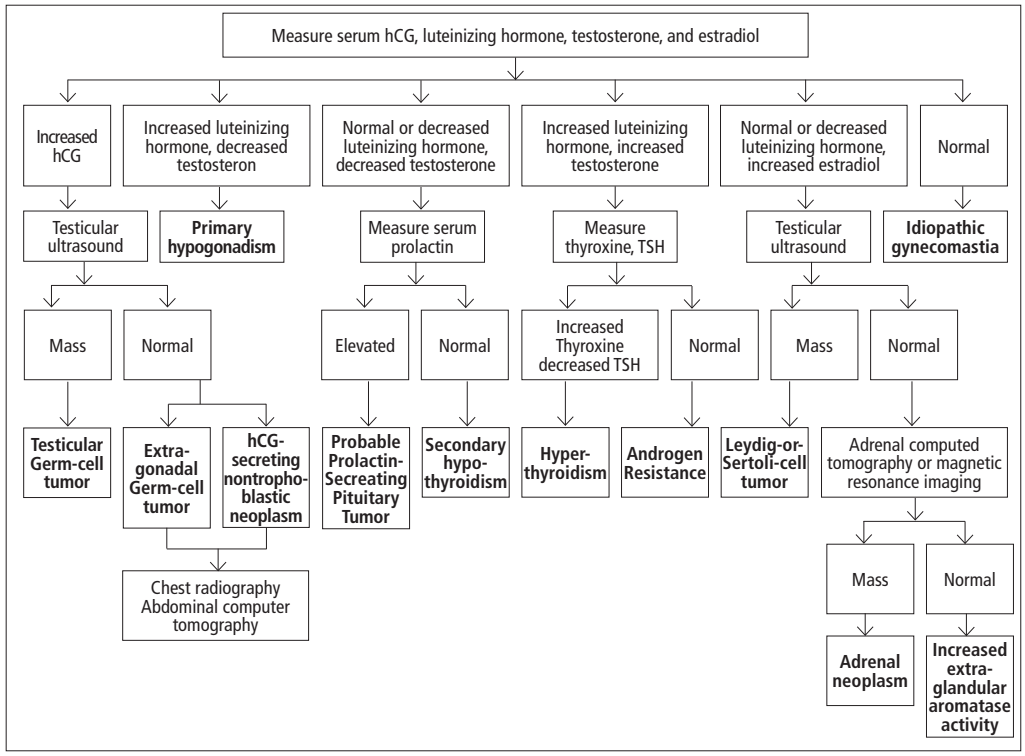

Figure 21-1.

and in the absence of recent origin or increasing breast enlargement, it might even be considered a normal finding [25]. Nevertheless, the necessity of excluding uncommon but potentially treatable underlying pathology mandates a careful clinical assessment.

SPECIAL CONSIDERATIONS

Breast cancer

The annual incidence of breast cancer in men has been estimated at approximately 1:100,000 [19,26,27]. In the US Veterans Affairs study, the risk ratio (RR) was increased by obesity (RR=1.9), orchitis/epididymitis (RR=1.8), gynecomastia (RR=5.1), and Klinefelter syndrome (RR=16.8) [27]. The association with gynecomastia may represent surveillance bias, but Klinefelter syndrome is an established risk factor [26,27]. Suspicion of malignancy is raised by the presence of unusual firmness, asymmetry, location not centered beneath the areola, fixation to skin, nipple retraction, bleeding, discharge, ulceration, or lymphadenopathy [7]. In such cases, imaging and biopsy are indicated.

Testosterone levels in aging men

As noted previously, T levels decline as men age [11-14]. T levels in the low-to-normal range have been associated with poorer health outcomes in epidemiological studies *(for reviews, see [28,29])*. These correspond to T levels of ~11 nmol/L (317 ng/dl), below which men are more likely to report sexual symptoms

consistent with hypogonadism [30]. Nevertheless, only a minority of middle-aged and older men would meet stringent criteria for the diagnosis of androgen deficiency [31,32]. Given the high prevalence of gynecomastia in middle-aged and older men, the risk of having gynecomastia might increase below a level of T that is still within the age-adjusted reference range. Alternatively, gynecomastia and low-to-normal T levels may be common co-existing conditions in older men.

Assays of sex steroids

T and E2 can be measured by immunoassay or by mass spectrometry-based methods. This is potentially problematic, as some commercial immunoassays for T levels show method-dependent bias and non-specificity [32,33]. At the lower levels found in men, immunoassay of E2 is less accurate, which can make data difficult to interpret [34]. Therefore, when investigating men with gynecomastia, accurate (preferably mass spectrometry-based) assays for T and E2 should be used.

TREATMENT OF GYNECOMASTIA

Clinicians should identify and treat any underlying causes of gynecomastia. Specific medical therapy to reduce breast volume and/or surgical excision depends on the man's preference and the severity and chronicity of the gynecomastia. In asymptomatic adult men with stable gynecomastia, if no sinister underlying condition is revealed following evaluation, simple reassurance may be appropriate. In men with acute onset of gynecomastia in whom treatment to reduce breast size is required, a trial of tamoxifen could be considered [6,7]. While not approved for this indication, tamoxifen at a dose of 20 mg daily for 3 months resulted in regression in the majority of patients[6]. Aromatase inhibitors have not been shown to be effective therapy [6,7]. If gynecomastia has been present for longer than a year, the presence of fibrosis makes spontaneous or tamoxifen-induced regression less likely. Surgical management could be offered, and both ultrasound-assisted liposuction and subcutaneous mastectomy via a circumareolar incision have been successful [20].

CASE 1

A 15-year-old male is seen for persistent breast enlargement that began at age 13. It was painful and tender in the beginning, but had improved over the subsequent 2 years. He experienced a growth spurt and deepening of his voice at age 13. He is active in sports but is embarrassed to take off his shirt. He denies taking any medications or illicit drugs. There is no family history of gynecomastia. He had a normal CBC, chemistry panel, and TSH.

On examination, his height is 68 inches, span is 68.5 inches, pubic-to-floor height is 39 inches. His BMI =29.6 kg/m2. He has bilateral 6 cm Tanner gynecomastia. His testes are 18 ml bilaterally and are of normal consistency. Pubic hair and genitalia are Tanner stage 5.

What is the likely cause of his gynecomastia?
What is the differential diagnosis?

What evaluation would you recommend?
Should he be treated? If so, how?

CASE 2

A 66-year-old male is seen for a viral upper respiratory infection. On examination he is found to have bilateral painless gynecomastia. When asked, he notes that his breasts have been ìbeefyî for many years, but he is not bothered by it. He has been in good general health, exercising 4 times a week. He does complain that he has problems losing weight and does admit to a diminished sex drive. He has morning erections and denies erectile dysfunction. Medications include a multivitamin and lisinopril.

On examination, his BMI is 28.5 and the rest of the exam, including testicular exam, is normal.

What is the likely etiology of his gynecomastia?
What diagnostic tests should be performed?
Should he be treated? If so, how?

CASE 3

A 48-year-old male is seen for decreased libido and erectile dysfunction. The initial onset occurred 3 years before, approximately 3 weeks following exposure to two pesticides: Propetamphos, an organophospate, and Methopren, an insect juvenile hormone analogue. He also noted decreased stamina, tiredness, and tender breasts. There was a gradual return of his libido and a decrease in his breast tenderness. Six months later he was exposed to the same pesticides and developed the same symptoms approximately 3 weeks later. Again, the symptoms improved over several months. He consulted many physicians and was found on a few occasions to have a borderline low testosterone. He was treated with multiple forms of testosterone, hCG, and clomiphene citrate without benefit. His medications include vitamins and St. John's wort. He drinks two beers a day and does not use illicit drugs.

On examination, he is 68 inches tall, weighs 147 lbs, and has a BMI of 22.4. His blood pressure is 150/98 and pulse is 76 bpm. He has bilateral, 3 cm, firm, painless gynecomastia. His right testicle is 25 ml and the left 20 ml with normal consistency and no masses.

Laboratory studies include a normal testosterone, free testosterone, estradiol, LH, FSH, hCG, and prolactin.

What is the differential diagnosis of his gynecomastia?
What additional diagnostic tests should be done?
Should he be treated? If so, how?

CASE 4

A 62-year-old male is found to have locally advanced prostate cancer following a prostatectomy. He is considering starting anti-androgen therapy, but is concerned about the high incidence of drug-induced gynecomastia, which he wants to avoid.

What is the best way to minimize the development of gynecomastia and mastalgia?

DISCUSSION

CASE 1

1. ***What is the likely cause of his gynecomastia?***
   A. Persistent pubertal gynecomastia is most likely, based upon the typical age of onset for pubertal gynecomastia, the 2-year duration of the breast enlargement without other etiologies being uncovered, and the normal physical examination.

2. ***What is the differential diagnosis?***
   A. In this age group, anabolic steroid use must be considered. This is unlikely because of the normal testicular size and the lack of acne. Also, marijuana contains phytoestrogens that may be associated with gynecomastia, so he should be carefully questioned about drug use. Rarely, a Leydig cell tumor of the testes can cause gynecomastia in this age group. Since both his testes were of equal size and normal consistency, it is unlikely that a tumor is present. However, the tumors are often small and require an ultrasound to detect them. The normal testes, pubertal development, and body proportions rule out Klinefelter syndrome.

3. ***What type of evaluation should be carried out?***
   A. First, it is important to make sure that the patient has gynecomastia and not pseudogynecomastia due to subareolar fat deposition. Assuming that it is gynecomastia, it is unlikely that any biochemical abnormality will be uncovered given that the history and physical examination are completely normal. A serum estradiol or estrone determination may be performed to see if there is increased testicular production from a small Leydig cell tumor or excessive aromatization of testosterone or androstenedione. An elevated level should prompt a testicular ultrasound.

4. ***How should he be treated?***
   A. Gynecomastia that has been present for over a year usually has a marked degree of fibrosis and is unlikely to respond to medical therapy. However, since the patient still has some breast discomfort, it is likely that he has at least some component of hyperplastic tissue that may

respond. Therefore, he could have a trial of tamoxifen for up to 3 months. This therapy is not approved by the FDA for the treatment of gynecomastia. Because he has a BMI of 29.6, he should be encouraged to lose weight because weight loss may reduce some of the subareolar fat. If neither of those approaches is effective, then surgical removal of the breast tissue is reasonable to reduce his embarrassment. Ideally, one would wait until he completed puberty in order to avoid regrowth of the breast glandular tissue.

CASE 2

1. ***What is the likely etiology of his gynecomastia?***
   A. Gynecomastia in older adults is often multifactorial. Aging males have a reduction in testosterone (especially free or bioavailable testosterone because of an increase in SHBG levels with aging). At the same time, there is increased estradiol and estrone production because each adipocyte increases its aromatase activity with age and also there is increased fat mass with age. This results in an imbalance, with a relatively higher estradiol/testosterone ratio than in younger men. Also, older males often take medications that may be associated with gynecomastia. Lisinopril has not been associated with gynecomastia.

2. ***What diagnostic tests should be performed?***
   A. In patients with incidental asymptomatic gynecomastia with an otherwise normal physical examination, the diagnostic yield from biochemical testing is low. Nevertheless, because of the relatively high prevalence of hypogonadism, a morning serum testosterone should be obtained to screen for this condition. This patient's complaint of a diminished sex drive is an additional stimulus for measuring a serum testosterone between 8 and 9 am. If his testosterone level is low, he should undergo repeat testing for serum testosterone plus FSH and LH levels in the morning. Further evaluation should be dictated by whether primary or secondary hypogonadism is confirmed.

3. ***How should he be treated?***
   A. If he is found to have hypogonadism, he should receive testosterone replacement therapy via a testosterone gel, patches, or injections. There may be an early exacerbation of his gynecomastia, but it usually subsides within a month or so. If he has normal testosterone levels and is not bothered by his gynecomastia, no specific therapy should be given.

CASE 3

1. ***What is the differential diagnosis of his gynecomastia?***
   A. At this time, we can only speculate about the cause of his gynecomastia, because his laboratory tests currently are all normal, indicating that whatever was the causative factor is no longer present, but the gynecomastia persists probably because of some fibrosis replacing the

glandular component. It is unlikely that he had more than transient hypogonadism, as his current testosterone is normal. He was treated with testosterone and hCG, both of which may cause gynecomastia, although these therapies began after he complained of tender breasts. There is a difference in the size of his two testicles, but this finding is a common normal variant. Both testes are normal sized and do not have masses. His hCG and estradiol levels are normal, and together with the testicular examination and the 3-year duration of his gynecomastia, rule out both a germ cell tumor and Leydig cell tumor of the testes. The history of beer use and onset of the symptoms following exposure to pesticides raise the interesting possibility that he developed gynecomastia from an environmental source. Environmental causes of gynecomasita include the following: inadvertent exposure to estrogens (e.g., estrogen creams used by some women), exposure to environmental estrogen-like substances (e.g., apigenin in marijuana plants), and exposure to environmental anti-androgens (e.g., lavender and tea tree oils and phenothrin in delousing agents).

An outbreak of gynecomastia was noted among Haitian immigrants who were detained in a camp in which a delousing agent that contained phenothrin was used. Phenothrin has anti-androgen activity. It is not known whether the pesticides that this patient was exposed to have similar anti-androgen activity or estrogenic activity. Bourbon and beer contain phytoestrogens but a causal relationship between these phytoestrogens and gynecomastia has not been established. Alcohol has a toxic effect on the testes and can reduce testosterone production.

2. ***What additional diagnostic tests should be done?***
   A. None

3. ***How should he be treated?***
   A. Plastic surgical removal of the breast tissue if it is cosmetically bothersome, otherwise no treatment for the gynecomastia. A trial of a PD5-inhibitor to treat his ED would be reasonable.

CASE 4

What is the best way to minimize the development of gynecomastia and mastalgia?

A. Several studies have shown that tamoxifen is superior to anastrazole and prophylactic radiotherapy.

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22 Contraception in Adolescents

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Endocrinologists see a wide range of patients for whom contraception is prescribed. There are a significant number of contraceptive options available, including barrier methods, intrauterine devices, and hormonal contraceptives that can be administered orally, transdermally, or transvaginally. Unique considerations arise depending on the needs of an individual patient and specific risk factors they may possess. Adolescent girls and young women often seek contraception in the setting of an endocrine disorder, such as polycystic ovary syndrome (PCOS) or premature ovarian insufficiency, that may or may not have been previously recognized. In such cases, hormonal contraceptives may be used for treatment of the underlying endocrine disorder or hormonal disturbance. The parents of many patients are also worried that concerns raised by recent studies of postmenopausal hormone replacement therapy might apply to the use of hormonal contraceptives in adolescents. All of the risks and benefits of contraceptives need to be carefully evaluated for a given patient.

BARRIERS TO OPTIMAL PRACTICE

Adolescents represent a "risk group" for suboptimal care as pediatricians are often not comfortable with issues related to contraception and reproductive endocrinology, and adult endocrinologists may not understand some of the compliance issues that can arise when caring for a young adolescent patient.

Contraceptive options for adolescents are also continuously changing, and warning labels can generate confusion in the absence of practical clinical experience.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Understand the efficacy, effectiveness, and acceptability of contraceptive methods that are available for adolescents, including unique issues that may arise with the first use of contraception.
- Understand the options for contraception in high-risk populations.
- Understand the use of hormonal contraceptives for management of an underlying endocrinopathy (e.g., PCOS, premature ovarian insufficiency, etc).

Practical management issues are discussed as viewed from both a pediatric and young adult perspective. Risk/benefit issues that arise for different contraceptive methods are also explored.Case examples are used to highlight key points.

CASE 1

A sexually active adolescent girl with irregular periods.

A 16-year-old who had menarche at age 12 years presents to you. She has always had irregular periods, but was told that this is a common finding in teenagers. She also has been bothered by light hair growth on her face and chest. She entered a new relationship 3 months ago and has just become sexually active.

On physical examination, she appears healthy, with a BMI of 21 kg/m2 and normal vital signs. She has mild hirsutism on her lateral face, neck, and lower back, with Tanner 6 pubic hair. You note mild, non-cystic acne on her face. She has no striae or acanthosis nigricans and no clitoromegaly or temporal recession. Her physical exam is otherwise within normal limits.

What additional information do you need?
What type of contraception should you prescribe?

DISCUSSION

The patient is a 16-year-old female with a history of oligomenorrhea from the time of menarche. Combined with hirsutism on physical examination, her presentation is consistent with polycystic ovary syndrome (PCOS), but pregnancy, hyperprolactinemia, thyroid abnormalities, and possibly late-onset congenital adrenal hyperplasia need to be excluded. This patient has just entered into a relationship and requests contraception to prevent pregnancy at her young age. You ask, and she is not a smoker and there is no family history of deep vein thromboses or other clotting problems.

It is important to take this opportunity to discuss sexually transmitted diseases and the critical importance of barrier contraception in all patient populations, but particularly in adolescents. With perfect use, condoms are 98% efficacious for contraception; however, they are only 85% effective with typical use. This patient likely has PCOS, and oral contraceptive pills (OCP) are a first-line therapy for hirsutism due to PCOS. Patients with PCOS have adequate estrogen stores, but increased levels of ovarian and often adrenal androgens. The first-pass hepatic effect of the estrogen in OCPs increases sex hormone binding globulin (SHBG) levels, resulting in lower free testosterone concentrations. OCPs can also decrease LH levels, which are commonly elevated in PCOS, thereby decreasing androgen levels. These hormonal changes can result in favorable cosmetic results, including thinning of terminal hairs and improvement in acne.

There are numerous pills on the market, with differing estrogen doses and progestins. All OCPs have a favorable safety profile in otherwise healthy adolescents and in young women with PCOS. In PCOS patients, it is generally better to prescribe a continuous, daily OCP containing 30–35 g of ethinyl estradiol and one of the less androgenic progestins (desogestrel, norgestimate, or gestodene). Medical therapy of hirsutism requires 6–12 months before there are visible effects. If hirsutism does not improve on this regimen at a follow-up visit in 6 months, clinicians in the United States could consider adding

spironolactone (50–100 mg orally twice a day), which competes at the androgen receptor peripherally and also inhibits 5-reductase. Spironolactone is not FDA approved for this indication, but it is commonly used for treatment of hirsutism. Its side effects include menstrual spotting and feminization of a male fetus (if the patient becomes pregnant). It is therefore important to begin with OCPs (or some other effecive contraceptive) before initiating an androgen blocker like spironolactone. Clinicians in other countries may prescribe an OCP containing cyproterone acetate, a progestin with an anti-androgenic effect.

When should your patient be referred to an endocrinologist? Young women whose hirsutism is resistant to standard treatment (e.g., OCPs ± spironolactone) or who have signs of virilization (e.g., voice changes, temporal recession, or clitoromegaly) should be evaluated by an endocrinologist. Hirsute women who desire pregnancy, but are unable to conceive, should also be referred to a reproductive endocrinologist who can provide expertise on the evaluation for, and management of, infertility.

CASE 2

An adolescent who has been receiving depot medroxyprogesterone acetate injection for 1 year, presents now concerned about potential side effects

A 17-year-old girl has been using Depo Provera® for the past year. She has been doing well with this contraceptive agent, with no significant weight gain, mood changes, or irregular bleeding. Her mother has accompanied the girl to this visit with concerns about an "FDA warning" about Depo Provera® that she has read about in a magazine. Her mother's medical history is remarkable for a deep venous thrombosis (DVT) at age 31 while she was receiving combined oral contraceptive pills; she was also recently found to have "osteopenia" on DXA scans (obtained after a radial fracture from a fall on the ice).

On examination, your patient's blood pressure is 108/72 and her weight is 123 lb (55.9 kg) with a BMI of 20.7 kg/m2. She is healthy appearing and her examination is unremarkable. Your work-up indicates a normal vitamin D status and PTH, serum calcium, and phosphorus, normal complete blood count, and a normal lipid panel.

What additional information do you want?
Should you continue to prescribe the Depo Provera®?
Should you obtain baseline bone density measurements by dual-energy x-ray absorptiometry (DXA)?
What about the family history of DVT in her mother? Should this raise concern regarding use of a progestin-only method?

DISCUSSION

Your patient has been doing well on the Depo Provera® for a full year. Many teens have difficulty adhering to this method because of undesirable side effects, including weight gain, prolonged vaginal spotting, and mood changes. Your patient has tried to use combined OCPs in the past, but has found it extremely difficult to adhere to a daily regimen.

In 2004, the U.S. Food and Drug Administration put a "black box" warning label on this agent, a move driven primarily by a concern about bone loss in adolescent girls. Routine bone density screening by DXA is not recommended because there are some data to suggest the reversal of bone loss after discontinuation of this contraceptive agent Scholes et al., 2005. However, if a patient has other risk factors for a low bone mass, consideration should be given to ordering a baseline bone density assessment.

In this patient, her mother's history of fracture and osteopenia on bone density screening raises some concerns about your patient's bone health, especially given the strong role of genetics in the determination of bone mass. You order DXA scans and her lowest BMD Z-score is –0.5 SD at the lumbar spine. These results are reassuring because they are within the normal range for an adolescent. As for any adolescent, daily supplementation with 600 IU of vitamin D (endorsed by the American Academy of Pediatrics), adequate dietary intake of calcium, and moderate or strenuous weight-bearing activity are beneficial for her long-term bone health.

The mother's history of a DVT raises interesting issues. If your patient were receiving a combined OCP, there would be concern about an estrogen-induced hypercoagulable state and an increased risk of thromboembolism. Your patient is an adolescent, active, not obese, and a non-smoker. Therefore, her risk of a thromboembolic event is likely extremely low.

A publication from the WHO (World Health Organization) showed that oral or injectable progestin-only contraceptives do not increase the risk of thrombosis (DVT, PE, heart attack, or stroke) in the general female population [WHO, 1998]. However, it is not well known whether progestin-only contraceptives are also safe in individuals who (a) have had a previous clot or (b) have factor V Leiden or other thrombophilia. There is one published study in individuals with thrombosis or with a family history of thrombosis who took a progestin-only pill [Conard, 2004]. That study showed that there was no increased risk of thrombosis with the progestin-only pill. However, the progestin pill evaluated in the study is not available in the U.S.

In view of the paucity of data, one can conclude that there might be a small increased risk of thrombosis with progestin-only contraceptives in individuals with previous blood clots or a thrombophilia. However, for your patient, since she has not suffered a DVT herself (only her mother has), the risk is likely very low. The risk of DVT during pregnancy is also undoubtedly higher than the risk associated with a progestin-only oral contraceptive. You can feel reassured that your patient is on a safe method of contraception, and you have carefully considered both her past medical history and family history. The concern about an increased risk of thrombosis with progestin-only contraceptives stems from the fact that progestins used at higher doses for purposes other than contraception (e.g., dysfunctional uterine bleeding) may be associated with an increased risk of thrombosis. In the future we expect to have more data to determine whether progestin-only contraceptives increase the risk for thrombosis in thrombosis-prone individuals.

When should your patient be referred to an endocrinologist? If the BMD

Z-score is –2.0 SD or less on bone density measurements by DXA, this would represent a significant low bone mass for age. A history of fracture, especially multiple fractures, should raise concerns about her skeletal health. Therefore, consultation by a bone health expert should be considered. For a patient receiving Depo Provera®, persistent abnormal vaginal bleeding would optimally be co-managed with a reproductive endocrinologist.

CONCLUSIONS

Many contraceptive methods are available for adolescents, and the choice of method should be carefully considered in each patient. What is optimal for one teenager might not be a reliable method for another. A significant number of contraceptive options are available, including barrier methods, intrauterine devices, and hormonal contraceptives that can be administered via various routes. The unique needs of the adolescent and specific risk factors that she may possess must be considered for each patient.

In a high-risk population, both safety and efficacy need to be considered. For example, there are thrombotic risks associated with use of a combined oral contraception (especially with the estrogen component) that need to be carefully evaluated. The risk of the contraceptive method should also be weighed against inherent health risks associated with pregnancy in a young adolescent.

Hormonal contraceptives may be used for the management of an underlying endocrinopathy, such as PCOS. OCPs may lead to the improvement of hirsutism and acne, while providing contraception. However, barrier contraception should always be encouraged, too, because sexually transmitted diseases are common among adolescents.

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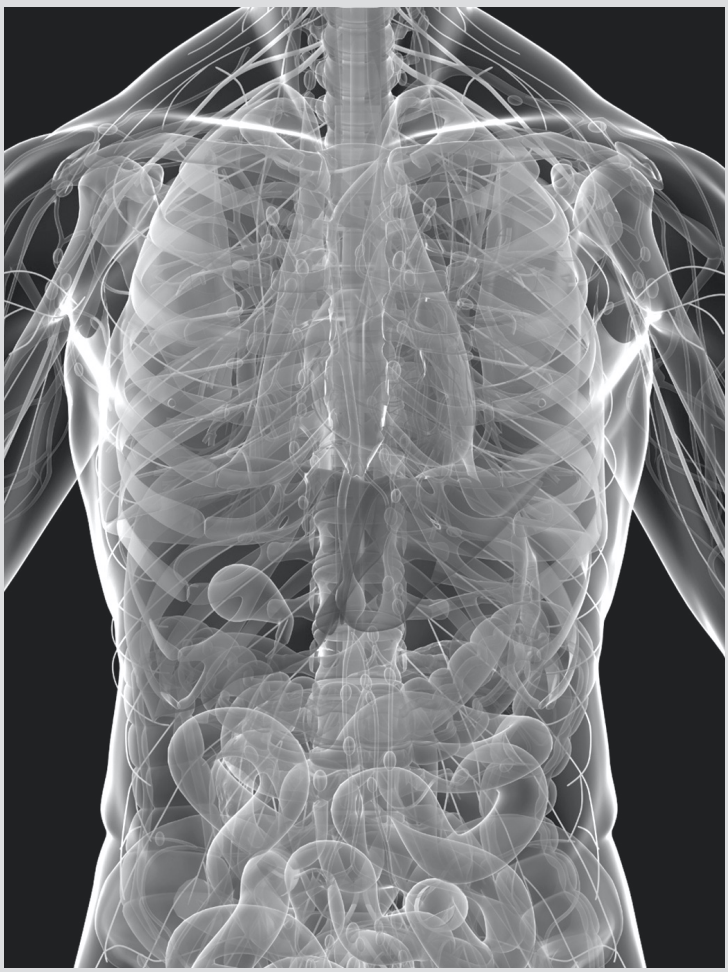
THYROID DISORDERS



23 Clinical Approach to Subclinical Hypothyroidism

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Subclinical hypothyroidism (SCHypo) is common, with an estimated 4–10% prevalence in the general population, and is more common in women and the elderly. The most common cause is autoimmune thyroiditis. Treatment remains controversial because of contradictory data on adverse effects of SCHypo and also of benefits of T4 therapy.

BARRIERS TO OPTIMAL PRACTICE

Since it is unclear what is the upper limit of normal TSH, it is difficult to know who has SCHypo. Also, it is debated whether or not we should treat patients with SCHypo. Finally, since SCHypo is often asymptomatic, the diagnosis may be overlooked unless serum TSH is routinely measured.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Appreciate the controversies surrounding the upper limit of normal serum TSH, as well as the effect of age and race on serum TSH levels
- Understand the definition, course, and consequences of SCHypo
- Understand the potential benefits of thyroxine therapy for SCHypo
- Understand what is normal TSH in pregnancy

Dr. Gharib and Dr. Ross have debated the evidence for and against treatment of SCHypo. Because more endocrinologists agree with Dr. Gharib's views, Dr. Ross has added comments where significant differences exist.

Serum TSH Level

Currently, the normal TSH reference range is 0.5 to 5.0 mIU/L. This reference range is derived from cross-sectional population studies without detailed knowledge of underlying or occult thyroid disease. Although some groups have suggested that serum TSH should have a narrower range, it remains controversial [1–4].

Recent reports show that TSH levels are higher in older people (>80 years) than in young people (20–29 years), and higher in whites than in blacks [5-7]. Others believe that the increase in serum TSH in the elderly is a reflection of increased autoimmune thyroid disease in the older population. In the NHANES-

III study, in a disease-free population of 13,344, 95% had a TSH range between 0.3 and 2.5 mIU/L [6]. Thus, the upper reference range for serum TSH continues to be debated [4].

Presence of thyroid peroxidase (TPO) antibodies is highly suggestive of underlying autoimmune disease. In the NHANES-III report, 80–90% of subjects with a TSH >10 mIU/L were positive for TPO. Moreover, a significant increase in TPO titers occurred at TSH levels of 2.0 mIU/L or more [6]. This would support the argument that TSH values greater than 2.5 mIU/L are "predictive of evolution into overt hypothyroidism." Patients with TSH greater than 2.5 mIU/L and positive TPO have a higher risk of hypothyroidism during long-term follow-up *(Table 23-1)*.

Dr. Ross: The NHANES-III data show that the shift towards higher TSH concentrations in older patients persists even when those with positive anti-TPO antibodies are excluded [7]. For example, the 97.5 percentile for TSH in individuals between ages 20 and 29 is 3.6 mIU/L, while the 97.5 percentile for TSH in individuals over age 80 was 7.5 mIU/L. Seventy percent of the older patients with TSH levels that exceed 4.5 mIU/L have TSH values that are within the age-adjusted normal range.

SCHypo

SCHypo is defined as an above-normal serum TSH level associated with normal FT4 and T3 levels. However, up to 62% of over 400,000 patients in a primary care network who had a TSH between 5.5 and 10 mIU/L had a subsequent normal TSH in the absence of treatment, suggesting that the diagnosis of SCHypo be made only after repeat thyroid function testing [8]. The overall prevalence is 4–10% in the general population, and maybe as high as 20% in elderly women [9, 10]. SCHypo is usually asymptomatic and is often discovered on routine TSH screening. The most common cause is autoimmune thyroiditis (Hashimoto thyroiditis).

Potential risks associated with SCHypo include progression to overt hypothyroidism, cardiovascular disease, hyperlipidemia, and neuropsychiatric effects [10]. The rate of progression to clinical hypothyroidism (elevated TSH and decreased FT4 levels) is approximately 2–5% per year, with a cumulative 20-year incidence of 27–55% *(Table 23-1)*. Patients with slight TSH elevation (>2.0 mIU/L) and positive TPO antibodies have a higher risk of conversion to overt hypothyroidism than TPO-negative patients [11]. Although most authors agree

Table 23-1.
Subclinical Hypothyroidism Whickham Study: Risk of Progression

Positive Test	Annual risk (%)	20-yr cumulative incidence (%)
TSH N, Ab+	2.1	27
TSH ↑, Ab-2.6	33	
TSH ↑, Ab+	4.3	55

Vanderpump M: Clin Endocrinol 43:55,1995

that elevated TSH levels, despite normal FT4 and T3 levels, represent mild, early thyroid failure that may be associated with hypertension, high cholesterol, and cardiac abnormalities, not everyone supports levothyroxine (T4) therapy [3, 10].

Meta-analyses show an increased risk of ischemic heart disease or mortality in patients with SCHypo under age 65, but not for patients with SCHypo and age 65 and over [12]. SCHypo is reported to cause left ventricular (LV) diastolic dysfunction and impaired exertional cardiac output, although LV systolic function remains normal [10]. Data on high cholesterol levels in SCHypo are inconsistent, and the benefits of T4 treatment are disputed. Most agree, however, that treatment is beneficial for patients with TSH >10 mIU/L [13].

Dr. Ross: In a recent meta-analysis of seven studies involving 25,977 participants, of whom 2020 had SCHypo, patients with TSH >10 mIU/L had an increase in coronary heart disease events (hazard ratio 1.89 [1.28–2.80]), but the hazard ratio for TSH 4.5–6.9 mIU/L was 1.00 [14].

One analysis of patients over age 85 demonstrated reduced mortality in those with SCHypo [15]. Another study of patients aged 70–79 demonstrated improved mobility and cardiorespiratory fitness when TSH was 4.5–7.0 mIU/L compared to "normal" [16]. SCHypo is also associated with a 35% lower prevalence of non-vertebral fracture in post-menopausal women [17].

There are no trials with levothyroxine treatment that assess coronary artery disease, heart failure, cardiovascular mortality, or all-cause mortality as outcomes. Because up to 41% of hypothyroid patients may be unintentionally overtreated with levothyroxine [18], it is prudent to follow patients carefully, particularly the elderly, because overtreatment may be associated with atrial arrhythmias, reduced bone density, or other unexpected adverse outcomes.

While many studies suggest improved symptoms following treatment of SCHypo, the few studies that limited patient enrollment to those with TSH levels under 10 mIU/L failed to show a benefit [19-20].

SCHypo in pregnancy

It is now established that SCHypo in pregnancy is associated with adverse outcomes in the mother as well as the fetus (miscarriage and premature delivery). Additionally, it has been suggested that positive thyroid autoantibodies (TPO) or TSH levels between 2.5 and 5.0 increase risks of spontaneous miscarriage and premature delivery in pregnant women [21-22]. Administration of thyroxine may reduce these complications. Therefore, these observations have supported the argument to screen pregnant women systematically for chronic autoimmune thyroiditis or SCHypo, and to offer these women the benefit of T4 therapy [3].

Thus, TSH screening during prepregnancy or early pregnancy has been advocated [23]. The increased rate of pregnancy loss in women with TSH in the range of 2.5–5.0 has led to the recommendation that normal TSH in early pregnancy should be <2.5 [21-22]. If a patient is already on T4 replacement and TSH is >2.5, the dose of T4 should be increased to keep serum TSH <2.5 mIU/L.

CONCLUSIONS

Management of SCHypo continues to remain controversial [3, 13]. Because SCHypo is common and asymptomatic, and is associated with potential significant cardiovascular or lipid complications, routine TSH screening for early diagnosis and T4 therapy have been recommended.

Dr. Ross: Although all professional endocrine groups, the American Academy of Family Physicians, and the American College of Physicians recommend screening (case finding) for selected groups, it is notable that the United States Preventative Services Task Force and the Institute of Medicine recommend against screening.

Table 23-2. Subclinical Hypothyroidism Favoring Treatment

• Younger pt
• TSH >5
• TPOAb+
• ↑ cholesterol
• Goiter
• Symptoms
• Infertility
• Pregnancy

Key points

- Serum TSH levels are influenced by age and race; the upper limit of normal TSH remains a matter of debate
- Thyroid failure is a graded phenomenon, with slight TSH elevation (5–10 mIU/L) representing early and mild disease
- Patients with SCHypo are likely to have subtle symptoms, cardiac problems, or lipid abnormalities
- Consider criteria to select who to treat *(Table 23-2)*: TSH >5.0; young pt (< 65 years); obesity; fatigue; hyperlipidemia; goiter; positive TPO; infertility
- Therapeutic target TSH level for those on T4 replacement therapy should reflect age-adjusted normal ranges for TSH, and should be <2.5 mIU/ml during pregnancy
- Normal TSH in early pregnancy is <2.5. Increase T4 dose or start T4 if TSH >2.5. Pregnant patients with positive TPO but normal TSH may still benefit from T4 replacement

- *Dr. Ross:* No blinded studies have demonstrated that levothyroxine ameliorates "hypothyroid symptoms" better than placebo when TSH is less than 10 mIU/L.

For cases:

The normal reference ranges for the hormone levels are:

- TSH 0.5–5.0 mIU/L
- Free T4 (normal 0.8–1.5 ng/ml)
- TPO antibodies

CASE 1

A 30-year-old woman is seen for a routine exam. She is obese, reports weight gain, complains of fatigue, and has hyperlipidemia. Exam is normal. Serum TSH is 6.9 mIU/L, FT4 1.0 ng/dl, and TPO antibodies are significantly elevated.

Repeat studies are nearly the same.

Would you treat with levothyroxine

A. Yes, should be on T4. Reasons: young patient, symptoms, positive antithyroid antibodies, and elevated TSH. If she does not want Rx, then carefully follow, with repeat TSH and FT4 in 3–6 months.

A. *Dr. Ross:* Maybe. It is unlikely that thyroid hormone would harm her. Both placebo and thyroid hormone are equally likely to improve her symptoms. She has antibodies and is more likely to progress to overt hypothyroidism. She likely expects to be treated.

CASE 2

A 74-year-old woman complains of fatigue, poor sleep, and mild depression. Thyroid gland is small, smooth, but firm. Serum TSH is 7.4, FT4 1.3, and TPO negative.

Should she be on T4?

A. No, no need for T4. TSH level might be normal for this older pt, FT4 is perfectly normal, and TPO is negative. Thyroid gland is not enlarged. Follow with repeat TSH and FT_4 in 3–6 months. Consult an endocrinologist for benefits and risks of treatment.

A. *Dr. Ross:* No. Not only is there no evidence supporting a benefit for treatment, it is possible that thyroid hormone therapy might be more harmful than beneficial to her, particularly because thyroid hormone therapy often is associated with periodic unintentional overtreatment.

CASE 3

A 46-year-old woman is on T4 0.125 mg/day for hypothyroidism. She complains of fatigue, dry skin, hair loss, and recent weight gain. Serum TSH is 5.8 and FT_4 0.9.

Would you increase her T4 dose?

A. Yes. She is already on T4 for hypothyroidism but dose is inadequate, as suggested by mild TSH elevation and low-normal FT4. Should increase T4 dose to 137 mcg per day and recheck TSH in 2 months. Target therapeutic TSH is 0.3–3.0. I expect her symptoms to improve.

CASE 4

A 26-year-old woman is planning to get pregnant. Thyroid palpation is normal. Serum TSH is 4.5 mIU/L. FT4 is 1.2 and TPO negative.

What is your advice?

A. Needs referral to an endocrinologist because this is a difficult case.

Recent evidence suggests increased pregnancy loss rate in women with TSH levels between 2.5 and 5.0 in first trimester of pregnancy. Accordingly, it is prudent to start this patient on T4. The discussion of outcomes and the decision on Rx and follow-up are best made by an endocrinologist.

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24 Management of Subclinical Hyperthyroidism

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SIGNIFICANCE OF CLINICAL PROBLEM

Subclinical hyperthyroidism is defined as a subnormal TSH concentration with a normal- range serum free thyroxine (FT4) and triiodothyronine (T3) concentrations and is usually asymptomatic. It is more common in women and older individuals and is most commonly caused by excess exogenous replacement with levothyroxine (LT4). The prevalence of subclinical hyperthyroidism is 0.7–12.4%, depending on the definition and population studied [3,4]. The frequency of progression from subclinical to overt hyperthyroidism (elevated serum T4 and T3 concentration) is low, between about .5 and 5% [4, 5]. Vadiveloo et al. [4] noted that after 7 years, about 63% of subclinical hyperthyroid patients had persistent subclinical hyperthyroidism, .5–.7% developed overt hyperthyroidism, and 35% had thyroid function tests that reverted to normal. The primary clinical manifestations of subclinical hypothyroidism are low bone mineral density and increased risk of cardiovascular disease and mortality. Although the clinical manifestations are generally related to the extent of TSH suppression, the appropriate threshold to initiate therapy needs to be clarified by more longitudinal studies.

The effect of subclinical hyperthyroidism on bone is primarily in postmenopausal women. In a study of 398 women over age 65, the fracture risk with levothyroxine therapy correlated inversely with serum TSH levels [6]. Patients with TSH <0.1 μU/ml had a 3.6 RR for hip and 4.5 RR for vertebral fractures. A history of thyrotoxicosis also was associated with a RR of 2.2 [6]. In a 6-year prospective study of 1,278 postmenopausal women from five European cities who were euthyroid on no medications, a higher free thyroxine was associated with lower BMD at hip and greater rate of bone loss, and a 20% increased risk of non-vertebral fracture [7]. The adverse effects of subclinical hyperthyroidism on bone can be partially ameliorated by bisphosphonates, vitamin D, calcium, exercise, and avoidance of alcohol, tobacco, caffeine, and glucocorticoids.

There are also adverse effects of subclinical hyperthyroidism on the heart. In a study of 1,191 patients >60 yrs, not receiving levothyroxine or antithyroid agents, patients were grouped according to initial TSH level (1988–1989). Mortality rates were based on follow-up and census records (June 1, 1999) and

were compared to age-matched mortality rates in England and Wales during the same time period. Cardiac mortality at 5 years was about doubled in patients with subclinical hyperthyroidism [8,9]. In a different study, Cappola et al.[10] found a risk ratio for atrial fibrillation of 1.98 ($p<.05$). There was no association with other cardiovascular abnormalities. A suppressed TSH is associated with increased cardiac mortality, and it is thought that normalizing the TSH should reduce this mortality. Prospective randomized studies, however, have not been done to determine if treatment is beneficial. Older individuals are most susceptible to the negative effects of subclinical hyperthyroidism, but the appropriate TSH threshold and age to initiate therapy are not established.

BARRIERS TO OPTIMAL PRACTICE

- Knowing the clinical significance of mild to moderate suppression of TSH in patients and the value of treatment.
- The extent to which the etiology of subclinical hyperthyroidism influences the decision to treat.
- The duration of time patients with subclinical hyperthyroidism should be treated.
- Knowing the full spectrum of clinical manifestations of subclinical hyperthyroidism and the benefits of treatment.

LEARNING OBJECTIVES

As a result of reading this chapter, learners should be able to:

- Understand the definition of subclinical hyperthyroidism, the spectrum of causes, and natural history.
- Describe a systematic approach to testing and evaluation of subclinical hyperthyroidism to establish etiology.
- Identify the appropriate treatment of subclinical hyperthyroidism and the influence of associated conditions and the age of the patient.

CASE 1

An 84-year-old woman presents with fatigue. She denies weight loss, palpitations, nervousness, insomnia, eye symptoms, or neck discomfort. Examination reveals minimally enlarged thyroid gland with no palpable nodules. No adenopathy. Pulse 86. Medications: Lisinopril 20 mg daily.

Thyroid Sonogram: Bilateral thyroid nodules. Right: 2.5 x 1.5 cm Left: 1.5 x 1.0 cm. No worrisome sonographic features of nodules. Bone mineral density T scores: Spine –1.49; Left hip –1.87

Laboratory Results: Complete blood count—chemistry panel normal; free T4 1.66 ng/dl (normal .8–1.9); total T3 163 ng/dl (normal 80–180); TSH .05 uU/ml (normal .4–4.2); thyroid peroxidase antibodies 320 U/ml (normal less than 40). Thyroglobulin antibodies 120 U/ml (normal less than 40). Thyroid stimulating immunoglobulins negative.

Is this subclinical hyperthyroidism?
What additional tests would you perform?
Should you perform a fine needle aspiration on any of her thyroid nodules?
Would you treat the patient? If so, how?

DISCUSSION

1. ***Does this patient have subclinical hyperthyroidism? What additional tests would you order?***
   A. In patients with a low TSH, the clinician determines whether the cause of the low TSH is due to hyperthyroidism or another etiology. The differential diagnosis of a low TSH level includes the following: overt or subclinical hyperthyroidism, euthyroid sick syndrome, normal pregnancy first trimester, recovery from hyperthyroidism, pituitary or hypothalamic disease, drugs (corticosteroids, dobutamine, dopamine, bexarotene), interference in TSH assay (e.g., hetorophilic antibodies, TSH glycosylation abnormalities), or laboratory error.

      This patient, with high normal T3 and T4 levels, very low TSH, and thyroid nodules may have subclinical hyperthyroidism due to autonomous hypersecretion of thyroid hormones from the nodules. A radioiodine uptake study and thyroid scan would be useful to make this diagnosis and to discriminate from other common causes of hyperthyroidism, such as mild Graves disease, exogenous thyroid hormone, or thyroiditis. A radioiodine uptake study is also useful in guiding therapy.

2. ***Should you perform a fine needle aspiration on any of her thyroid nodules?***
   A. The decision to perform a fine needle aspiration (FNA) of a thyroid nodule is based largely on risk factors for thyroid cancer plus sonographic appearance. Patients with multinodular goiter (MNG) have the same risk of malignancy as those with solitary thyroid nodules. Nodules that have hypoechogenicity, the presence of microcalcifications, increased vascular flow, irregular borders, and the absence of a halo should prompt consideration of an FNA [11, 12]. Patients with MNG should be followed with periodic neck examination and ultrasoun. A repeat biopsy should be considered if there is significant growth of a nodule or other worrisome clinical (persistent hoarseness, dysphagia, adenopathy, etc.) or worrisome sonographic features develop on follow-up. Patients with MNG should be followed with ultrasound within 6 to 18 months of initial FNA and periodically thereafter (every 3–5 years) to evaluate for nodule growth [11]. The ATA task force guidelines recommend repeating the biopsy when there is a ≥50% increase in nodule volume within the first 6–18 months after initial FNA [11]. If FNA is negative, repeat thyroid ultrasound within 6 to 18 months of initial FNA and periodically thereafter (every 3–5 years) to evaluate for nodule growth. Repeat the biopsy when there is a ≥50% increase in nodule volume within the first 6–18 months after initial [11, 12].

3. ***Would you treat this patient? If so, how?***

A. This elderly woman has a higher risk of bony and cardiovascular complications due to subclinical hyperthyroidism. The clinician should have a low threshold to treat her subclinical hyperthyroidism. Radioiodine ablation and surgery are the two principal options. If her radioiodine uptake is high-normal or elevated or thyroid scan reveals hyperfunctioning nodules, treatment with radioiodine ablation is an option. Another option is surgical extirpation; surgery is indicated as the preferred therapy in patients with large bulky thyroids that are causing obstructive symptoms. According to the ATA Guidelines, total thyroidectomy should be the procedure of choice for patients with MNG who opt for surgical therapy. Complications include injury to the recurrent laryngeal nerve, trachea, and parathyroid glands. Complications are more common in patients with large, substernal goiters. Patients should be rendered euthyroid prior to surgery, if possible. [11, 12].

CASE 2

An 87-year-old woman is referred for nervousness, tremor, insomnia, and fatigue of 2 months' duration. On PE she is asthenic and has a pulse of 100/min with BP 150/80. Thyroid gland not palpable. She has a bilateral hand tremor. Her eyes, lungs, and abdomen are normal. Laboratory: TSH .01 uU/ml (normal .4–4.2); free T4 0.46 ng/dl (normal .8–1.9); total T3 293 ng/dl (normal 80–180).

Radioiodine uptake 2% at 24 hours (normal 10–30%); urine iodine 245 ug/day (normal > 100); ESR 5 mm/hr (normal < 30); serum thyroglobulin 3 ng/ml

Thyroid sonogram: Small heterogeneous gland.

Thyroid antibodies negative. Thyroid-stimulating immunoglobulins negative. Pituitary MRI negative. Alpha subunit 1 ng/ml. Prolactin 15 ng/ml, morning cortisol 22 ug/dl, FSH 56 U/L, LH 45 U/L. T3/T4/TSH antibodies negative.

What could be causing the abnormal thyroid function tests?

A. The differential diagnosis of a low TSH, low T3 and high T4 include laboratory error, ingestion of T3 (Cytomel) or triidothyroacetic acid (Triac). Patient vigorously denies taking any type of thyroid medication, including levothyroixine or Cytomel. She lives alone and has very little contact with anyone and not with anyone who could prescribe these medications.

Further discussion, however, reveals she has been taking over-the-counter weight loss supplements that contain Triac (triidothyroacetic acid) [6].

Following discontinuation of supplements, thyroid function tests demonstrated the following: TSH 3.8 uU/ml (normal .4–4.2); free T4 1.4 ng/dl (normal .8–1.9) andTT3 98 ng/dl (normal 80–180).

DISCUSSION OF CASE 2

Triac cross-reacts in T3 assays to a variable extent. In this assay, Triac cross-reacted 33%.

Triax, Tricana, and Tria-cutz each contain 1000 ug Triac. Internet search has shown that Triac is still available, with unproven claims of ìsafeî weight loss. Dietary supplements are used by 71% of U.S. households (FDA MedWatch Program).

Triiodothyroacetic acid (Triac) has a 6–8 hour half-life. Triac binds to liver nuclear thyroid hormone receptor with an affinity equal to that of T3 or T4 and inhibits circulating TSH as efficiently as T3 or T4. Triac had been thought to have a selective action at the pituitary level, with almost no effects peripheral effects. However, Triac is not pituitary selective. Triac therapy has similar cardiovascular action and greater hepatic and skeletal thyromimetic actions than levothyroxine therapy.

CASE 3

A 76-year-old man has had mycosis fungoides since 2002. He has no specific symptoms of thyroid problems on physical examination, no goiter was palpable. P 80/reg; BP 110/70. His skin exam shows mycosis fungoides but eyes, heart, lungs, and abdomen are normal. No pretibial myxedema.

Laboratory tests included serum TSH 0.08 mU/L (normal .4–4.2), and serum total free T4 of 0.6 ng/dl (normal .8–1.9).

What additional tests do you want, and what is your differential diagnosis? What is the most likely cause of his abnormal thyroid function tests?

Measurement of T3 would be useful to exclude T3 thyrotoxicosis *(see Case 2)*. A thyroid ultrasound might be useful to confirm the absence of a goiter and look for nodules. Sella imaging and assessment of pituitary function may be indicated to exclude a mass that is causing secondary hypothyroidism.

Bexarotene, a common treatment of mycosis fungoides, suppresses TSH levels. After serum T3 measurement, thyroid ultrasound, sella imaging and pituitary function tests yielded normal results, he was diagnosed with secondary hypothyroidism due to bexarotene.

DISCUSSION OF CASE 3

Bexarotene is a ligand whose specificity for retinoid X receptors is 100 times its specificity for retinoic receptors [13-15]. The secretion of TSH is regulated by T3 bound to thyroid hormone receptor acting at a response element near the transcription start site of the TSH beta-subunit gene, involving interaction with nuclear cofactors, including the retinoid X receptor. At the doses of bexarotene used in oncology, TSH suppression is observed in a significant number of patients, and in most patients is sufficient to reduce serum T4 concentrations. Many of these patients may benefit from levothyroxine therapy to restore serum T4 levels to the mid-normal range.

CASE 4

A 28-year-old G1P0 woman with a history of Graves' disease is seen for evaluation and is in her 6th week of pregnancy. She was diagnosed with Graves disease 3 years ago and was treated with a modest dose of radioiodine 1 year ago (24-hour RAIU 77% and given 3.58 mCi I-131). She had persistent hyperthyroidism and was restarted on PTU to a dose of 100 mg BID. She then developed hypothyroidism, such that her TSH rose to 100 uIU/ml (normal 0.35–5.50) and 3 months ago her PTU was discontinued. Follow-up thyroid studies 2 months later, off PTU, showed a normal range of free T4 and T3, but a TSH of .01 uIU/ml. The patient has no complaints, has had a good appetite, and has had no change in weight.

Physical examination: pulse 85, blood pressure 115/71, height 63î, weight 152 pounds, BMI 27. No significant ophthalmopathy, no tremor, no palpable thyroid enlargement.

Laboratory Results: TSH 0.01 uIU/ml (normal .4–4.2), total T3 124 ng/dl (normal 60–180), and free T4 1.36 ng/dl (normal .8–1.9)

1. ***What might be causing a suppressed TSH in this patient?***
   A. A suppressed TSH is seen in 15% of normal women in the first trimester, in 10% in the second trimester, and in 5% in the third trimester. The possibilities for a suppressed TSH in the first trimester include: normal thyroid function test changes in pregnancy, Graves disease, and thyroid changes associated with hyperemesis gravidarium [16]. In this patient, with a history of radioiodine treatment for Graves disease, it is possible that she has had incomplete treatment for her Graves disease, with residual autonomy [17].

2. ***Does she require treatment? If so, what treatment?***
   A. The primary concern in treatment of Graves disease during pregnancy has been over-treatment of the mother, producing fetal hypothyroidism and goiter. For this reason, pregnant women were generally treated with antithyroid drugs to a target of upper normal-range serum T4 concentration, usually with a persistent suppressed TSH. As long as the mother is gaining weight and the pregnancy is progressing normally, the minimal amount of antithyroid drug is used. A study in women with resistance to thyroid hormone RTH examined the influence on the RTH-affected and unaffected fetus [18]. When the pregnant mother with RTH had a fetus with RTH there were no adverse pregnancy outcomes. When the pregnant mother had RTH, but the fetus was normal and exposed to the elevated maternal thyroxine concentrations, there was a significant increase in fetal death, reduced birth weight, and a pattern of neonatal central hypothyroidism. Although the mothers in this study had serum T4 concentrations approximately 2 times normal, there is concern that excessive maternal T4 may also have adverse consequences for the fetus. The target of an upper normal free T4 concentration is still

likely to be reasonable. A study of pregnant women with ìsubclinicalî hyperthyroidism, suppressed serum TSH but normal-range serum T4 and T3 concentration, showed no adverse outcome for mother or fetus [19]. In the patient in this case, with a normal range FT4 and T3, antithyroid drug treatment should not be used.

3. ***How should this pregnant patient be followed?***
   A. Since her TSH is suppressed, it is especially important to follow both TSH and FT4 at frequent intervals. This patient had a fall in free T4 and ultimately required levothyroxine to maintain her TSH and FT4 in a normal range.

4. ***Is this patient's fetus at risk for neonatal Graves disease?***
   A. Yes, the thyroid-stimulating antibodies that cause Graves disease cross the placenta and may cause neonatal Graves disease. The fetus should be monitored by fetal heart rate, parameters of somatic growth, and examination for goiter [20]. In difficult cases, amniotic fluid or even fetal umbilical blood samples for thyroid hormone can be obtained. Neonatal Graves disease is seen in approximately 1% of the offspring of mothers with Graves disease during pregnancy. It is generally seen in mothers with the most active Graves disease at the time of presentation, as evidenced by high levels of serum FT4 and FT3 and high levels of TSI. According to some studies, marked elevation of TSI levels in the second trimester (even in women with treated Graves disease) is predictive of neonatal Graves disease.

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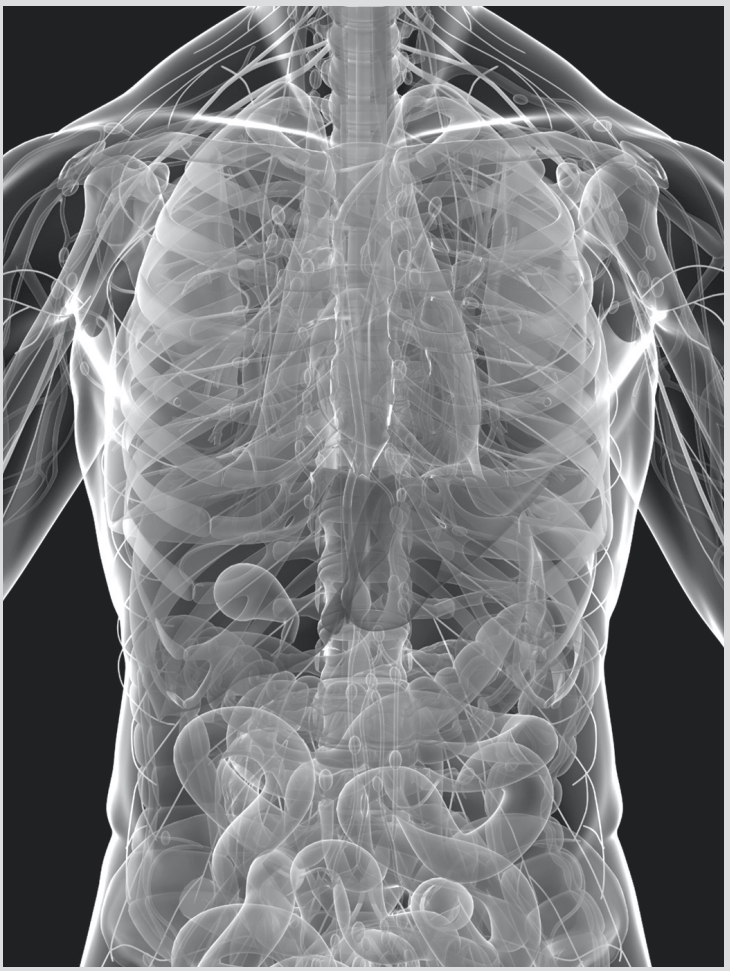
INDEX AND CME POST TEST



INDEX

CME POST TEST

Endocrine Essentials: Endocrine Update for General Medicine
Please select the best answer to each question on the online answer sheet.
Go to http://www.endo-society.org/EndocrineEssentialsEndocrineUpdate

BONE AND MINERAL HOMEOSTASIS

1. A 71-year-old man has a low trauma-vertebral compression fracture. His bone densitometry by DXA reveals a T score of –2.7 in the spine and –2.2 in the hip. His laboratory evaluation for osteoporosis is remarkable for a 25-OHD level of 8 ng/ml. You decide that his target 25-OHD level should be 30 ng/ml.

You treat him with 50,000 units of vitamin D weekly for 8 weeks, and his 25-OHD level rises to 22 ng/ml.

Based on the "rule of thumb" vitamin D dosage rule, what is the minimum dosage of daily vitamin D that you would recommend to treat his vitamin D deficiency and raise his level to at least 30 ng/ml?

a. 600 IU
b. 800 IU
c. 1000 IU
d. 3000 IU
e. 5000 IU

2. ***Based on the FRAX calculator, which patient has the highest 10-year risk of hip fracture?***

a. A 60-year-old man who weighs 70 kg and has a significant history of glucocorticoid use for polymyalgia rheumatica
b. A 60-year-old woman who weighs 70 kg and has a history of smoking 1 pack of cigarettes daily
c. A 60-year-old woman who weighs 70 kg and drinks 3 to 4 cocktails daily
d. A 60-year-old woman who weighs 50 kg and has a history of smoking 1 pack of cigarettes daily
e. A 75-year-old woman who weighs 70 kg and has a significant history of glucocorticoid use for asthma

3. A 64-year-old woman was placed on an oral bisphosphonate 5 years ago (by another physician) based on bone densitometry that revealed a T score of –2.5 in the spine and –2.2 in the hip. She enquires about how long she has to take an oral bisphosphonate.

She is a healthy woman with a history of hypertension treated with an ACE inhibitor and hydrochlorothiazide. She has no major risk factors for osteoporosis. She has no history of fractures. She has never smoked and drinks alcohol occasionally. She is physically active, and she takes 1000 IU of vitamin D and a total of 1200 mg of calcium daily.

Her recent bone densitometry reveals a T score of –2.2 in the spine and –2.1 in the hip.

You calculate her FRAX score for 5 years ago (prior to bisphosphonate therapy).

FRAX 5 years ago: 2% risk of hip fracture and 12% risk of any osteoporotic fracture.

What would be the most appropriate next step in management?

a. Discontinue bisphosphonate therapy
b. Continue bisphosphonate therapy indefinitely
c. Switch to teriparatide daily
d. Switch to oral raloxifene therapy
e. Switch to denosumab injections every 3 months

4. A 63-year-old woman with newly diagnosed rheumatoid arthritis has severe osteoporosis by DXA performed last week. (T scores are –3.6 in the spine, –3.2 in the right wrist, and –3.0 in the hip.) She has just been started on systemic corticosteroid therapy. You decide to administer intravenous zoledronic acid.

The patient returns to your clinic in 1 month later. She is very interested in knowing whether the zoledronic acid is helping her.

Which of the following would be the most appropriate test to order now?

a. Serum procollagen type 1 propeptide and cross-linked C-telopeptide levels
b. DXA of the wrist
c. DXA of the hip
d. Quantitative CT of the spine

5. Mrs. Smith has rheumatoid arthritis that has been managed with oral corticosteroid therapy for 8 years. She has recently suffered a vertebral compression fracture that is quite painful. Her bone densitometry reveals a T score of –3.0 at the spine and –2.8 in the hip.

Which of the following interventions is likely to decrease future vertebral compression fractures and maximally increase her bone mineral density?

a. Subcutaneous calcitonin
b. Oral alendronate
c. Subcutaneous teriparatide
d. Balloon kyphoplasty

6. A 65-year-old man presents with weakness and easy fatigability. During the course of evaluation, he is noted to be hypocalcemic. He denies tetany or oral paresthesias.

Past medical history: He has a history of thyroid cancer that was treated with total thyroidectomy 1 year ago followed by radioiodine ablation. He also has hypertension and mild chronic kidney disease thought to be due to hypertension.

Physical examination is remarkable for a well-healed midline neck scar, no cervical masses or adenopathy and negative Chvostek's and Trousseau's signs.

Laboratories: Creatinine 1.6 mg/dl (normal 0.7–1.2), Total calcium 7.5 mg/dl (normal 8.8–10.4), Albumin 4.0 g/dl (normal 3.5–5.0), Phosphate 6.5 mg/dl (normal 3.5–5.0), Mg 1.8 mg/dl (normal 1.5–2.5), Alkaline phosphatase 110 U/L (normal 20–120), 25-OHD 25 ng/ml (see text re normal range), Intact PTH 25 pg/ml (normal 10–65), 1,25(OH)2D 64 pg/ml (normal 16–56).

He has a normal liver function panel.

What is the most likely explanation for his hypocalcemia?

a. Hypoparathyroidism
b. Renal disease
c. Vitamin D deficiency
d. CASR receptor activating antibody
e. Wilson disease

7. A 55-year-old man is evaluated for severe osteopenia (by DXA). He has a history of hypertension and dyslipidemia. He passed a single kidney stone 5 years ago. He takes losartan and simvastatin. He has no family history of autoimmune diseases. His physical exam is normal.

His lab results include a normal serum creatinine, calcium, phosphate, and TSH, but his serum PTH is slightly elevated at 80 pg/ml (normal 10–65). Repeat PTH is 78.

Of the following, which pair of tests would be most appropriate to measure?

a. 1,25-hydroxyvitamin D and anti-tissue transglutaminase antibodies
b. 25-hydroxyvitamin D and anti-gliadin antibodies
c. 1,25-hydroxyvitamin D and anti-gliadin antibodies
d. 25-hydroxyvitamin D and 24-hour urine calcium

8. A 62-year-old woman was seen 6 months ago for fatigue. Her energy level has improved significantly since she has been treated for depression. However, when she was evaluated for fatigue 6 months ago, a serum calcium level was orderedand the result was 10.5 mg/dl (normal 8.8–10.2). Her past medical history is remarkable for HTN and arthritis. She takes lisinopril and acetaminophen.

Today's labs:

- Serum calcium = 10.6 mg/dl (normal 8.8–10.2)
- Albumin = 4.0 g/dl (normal 3.5–5.0)
- Serum phosphate = 3.5 mg/dl (normal 3.5–5.0)
- Creatinine = 0.9 mg/dl (normal 0.5–1.3)
- PTH = 82 pg/ml (normal 10–65 pg/ml)
- 25-hydroxyvitamin D = 36 ng/ml (normal 10–45 ng/ml)
- 24-hour urine calcium = 220 mg (normal <250)

Recent DXA:

- Lumbar spine T score = –2.3
  Total hip T score = –1.9
  Forearm T score = –2.0

The patient does not meet surgical criteria for parathyroidectomy. Of the following, which medical treatment would be the best option for her?

a. Estrogen-progestin hormone therapy
b. Raloxifene
c. Alendronate
d. Cinacalcet
e. Teriparatide

DIABETES MELLITUS

9. ***Which of the following patients is most likely to have monogenic diabetes mellitus (MODY)?***

a. A 62-year-old obese woman with acanthosis nigricans, newly diagnosed diabetes mellitus type 2, and an extensive family history of type 2 diabetes mellitus
b. A 33-year-old woman with a 21-year history of type 1 diabetes mellitus and no diabetic complications despite a history of non-compliance with insulin therapy
c. An 8-year-old boy who is slender and has newly diagnosed diabetes mellitus and positive pancreatic islet cell antibodies
d. A 48-year old man with a family history of type 2 diabetes mellitus who has a 10-year history of poorly controlled diabetes mellitus while on sulfonylurea and metformin therapy.

10. A 54-year-old man with type 2 diabetes mellitus and diabetic nephropathy started dialysis 3 months ago. He was diagnosed with type 2 diabetes mellitus 14 years ago and was treated with a sulfonylurea, metformin, and pioglitazone until 9 months ago, when he was switched to NPH 18 units twice daily. His current A1c is 7.0%. He checks his blood sugar levels 1–2 times daily, before breakfast and at bedtime, and his blood sugar levels are "always ~ 180–200 on the dialysis days and ~200–250 on the other days." He has had no difficulty getting his prescriptions covered by his insurance company.

Which of the following is the best management strategy for his blood glucose levels?

a. Increase NPH to 25 units twice daily
b. Add regular insulin with meals on the non-dialysis days
c. Start sitagliptin
d. Add exenatide
e. No change in his regimen

11. A 67-year-old man was diagnosed with type 2 diabetes mellitus 7 years ago. His glycemic control is excellent on metformin. This man is suspicious of pharmaceutical companies and wants of avoid any medications that he can.

Past medical history: Type 2 diabetes mellitus, hypertension. He has had high blood pressure readings at his last five visits, but he would argued against treatment by declaring that he would improve his blood pressure by reducing salt intake, losing weight, and reducing alcohol intake.

Family medical history: Father with myocardial infarction at age 66

Social history: Does not smoke. Drinks an occasional glass of wine.

Medications: Metformin 1 g bid

Physical examination normal except blood pressure is 146/84. Pulse is 72.

Labs: Normal blood chemistries. Fasting blood glucose 112. A1c 6.9%

Fasting lipid panel: LDL 122, HDL 41, Triglycerides 137

He might be willing to take one additional medication.

Of the following choices, which single medication would be most useful to decrease his risk of myocardial infarction?

a. Aspirin
b. Fenofibrate
c. Lisinopril
d. Atorvastatin

12. A 48-year-old woman has just been diagnosed with type 2 diabetes mellitus. Her older brother is on dialysis due to diabetic nephropathy, and she is terrified of the prospect of being on dialysis. She has a history of hypertension that has been treated with amlodipine 10 mg daily. She takes no other medications. Her blood pressure is 125/84(similar to other recent clinic visits). Her A1c is 8.7%.

Her estimated GFR is normal. Her albumin excretion rate is normal. Her fasting lipid panel reveals the following: LDL 134, HDL 48, Triglycerides 190.

What is the most effective intervention to prevent diabetic nephropathy in this woman?

a. Switch amlodipine to lisinopril
b. Add lisinopril to lower her blood pressure to <120/80
c. Tight glycemic control with a target A1c of <7.0%
d. Start atorvastatin
e. Start a low-protein diet

13. A 55-year-old man has had well-controlled diabetes mellitus for 12 years. For the past 5 years, he has been taking maximum dosages of a sulfonylurea and metformin. His A1c has risen from 6.9% to 8.2% over the past year despite excellent adherence to diet, exercise, and his medication regimen. His blood sugar levels range between 160 and 220 mg/dl in the morning, and 130 and 165 mg/dl at dinner and bedtime. His weight is 80 kg.

You decide to reduce the dose of his sulfonylurea and start insulin therapy.

What would you recommend as the initial insulin regimen?

a. Detemir 16 units at night plus 4 units of lispro before meals
b. NPH 16 units at night
c. Glargine 16 units at night
d. NPH 16 units at night plus 4 units of lispro before meals
e. Glargine 32 units at night

14. A 22-year-old man with type 1 diabetes for 7 years has had poor glycemic control. His A1c levels have been 9–11%, and he has severe hypoglycemic reactions several times per month. He checks his blood sugar levels irregularly. He has read that the insulin pump can dramatically improve glycemic control.

Which of the following is true about insulin pump therapy for this patient?

a. An insulin pump would make the management of his diabetes mellitus easier for him.
b. He could benefit from an insulin pump if he can demonstrate that he can check his blood sugar levels regularly, count carbohydrates, and adjust insulin dosing.
c. An insulin pump is contraindicated in patients with severe hypoglycemic episodes.
d. He would never be a good candidate for an insulin pump.

15. A 27-year-old woman with type 1 diabetes mellitus diagnosed 3 years ago comes to your office for follow-up. She uses an insulin pump. Her A1c levels have fluctuated from 7.5% to 8.5% since her diagnosis. She has had two episodes of severe hypoglycemia (requiring intervention by paramedics) in the past 9 months. During the course of her visit, she shyly discloses that she and her husband are trying to have a baby. She declares "I will do whatever it takes to have a healthy baby!" She has heard about CGM and wants to know if she can use this technology. Her A1c today is 7.8%.

Which of the following is the most important barrier to optimal use of CGM for this patient?

a. Determination of whether her insurance company will cover CGM
b. Availability of downloading software for CGM devices
c. Patient's commitment to using sensor data to adjust caloric intake and insulin dosages
d. Clinician commitment to reviewing CGM data to make adjustments in insulin dosages
e. Patient must be evaluated for hypoglycemic unawareness prior to implementation of CGM

CARDIOVASCULAR ENDOCRINOLOGY

16. A 52-year-old woman with chronic kidney disease (GFR = 40 ml/min) had a myocardial infarction 1 month ago. She was treated with simvastatin, but she complained of severe muscle aches, and she stopped the medication. Her fasting lipid panel (off simvastatin) reveals an LDL of 150 mg/dl, triglycerides 210 mg/dl and HDL 38 mg/dl. Serum CPK is normal.

Which is the best next therapeutic regimen for this patient's dyslipidemia?

a. Niacin (at dosage adjusted for renal function)
b. Ezetimibe
c. Gemfibrozil
d. Stanol pills
e. Rosuvastatin (low dosage)

17. A 56-year-old man seeks your advice on whether to start lipid-lowering therapy. He has been advised to start a statin, but he is reluctant to do so and wants a second opinion. He runs 3 miles four times a week and lifts weights three times a week. He does not have a personal history of CHD or a family history of premature CHD. He takes lisinopril for hypertension. His blood pressure is 135/80. He has never smoked. His fasting lipid profile reveals the following: total cholesterol 240 mg/dl, HDL 40 mg/dl, LDL 180 mg/dl, and triglycerides 200 mg/dl. His Lp(a) level is at the 10th percentile.

Based on current evidence, which of the following tests would be the most useful adjunctive test to determine whether statin therapy should be initiated?

a. Serum CRP in a highly sensitive assay
b. Carotid intimal medial thickness by ultrasound
c. Carotid intimal medial thickness by ultrasound
d. Coronary artery calcification score by CT

18. A 44-year-old man has a 12-year history of hypertension that has recently become more difficult to control. He takes losartan, amlodipine, and hydrochlorothiazide. His aldosterone-plasma renin activity ratio is 28. His renin level was 0.6 ng/ml/hour (normal 0.6–3.6). His serum potassium and creatinine, measured at the same time that his RAA was assessed, were 3.9 meq/L and 1.0 mg/dl, respectively. A recent CT of the abdomen revealed a 1.2 cm left adrenal nodule that was interpreted by the radiologist as "consistent with a functional adenoma."

The patient would like surgery if it will help limit the number of medications that he needs to control his blood pressure.

What would be the most appropriate next step in management?

a. Surgical consultation for left adrenalectomy
b. MRI of bilateral adrenals
c. Adrenal venous sampling for aldosterone
d. 24-hour urine for aldosterone and sodium while on a high-sodium diet (>6 g sodium)
e. Repeat ARR after holding all anti-hypertensive medications for at least 2 weeks

MEN'S AND WOMEN'S HEALTH

19. A 68-year-old man is diagnosed with hypogonadism based on symptoms (low libido, decreased morning erections, and erectile dysfunction) plus low serum total and free testosterone levels in two blood samples drawn in the early morning (1 week apart). He has hypertension, diabetes mellitus type 1, and obesity.

- Physical exam
- BMI 32, BP 142/92, HR 92
- Normal cardiac and pulmonary exam
- Abdomen obese but not organomegaly
- 2.5 cm nontender bilateral gynecomastia
- Testes 20 cc bilaterally
- No prostate nodules

Which of the following benefits is this patient most likely to experience with testosterone therapy?

a. Increased libido
b. Improved erectile function
c. Decreased blood pressure
d. Decreased hemoglobin A1c
e. Decreased body mass index

20. A 58-year-old man complains of erectile dysfunction (ED). He is able to achieve partial tumescence, but it is not sufficient for vaginal intercourse. His wife is interested in having sexual intercourse. The patient's medical history is remarkable for diabetes mellitus, coronary artery disease, hypertension, and arthritis. He had a myocardial infarction 4 years ago that was treated with a stent. His medications include metformin, lisinopril, atorvastatin, aspirin, and prn ibuprofen. He golfs twice a week and walks the 18-hole course without angina. He denies decreased libido, depressed mood, or symptoms of hypo- or hyperthyroidism.

- On exam, his blood pressure is 128/80 and pulse is 68. BMI = 28.
- He has no thyroid, cardiopulmonary, breast, genitourinary, or neurologic abnormalities.
- Blood chemistry panel and serum TSH are normal.
- His testosterone, FSH, and LH levels are normal.
- His HbA1c is 7.2%.
- His fasting lipid panel reveals the following: LDL cholesterol 105, HDL cholesterol 45, triglycerides 180.

Of the following, which is the best initial management of his erectile dysfunction?

a. Optimize his glycemic control and dyslipidemia prior to any specific therapy for ED
b. Switch lisinopril to amlodipine
c. Trial of an oral phosphodiesterase inhibitor
d. Trial of a vacuum erection device with a constrictive ring
e. No treatment of ED until he undergoes an exercise tolerance test

21. A 42-year-old man complains of a three-month history of breast tenderness and swelling. He is very embarrassed by his "large breasts" and has been avoiding his favorite exercise, swimming, as a result. He takes no medications and denies using marijuana, opiates or other illegal drugs of abuse. He has no occupational exposures that might cause gynecomastia.

Physical exam:

- BMI 26, blood pressure 128/80, heart rate 84
- *Neck:* No goiter or thyroid nodules
- *Cardiac:* normal
- *Pulmonary:* normal
- *Abdomen:* no masses, organomegaly
- *Breast:* 4 cm tender bilateral gynecomastia
- *Testes:* 20 cc bilaterally; no masses
- *Skin:* no rashes

A complete diagnostic evaluation, including serum testosterone, FSH, LH, hCG, TSH, and scrotal ultrasound, reveals no significant abnormalities. You diagnose idiopathic gynecomastia. The patient is very interested in treatment of his gynecomastia so that he can resume swimming.

What treatment do you recommend?

a. Clomiphene for 3 months
b. Raloxifene for 6 months
c. Tamoxifen for 3 months
d. Anastrazole for 6 months
e. Exemestane for 3 months

22. A 16-year-old girl requests an oral contraceptive. She is mildly hirsute and has mild acne. Her mother has accompanied her and agrees with the patient's request. The patient has no medical problems. There is no family history of deep venous thrombosis.

You counsel the patient to use barrier contraceptive methods to reduce the risk of sexually transmitted disease.

In addition, which of the following would be most appropriate therapy for contraception and hirsutism?

a. Depo Provera im every 3 months
b. Oral contraceptive with ethinyl estradiol plus desogestrel daily
c. Mini-pill (progestin-only pill) daily
d. Condoms plus spironolactone

THYROID DISORDERS

23. A 26-year-old woman complains of feeling tired and has gained 5 pounds. Her last normal period was 6 weeks ago. She is no medical problems and takes no medications. Family medical history is unremarkable. On exam she is a slender, healthy woman with a BMI of 22. She sees her primary care provider, who obtains the following laboratory tests:

- Free T4 1.2
- TSH 8.5
- Pregnancy test positive

What is the most appropriate management of her thyroid function tests?

a. Repeat thyroid function tests in 3–4 months
b. Measure anti-TPO antibodies; if elevated, then start levothyroxine therapy
c. Begin levothyroxine therapy with target TSH 0.5–2.5 mIU/L
d. Begin levothyroxine therapy with target TSH 0.5–5.0 mIU/L

24. A 58-year-old woman is seen in clinic for evaluation of decreased energy and easy fatigability. Review of her labs reveals the following: Free T4 1.6 ng/dl (0.8–1.9), total T3 80 ng/dl (80–100), and TSH 0.2 (normal 0.4–4.2).

Which of the following medications is the most likely explanation for her thyroid function tests?

a. Ingestion of dietary supplements containing Triac
b. Recent initiation of high-dosage prednisone for asthma
c. Effects of bexarotene for treatment of cutaneous T-cell lymphoma
d. Recent initiation of carvedilol for treatment of hypertension

Answers

1, c; 2, e; 3, a; 4, a; 5, c; 6, a; 7, d; 8, c; 9, b; 10, c; 11, d; 12, c; 13, b; 14, b; 15, c; 16, e; 17, a; 18, d; 19, a; 20, c; 21, c; 22, b; 23, c; 24, b

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